Understanding the biological and clinical correlates of delirium: Development of Reporting Essentials for Delirium bioMarker Studies (REDEEMS)

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Abstract

Background

Delirium is a common, serious and complex neurocognitive condition that is associated with negative impacts for both the person with delirium and their family/carers. Despite the significant burden, the pathophysiology of delirium remains unclear. To improve our understanding of delirium pathophysiology, robust delirium biomarker studies with optimal reporting are urgently needed to ensure each of these studies contribute to accelerate our knowledge.

Aim

To evaluate and optimize the methodological approaches in research evaluating biological and clinical correlates of delirium and underlying conditions.

Design

A multiple methods project, involving three discreet but inter-related studies conducted over three stages.

Methods

Study 1 was a systematic review of the overlap of delirium and advanced cancer-related syndrome biomarkers as an 'examplar' of the potential for interaction between the underlying condition and delirium; Study 2a was a three-stage modified Delphi study with delirium researchers and study 2b was a follow-up consensus meeting to generate a reporting guideline specific to delirium biomarker studies (REDEEMS). Study 3 comprised a series of semi-structured interviews which sought delirium researchers' perceptions of the key challenges of conducting delirium biomarker studies.

Results

The systematic review identified considerable overlap of delirium and advanced cancer biomarkers, with 41 biomarkers that had been studied in relation to both delirium and either an advanced cancer-related syndrome or prognosis. It also revealed a significant gap in the consistency and reporting of delirium biomarker studies. Considering this unexpected finding of poor quality, a drive to improve the methods of reporting delirium biomarker studies was warranted. The international Delphi study and consensus meeting (study 2) revealed a total of nine items which were deemed critical elements by delirium researchers for inclusion in the REDEEMS guideline. Finally, the third qualitative study identified a range of factors that contribute to the challenges and overall quality of delirium biomarker research. Delirium researchers concurred that delirium biomarker research is both an extremely difficult and complex field. and that the quality of reporting delirium biomarker research is poor, which contribute to lack of progress in scientific understanding. Analysis revealed two major themes and ten sub-themes, outlining key considerations to advance the field of delirium biomarker research. The major themes were: 1) Practical and scientific challenges of delirium biomarker research: stagnation versus driving improved methods and reporting; and 2) Valuing delirium research through investment and collaboration.

Conclusion

The REDEEMS guideline is the first reporting guideline specific for delirium biomarker studies aligned with impacts of reporting guidelines in other research methods. It aims to guide improvements in consistency and transparency of reporting future biomarker studies in delirium, conceivably permitting accurate replication and synthesis, and improving scientific rigor in the field. A collaborative effort to increase

awareness of, and improve research funding for delirium is needed, along with increased education and training in delirium biomarker methodology. These advancements will lead to significant improvement of our understanding of delirium pathophysiology and ultimately improve outcomes for people with delirium.

Certificate of original authorship

I, Ingrid Kathrine Viktoria Amgarth-Duff declare that this thesis, is submitted in fulfilment of the requirements for the award of Doctor of Philosophy in faculty of health at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise referenced or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis. This document has not been submitted for qualifications at any other academic institution.

This research is supported by the Australian Government Research Training Program.

Signature of candidate:

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Subsidiary Research Outputs

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Book chapter

Hosie, AM., **Amgarth-Duff, I.**, Agar, M. (2017). Delirium and Terminal Agitation. MacLeod, R & Van Den Block, L (Eds.) In *Textbook of palliative care.* Sydney, Australia: Springer.

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Abbreviations

ADA	Australasian Delirium Association
ADS	American Delirium Society
APA	American Psychiatric Association
BRISQ	Biospecimen Reporting for Improved Study Quality
CAM	Confusion Assessment Method
CNS	Central nervous system
CONSORT	CONsolidated Standards Of Reporting Trials
CSF	Cerebrospinal fluid
DSD	Delirium superimposed on dementia
DSM	Diagnostic and Statistical Manual of Mental Disorders
E&E	Explanation and Elaboration document
EDA	European Delirium Association
ELISA	Enzyme-Linked Immunosorbent Assay
EQUATOR	Enhancing the QUAlity and Transparency Of Reporting
HREC	Human Research Ethics Committee
ICD-10	International Classification of Disease, edition 10
LP	Lumbar puncture
N/A	Not applicable
POD	Post-operative delirium
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised Controlled Trial
REDEEMS	Reporting Essentials for DElirium bioMarker Studies
REMARK	Reporting rEcommendations for tumour MARKer prognostic studies
SAGES	Successful Aging after Elective Surgery
SSD	Subsyndromal delirium
STARD	Standards for Reporting of Diagnostic Accuracy Studies
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
UK	United Kingdom
USA	United States of America

Glossary of terms

Advanced cancer	Inclusive of stage III cancer (locally advanced with spread to nearby tissues or lymph nodes) and Stage IV cancer (metastatic disease).[1]
Anorexia cachexia	A complex metabolic syndrome of involuntary weight loss associated with cancer and some other palliative conditions.[2]
Biomarker	A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease.[3]
Cancer prognosis	The likely outcome or course of the disease; the chance of recovery or recurrence. Cancer prognosis is assessed by cancer-specific survival, overall survival, progression free survival or relative survival.[4]
Cancer-related cognitive impairment	Cognitive impairment that is commonly experienced by cancer patients and those in remission. The cognitive domains most commonly affected are memory, concentration, information processing speed and executive function.[5]
Cancer-related fatigue	A distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer and/or cancer treatment that is not proportional to recent activity and interferes with usual functioning.[6]
Cancer-related pain	An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.[7]
Classical Delphi Methodology	A research methodology with an aim to achieve consensus on a research question, using an expert panel, in an iterative and controlled survey process.[8]
Delirium	A neurocognitive disorder, characterised by acute disturbance to attention, awareness and cognition, affecting memory, language, visuospatial ability, orientation and perception.[9]
e-Delphi	A Delphi research method that involves the distribution of a survey electronically to panellists via email.
Hyperactive delirium	Delirium subtype where the patient has an increased level of psychomotor activity. There may also be lability of mood, agitation and resistance to medical care.[9]
Hypoactive delirium	Delirium subtype where the patient has a decreased level of psychomotor activity, along a continuum from lethargy to stupor.[9]
Incidence	The occurrence of new cases of a disease in a population over a specified period of time.[10]
Mixed delirium	Delirium subtype where the patient has either a normal or fluctuating level of psychomotor activity.[9]
Modified Delphi	Describes any methodological variation of the Classical Delphi method described by Dalkey and Helmer (1962).[11]
Morbidity	Non-fatal event.
Mortality	Fatal event/death.
Multiple methods	The use of two or more research methods in one research project.[12]
Persistent delirium	Full syndromal delirium at the time of admission (or shortly after admission) that continues to meet the criteria for delirium at the time of discharge or beyond.[13]
Prevalence	The proportion of a persons in a population who have a particular disease or attribute at a specified point in time or over a specified period of time.[10]
Point prevalence	The proportion of persons with a particular disease or attribute at a particular point in time (on a particular date).[10]

Prodromal delirium	Manifestation of symptoms such as changes to concentration, mood (irritability, anxiety, depression), sleep patterns (including vivid dreaming), cognition (e.g. disorientation), tiredness or noise sensitivity, that can occur in the hours, days or weeks prior to full syndromal delirium.[14]
Qualitative research	A means for exploring and understanding the meaning of individuals or groups ascribed to a social or human problem.[15]
Quantitative research	A means for testing objective theories by examining the relationship among variables.[15]
Reporting guideline	A checklist, flow diagram, or explicit text to guide authors in reporting a specific type of research, developed using explicit methodology.[16]
Sickness behaviour	The coordinated set of behavioural changes that develop in sick individuals during the course of an infection. Sickness behavior is also seen in other illness including cancer.[17,18]
Sub-syndromal delirium	Presence of one or more symptoms of delirium, where the patient does not meet the criteria for delirium.[19] Termed 'attenuated delirium syndrome' by the DSM-5.[9]

References

1. Cancer Institute NSW. Stages of Cancer. Accessed 19 July 2018.

2. CareSearch. Cachexia Anorexia Syndrome 2017; https://www.caresearch.com.au/caresearch/tabid/183/Default.aspx. Accessed July 19, 2018.

3. National Cancer Institute. NCI Dictionary of Cancer Terms. https://www.cancer.gov/publications/dictionaries/cancer-terms/?CdrID=45618. Accessed November 28, 2017.

4. National Cancer Institute. Understanding Cancer Prognosis 2018; https://www.cancer.gov/about-cancer/diagnosis-staging/prognosis. Assessed November 28, 2017.

5. Bray V, Dhillon H, Vardy J. Cancer-related cognitive impairment in adult cancer survivors: A review of the literature 2017; https://cancerforum.org.au/forum/2017/march/cancer-related-cognitive-impairment-in-adult-cancer-survivors-a-review-of-the-literature/.

6. Bower JE. Cancer-related fatigue—mechanisms, risk factors, and treatments. *Clinical Oncology.* 2014;11(10):597.

7. International Association for the Study of Pain. IASP Terminology. 2017; https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698&navItemNumber=576 - Pain.

8. Keeney S, McKenna H, Hasson F. *The Delphi technique in nursing and health research.* John Wiley & Sons; 2011.

9. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).* Arlington, VA: American Psychiatric Publisher; 2013.

10. Centers for Disease Control and Prevention. Lesson 3: Measures of Risk. 2012; https://www.cdc.gov/csels/dsepd/ss1978/lesson3/section2.html. Accessed 27 July 2020.

11. Dalkey N, Helmer O. An experimental application of the Delphi method to the use of experts. *Management Science.* 1963;9(3):458-467.

12. Brannen J. *Mixing methods: Qualitative and Quantitative research.* Routledge; 2017.

13. Cole MG, Ciampi A, Belzile E, Zhong L. Persistent delirium in older hospital patients: a systematic review of frequency and prognosis. *Age and Ageing.* 2009;38(1):19-26.

14. Gupta N, de Jonghe J, Schieveld J, Leonard M, Meagher D. Delirium phenomenology: What can we learn from the symptoms of delirium? *Journal of Psychosomatic Research.* 2008;65(3):215-222.

15. Creswell JW, Creswell JD. *Research design: Qualitative, quantitative, and mixed methods approaches.* SAGE Publications; 2017.

16. Moher D, Weeks L, Ocampo M, et al. Describing reporting guidelines for health research: a systematic review. *Journal of Clinical Epidemiology.* 2011;64(7):718-742.

17. Dantzer R. Cytokine-induced sickness behaviour: a neuroimmune response to activation of innate immunity. *European Journal of Pharmacology.* 2004;500(1-3):399-411.

18. Dantzer R. Cytokine-induced sickness behavior: where do we stand? *Brain, Behavior, and Immunity.* 2001;15(1):7-24.

19. Cole MG, Ciampi A, Belzile E, Dubuc-Sarrasin M. Subsyndromal delirium in older people: a systematic review of frequency, risk factors, course and outcomes. *International Journal of Geriatric Psychiatry.* 2013;11(4):534-543.

Chapter 1: Introduction

This introductory chapter describes the background, rationale, aim and objectives of this doctoral research program, and outlines the structure and content of the thesis.

1.1 Overview

Delirium is a serious and complex neurocognitive condition manifesting as an acute change in mental status, that commonly complicates medical illness. The hallmark features of delirium include acute changes in attention, awareness and cognition; which variously affects memory, language and visuospatial ability, orientation and perception.[1] Delirium is a direct physiological consequence of another illness, substance intoxication or withdrawal, or multiple etiologies.[1]

Delirium is a multifactorial syndrome with multiple risk factors resulting from a complex interaction of predisposing and precipitating risk factors.[2] Delirium frequently occurs in people who are medically unwell, due to the underlying disease which has put them at risk (for example prior dementia or cancer) or due to the medical precipitants which have led to delirium (for example, infection and metabolic disorders such as renal impairment).[2] Although delirium can occur in anyone, epidemiological studies have shown that older people, and those with advanced illness and/or prior cognitive impairment, are most at risk of developing delirium.[3]

There is a significant burden associated with delirium. It is associated with multiple adverse clinical outcomes, including high levels of patient and caregiver distress, significant morbidity and mortality, impairment of activities of daily living and significant costs to the healthcare system.[4-7] Compared to people who do not develop delirium, people who experience delirium are more likely to have longer hospital stays,

increased incidence of dementia, have more hospital-acquired complications such as falls and pressure sores, and are more likely to die.[8]

People with delirium often experience fear, anxiety, and confusion during an episode of delirium. They may struggle to communicate their experiences with others during delirium and as a result feel distressed and humiliated.[9,10] Caregivers, especially family members, when delirium causes sudden decline and changes in behaviour in a loved one, also experience high levels of distress.[11]

The prevalence of delirium is high. Hospital-wide, approximately one in five (20%) of patients will develop delirium at any one time,[12] with an occurrence rate that is even greater in intensive (31.8%) and inpatient palliative care units (point prevalence 6%-74%).[5,13] Delirium also has significant implications for patients, their families and the health care system. In Australia, the total costs of delirium on the healthcare and aged care systems was estimated to be AU$8.8 billion in 2016-2017.[6] These costs include those to the healthcare system, aged care, loss of well-being, informal care, absentees from work, and funeral costs.[6] A previous costing study in the US found that hospital admissions for elderly patients with delirium cost two and a half times more than those who did not experience an episode.[14]

Delirium is a complex condition, due to the heterogeneity, multiple risk factors and precipitants and the complex array of outcomes, posing a significant challenge for mechanistic exploration.

1.2 Delirium pathophysiology

Despite the high prevalence and immense burden of delirium, knowledge of its pathophysiology remains poor, limiting the development of effective therapeutic interventions. The understanding of the pathophysiology of delirium remains largely

hypothetical, with some underpinning empirical data supporting some theories including involvement of inflammatory systems, neurotransmitter alterations, and glucose metabolism. Although there are a large and an increasing number of pathophysiological studies in delirium, results have been inconsistent. This means it has been difficult to elucidate biomarker correlations and further infer pathophysiological pathways associated with delirium across different study populations.

1.2.1 The role of biomarkers in understanding delirium pathophysiology

Biomarkers are defined as 'a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease'.[15] Measuring biomarkers can be done using several methods, including laboratory assays (body fluids, such as blood, cerebrospinal fluid (CSF), physical examinations, or medical imaging). Three patterns of biomarkers are common: 1. A risk marker for a disease: a biomarker that is present before disease onset that can help identify individuals who are most at risk of a particular disease (for example, genetic markers), 2. A disease marker: a biomarker that increases during disease progression, and decreases after resolution and 3. A biomarker as an end-product of a disease: this type of biomarker increases after the onset of the disease in proportion to the severity of the disease, indicating damage caused by the disease.[16]

Biomarkers can offer a window into better understanding of the pathophysiology of delirium, with peripheral signals related to precipitants of delirium as well as consequent alterations that may also be occurring in the brain. However, because biomarkers are not able to directly measure central brain processes, nor are all brain abnormalities that may be occurring in delirium detectable in peripheral body fluid/tissue, they are therefore not the sole approach. Several prognostic and diagnostic

biomarkers have been studied in relation to delirium onset and delirium severity to help improve delirium diagnosis and recognition. These biomarkers can act as potential diagnostic and therapeutic tools to assist in developing new therapies.[17] Challenges to understanding the pathophysiology of delirium to date include the heterogeneity of the clinical syndrome (including precipitants), and the concomitant impact of pre-existing cognitive impairment, co-morbidities and severity of illness on human physiology.

An understanding of delirium at the cellular and molecular level may lead to early intervention and thus prevent permanent cognitive damage and improve patient outcomes. In particular, elucidation of biochemical changes that occur within the brain during delirium episodes could prove effective in advancing our understanding into what factors contribute to its development and may provide further insight into the interrelationship with other underlying conditions such as cancer.

1.2.2 Reporting guidance to improve our understanding of delirium pathophysiology

Deficiencies in the reporting of research studies are well documented.[18,19] High-quality reporting in scientific studies are crucial for the implementation and dissemination of research findings. Inconsistent reporting in delirium biomarker studies makes synthesis difficult and, despite the large investment of time and effort into delirium biomarker research, understanding of its pathophysiology remains unclear. Reporting guidelines exist to help authors to meet reporting standards by providing a checklist of items to adhere to for best practice methods.[20] Without diligent, standardised reporting of biomarker research, synthesis of studies will remain problematic due to variable reporting and will continue to hinder our understanding of delirium pathophysiology.

1.3 Doctoral research project

1.3.1 Aim

The intended aim was to explore and further understand the pathophysiology of delirium in cancer patients. However, due to the results of Study 1, the direction of the project changed. Therefore, the aim of this doctoral research project was to evaluate and optimize the methodological approaches in research evaluating the biological and clinical correlates of delirium and underlying conditions.

1.3.2 Research questions

The research questions guiding this doctoral research program were:

1. What is the overlap between the biomarkers of delirium and the biomarkers of advanced cancer-related syndromes and prognosis?
2. What are the critical elements of high quality conduct and reporting for delirium biomarker studies?
3. What are the key methodological challenges in conducting delirium biomarker research?

1.3.3 Research design

A multiple methods design was employed to answer the research questions of this doctoral research project. A multiple methods design comprises two or more research methods, each conducted separately and complete in itself, but in one research project.[21,22] Although this doctoral research project used both quantitative and qualitative methods as in a mixed methods approach, the quantitative and qualitative studies answered different research questions and no methods were used to formally integrate the findings.[23-25]

1.3.4 Thesis outline

This doctoral thesis includes a detailed description of delirium epidemiology, pathophysiology and treatment, three interrelated studies (reported in four chapters), and conclusions and recommendations of the doctoral research project. An outline of the three studies is illustrated in Figure 1.1, and explained below. Of note, the doctoral research resulted in three peer-reviewed journal publications. The three chapters in this thesis corresponding to the journal publications have undergone minor edits to minimize repetition and ensure consistency of terminology and a logical flow throughout the thesis.

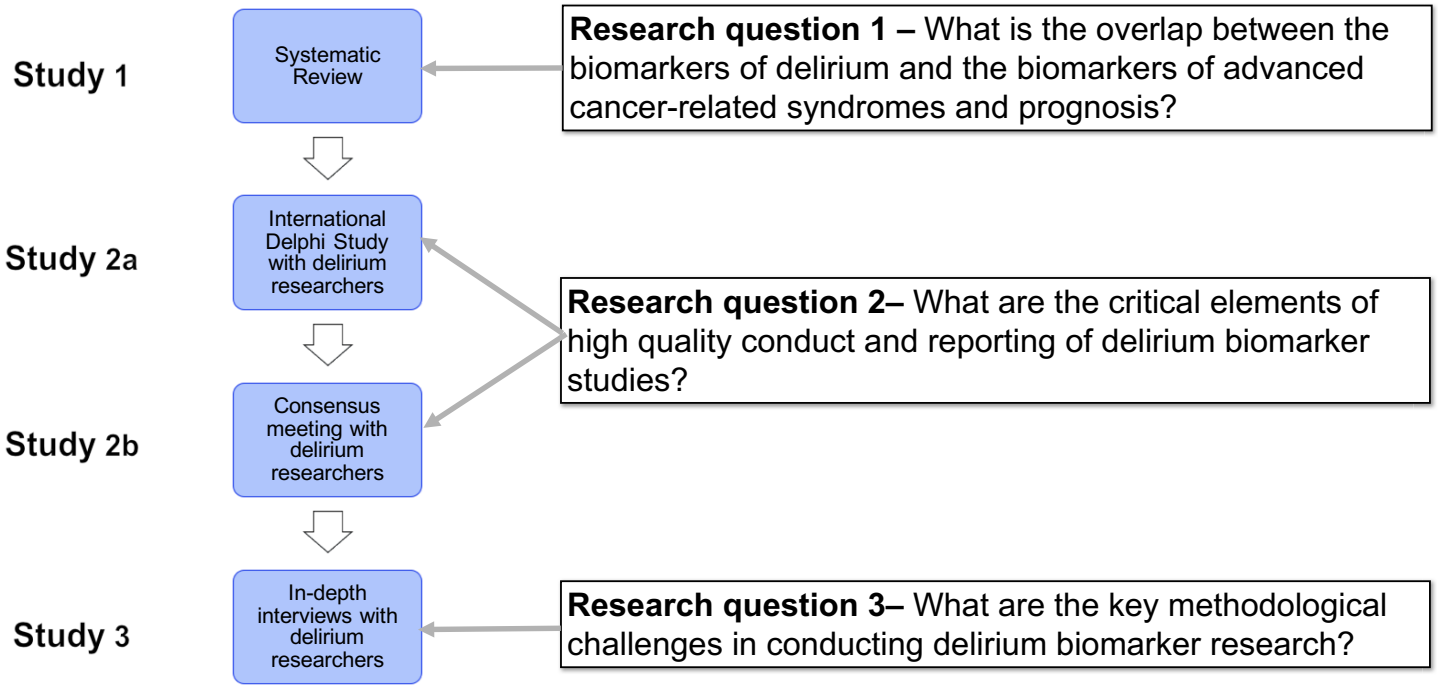

Figure 1.1 Outline of the three studies in this doctoral research project

Chapter two - Background

A background to delirium: including the diagnostic criteria, phenomenology, epidemiology, hypotheses in delirium pathophysiology, and the current state of evidence for the prevention and management of delirium.

Chapter three: Study 1- Systematic review

A systematic review was conducted with the aim of investigating the overlap of biomarkers in delirium and underlying medical conditions using advanced cancer-related syndromes as a case study. This aimed to understand the implications for biomarker studies of delirium in people with cancer, but also consider implications in other clinical conditions. This study was published in *BMC Psychiatry* in 2020, and is presented in Chapter three.

Although the aim of the systematic review was to explore the overlap in delirium and cancer syndrome biomarkers, quality appraisal of the included studies highlighted a systemic problem of poor quality methodology and reporting of delirium biomarker studies. The findings from this systematic review informed the direction of the succeeding studies.

Chapter four: Study 2a - An international modified Delphi study and Study 2b- a follow-up consensus meeting

Study 2a aimed to generate evidence-based and international expert recommendations for the conduct and reporting of delirium biomarker studies. Stage one of the delirium biomarker reporting guideline (REDEEMS) development employed a modified Delphi method and was informed by the findings of the systematic review (Study 1). Study 2a was published in the *International Journal of Geriatric Psychiatry* in 2020.

Study 2b consisted of a consensus meeting undertaken with experts in delirium research. Those items that achieved only a borderline consensus (70-80%) from the preceding Delphi study were brought forward to the consensus meeting. After refinement and critical feedback on the checklist, the final items of the REDEEMS reporting guidelines were developed. Study 2a and 2b are presented in Chapter four.

Chapter five: Study 3: In-depth interviews with delirium researchers

Study three expanded on study two by in-depth exploration of the perspectives of delirium researchers regarding the challenges involved in conducting delirium biomarker research. This study consisted of 15 semi-structured interviews and was published in PLOS ONE in 2021. Study three is presented in Chapter five.

Chapter six: Explanation and Elaboration (E&E)

This chapter describes the final stage in the development of the REDEEMS guidelines. An E&E document is considered standard practice when developing reporting guidelines in health research and was undertaken to facilitate understanding, uptake and dissemination of the REDEEMS guidelines.

This E&E paper is presented as Chapter six and is under review in the Journal of the Academy of Consultation-Liaison Psychiatry.

Chapter seven: Conclusion and recommendations

This chapter presented conclusions of the doctoral research program and recommendations for future research and practice.

The content of these chapters is presented in the navigational Table 1.1 below.

Table 1.1 Thesis navigation tool

Content	Chapter
Introduction	One
Background to delirium epidemiology, pathophysiology and treatment	Two
Study 1: Systematic review	Three
Study 2: Guideline development (Stage 1 & 2): International modified Delphi study and consensus meeting	Four
Study 3: Qualitative study of semi-structured interviews	Five
Guideline development (Stage 3): Elaboration and Exploration (E&E) paper	Six
Conclusion and recommendations	Seven

The appendices are presented within the navigational Table 1.2, below.

Table 1.2 Appendices content and navigation

Appendix number	Content	Relating to chapter
1.1	Copy of Study 1 (systematic review) publication in *BMC Psychiatry*	Three
1.2	Copy of Study 2a: Stage 1 (Delphi) publication in the *International Journal of Geriatric Psychiatry*	Four
1.3	Copy of Study 3 (Qualitative study) publication in *PLOS ONE*	Five
2	MEDLINE search strategy	Three
3.1	Quality assessment of included delirium studies	Three
3.2	Quality assessment of included cancer studies	Three
4	Human Research Ethics Committee (HREC) approval - Study 2 and 3	Four and five
5.1	Participant information sheet (PIS): Study 2a	Four
5.2	Participant information sheet (PIS) and consent form: Study 2b	Four
5.3	Participant information sheet (PIS) and consent form: Study 3	Five
6	Round 1 Delphi survey	Four
7	The REDEEMS checklist: using examples from published delirium biomarker studies	Three and Six

1.4 References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. *Arlington: American Psychiatric Publishing.* 2013.
2. Inouye S. Predisposing and precipitating factors for delirium in hospitalized older patients. *Dementia and Geriatric Cognitive Disorders.* 1999;10(5):393-400.
3. National Clinical Guideline Centre for Acute and Chronic Conditions. Delirium: diagnosis, prevention and management. 2010 https://www.nice.org.uk/guidance/cg103.
4. Bruera E, Bush SH, Willey J, et al. Impact of delirium and recall on the level of distress in patients with advanced cancer and their family caregivers. *Cancer.* 2009;115(9):2004-2012.
5. Salluh JI, Wang H, Schneider EB, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. *Bmj.* 2015;350:h2538.
6. Pezzullo L, Streatfeild J, Hickson J, Teodorczuk A, Agar MR, Caplan GA. Economic impact of delirium in Australia: a cost of illness study. *Bmj.* 2019;9(9):e027514.
7. Williams ST, Dhesi JK, Partridge JS. Distress in delirium: causes, assessment and management. *European Geriatric Medicine.* 2020:1-8.
8. National Institute for Health and Clinical Excellence (NICE). Delirium: diagnosis, prevention and management. 2010; http://www.nice.org.uk/nicemedia/live/13060/49908/49908.pdf. Accessed July 13th, 2011.
9. O'Malley G, Leonard M, Meagher D, O'Keeffe ST. The delirium experience: a review. *Journal of Psychosomatic Research.* 2008;65(3):223-228.
10. Bélanger L, Ducharme F. Patients' and nurses' experiences of delirium: a review of qualitative studies. *Nursing in Critical Care.* 2011;16(6):303-315.
11. Finucane AM, Lugton J, Kennedy C, Spiller JA. The experiences of caregivers of patients with delirium, and their role in its management in palliative care settings: an integrative literature review. *Psycho-oncology.* 2017;26(3):291-300.
12. Ryan DJ, O'Regan NA, Caoimh RÓ, et al. Delirium in an adult acute hospital population: predictors, prevalence and detection. *BMJ open.* 2013;3(1).
13. Watt CL, Momoli F, Ansari MT, et al. The incidence and prevalence of delirium across palliative care settings: A systematic review. *Palliative Medicine.* 2019:0269216319854944.
14. Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK. One-year health care costs associated with delirium in the elderly population. *Archives Internal Medicine.* 2008;168(1):27-32.
15. National Cancer Institute. NCI Dictionary of Cancer Terms. https://www.cancer.gov/publications/dictionaries/cancer-terms/?CdrID=45618. Accessed 28th November, 2017.

16. Marcantonio ER, Rudolph JL, Culley D, Crosby G, Alsop D, Inouye SK. Serum biomarkers for delirium. *Journals of Gerontology Series A-Medical Sciences.* 2006;61(12):1281-1286.

17. Khan BA, Zawahiri M, Campbell NL, Boustani MA. Biomarkers for delirium--a review. *Journal of the American Geriatrics Society.* 2011;59 Suppl 2:S256-261.

18. Simera I, Moher D, Hirst A, Hoey J, Schulz KF, Altman DG. Transparent and accurate reporting increases reliability, utility, and impact of your research: reporting guidelines and the EQUATOR Network. *BMC Medicine.* 2010;8(1):24.

19. Simera I, Altman DG, Moher D, Schulz KF, Hoey J. Guidelines for reporting health research: the EQUATOR network's survey of guideline authors. *PLoS Medicine.* 2008;5(6):e139.

20. Simera I, Moher D, Hoey J, Schulz KF, Altman DG. A catalogue of reporting guidelines for health research. *European Journal of Clinical Investigation.* 2010;40(1):35-53.

21. Morse J. Principles of mixed methods and multimethod research design. A. Tashakkori, & C. Teddlie (Eds.), Handbook of mixed methods in social and behavioral research (pp. 189–208). Thousand Oaks: Sage Publications; 2003.

22. Brannen J. *Mixing methods: Qualitative and quantitative research.* Routledge; 2017.

23. Anguera MT, Blanco-Villaseñor A, Losada JL, Sánchez-Algarra P, Onwuegbuzie AJ. Revisiting the difference between mixed methods and multimethods: Is it all in the name? *Quality & Quantity.* 2018;52(6):2757-2770.

24. Creswell JW, Clark VLP. *Designing and conducting mixed methods research.* 3rd ed. ed. California, USA: SAGE Publications; 2018.

25. Creswell JW, Creswell JD. *Research design: Qualitative, quantitative, and mixed methods approaches.* SAGE Publications; 2017.

Chapter 2: Background

This chapter provides a comprehensive overview of delirium. Firstly, it covers historical and current diagnostic criteria, phenomenology, epidemiology, and hypotheses in delirium pathophysiology. The current state of evidence for the prevention and management of delirium is then summarised.

2.1 The history of defining delirium

This section presents a summary of the historical development of the classification of delirium and describes the challenges posed by the imprecise diagnostic methods and nomenclature which continues to hinder scientific understanding of delirium.

Delirium is not a new phenomenon; it has been a recognised condition for three millennia, although the terms used to describe and classify the syndrome have varied over time. In 500 BC, Hippocrates used approximately 16 different words to refer to and name the clinical syndrome which is now referred to as 'delirium'.[1] Prior to the first inclusion of delirium in the Diagnostic and Statistical Manual of Mental Disorders III (DSM-III) in 1980, common terms used to describe delirium were: 'acute confusional state', 'acute brain failure', 'encephalopathy', 'intensive care psychosis', 'subacute befuddlement' and 'terminal agitation'.[2] The word delirium derives from the Latin phase *de-lira,'* meaning to 'to go out of the furrow'- i.e. to deviate from a straight line, to be crazy or deranged.[1] The term delirium as a diagnostic entity did not appear in the American Psychiatric Association Diagnostic and Statistical Manual (APA-DSM) until 1980 (DSM-III). Prior to this, a 'Statistical Manual for the Use of Hospitals' was used primarily in psychiatric hospitals.[3] It was not until World War II that the lack of a diagnostic classification system became an issue due to an increase in psychiatric cases, when it was found that the Statistical Manual for Hospitals only

classified approximately 10% of the cases seen.[3] This state of affairs resulted in a terminological chaos for psychiatric conditions, which instigated the creation of a uniform and consistent diagnostic system, and the two classification systems emerged: The American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM) and the World Health Organisation International Classification of Diseases (ICD).

2.1.1 Development of the classification systems of delirium

Since the 1980's, there have been five iterations of the diagnostic criteria of delirium, with a shift from purely descriptive symptomatology to a focus on two essential pathophysiological concepts of disordered attention (arousal) and cognition.[4] Table 2.1 outlines the key differences, similarities and changes from DSM-III (1980) through to DSM-5 (2013). The key difference between the DSM-III and the DSM-III-R is that 'clouding of consciousness' was replaced with 'reduced ability to maintain and shift attention to external stimuli', and 'disorganised thinking' was also added.[3] The shift towards attention was driven by a recognition that the construct 'consciousness' is difficult to assess objectively.[5] A consistent feature of all DSM versions is that alterations in the content (attention) and/or level (arousal) of consciousness are core to the diagnosis of delirium.[6] However, the new Criterion D in the DSM-5 distinguishes that inattention (Criterion A) or changes in cognition (Criterion C) should not be better explained by a pre-existing, established or evolving neurocognitive disorder nor occur in the context of a severely reduced level of arousal such as coma' (Table 2.1). These changes indicate the shifting emphasis of various delirium criteria in the revisions of DSM and ICD classification systems. Delirium diagnostic criteria are likely to continue to evolve as understanding of its features and pathophysiology develops.

As stated above, the two current classification systems are the DSM, Fifth Edition (DSM-5)[2] and the ICD-10 (version 10).[7] The American Psychiatric Association's DSM-5 (published in 2013) definition of delirium is used in this thesis. This version classifies delirium as a neurocognitive condition characterized by an acute and fluctuating disturbances in attention, awareness, and cognition that are a direct consequence of another medical condition, substance intoxication or withdrawal, exposure to a toxin, or due to multiple etiologies.[2] The ICD-10 classification for delirium due to known physiological causes describes: impairment of consciousness and attention, global disturbance of cognition, psychomotor disturbance, disturbance of sleep-wake cycle, and emotional disturbance.[7] The exemplar National Institute for Health and Clinical Excellence (NICE) guideline on delirium diagnosis, prevention, and management recommends using the DSM-5 criteria as the standard operational definition for delirium because it is more inclusive than the ICD-10.[8]

Limitations and challenges in delirium classification and nomenclature

Firstly, a noteworthy limitation to these classification systems is that no specific criteria is provided to assist with the diagnosis of delirium superimposed on dementia (DSD). The DSM-5 simply states that the cognitive deficit should not be better explained by a pre-existing, established, or evolving neurocognitive disorder, and in the ICD-10 pre-existing cognitive deficits are not considered. Yet the concept of DSD is an important one, as discussed in further detail in section 2.2.2.

Secondly, no definitive diagnostic tests for delirium exist. This absence is related to no biomarker being consistently associated with delirium. Delirium diagnosis therefore relies on establishing the presence of each criterion through clinical examination of people using a combination of interview, cognitive testing, observation and informant history. However, there is little consensus on how the specific criterion

are assessed, with large variation in both clinical practice and research methods.[9] Development of a reliable, valid and reference standard delirium diagnosis method is crucial to progress research in delirium, including its pathophysiology, as well as clinical practice.

Thirdly, the lack of consistent terminology for delirium remains present in the literature and in clinical practice. This issue is both indicative and causative of impeded scientific progress, collaborative research efforts, and recognition of delirium.[10,11] For example, 'encephalopathy' is an umbrella term that has been used to describe delirium and include terms such as acute encephalopathy, acute confusional state, acute brain dysfunction, acute brain failure and altered mental status. The issue is that these terms lack standardised definitions and are not included in the formal diagnostic systems.[11] Aligning the semantic disparities will allow for more consistent and standardised research and greater ability to compare across studies.[6]

Table 2.1 History of the evolving DSM diagnostic criteria for delirium (1980-2013) compared to current ICD diagnostic criteria

DSM-III (1980)	DSM-III-R (1987)	DSM-IV (1994)	DSM-IV-R (2000)	DSM-V (2013)[1]	ICD-10 (1993)
Clouding of consciousness	Impairment of attention	A disturbance of consciousness (i.e. reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention	A disturbance of consciousness with reduced ability to focus, sustain, or shift attention	Criterion A A disturbance in attention (i.e. reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment)	Criterion A Clouding of consciousness, i.e. reduced clarity of awareness of the environment, with reduced ability to focus, sustain or shift attention
Impairment of attention	Disorganised thinking or incoherent speech	The disturbance develops over a short period of time (hours to days) and tends to fluctuate during the course of the day	A change in cognition, such as memory deficit, disorientation, language disturbance OR development of a perceptual disturbance that is not better accounted for by a pre-existing, established, or evolving dementia	Criterion B The disturbance develops over a short period of time (usually hours to a few days), represented a change from baseline attention and awareness, and tends to fluctuate in severity during the course of the day	Criterion B Disturbance of cognition, manifested by both: 1. Impairment of immediate recall and recent memory, relatively intact remote memory; 2. Disorientation in time, place or person

Disorientation	Rapid onset and fluctuation of symptoms	A change in cognition of the development of a perceptual disturbance that is not better accounted for by a pre-existing, established or evolving dementia	Rapid onset and fluctuation of symptoms	Criterion C An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception)	Criterion C At least one of the following psychomotor disturbances: - Rapid, unpredictable shifts from hypo-activity to hyper-activity; - Increased reaction time; - Increased or decreased flow of speech; - Enhanced and startled reaction
Memory impairment	Evidence of a physiological cause OR exclusion of a non-organic cause when a physiological cause cannot be identified	There is evidence from the history, physical examination or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition	Evidence of a physiological cause related to a general medical condition	Criterion D The disturbances in Criteria A and C are not better explained by a pre-existing, established or evolving neurocognitive disorder and do not occur in the context of a severely reduced level	Criterion D Disturbance of sleep or the sleep-wake cycle, manifested by at least one of the following: 1. Insomnia, which in severe cases may involve total loss of sleep, with or without daytime drowsiness, or reversal of the

					of arousal, such as coma	sleep-wake cycle; 2. Nocturnal worsening of symptoms; 3. Disturbing dreams and nightmares, hallucinations or illusions when awake
Rapid onset and fluctuation of symptoms	Additional items: At least two of the following are required: Chapter 2: Perceptual disturbance: illusions, delusions or hallucinations, Chapter 3: Memory impairment Chapter 4: Disorientation Chapter 5: Disturbance of sleep/wake cycle Chapter 6: Increased or decreased motor activity Chapter 7: Clouding/disturbance of consciousness		Additional items: At least two of the following are required: Chapter 2: Perceptual disturbance: illusions, delusions or hallucinations Chapter 3: Disorganised thinking or incoherent speech Chapter 4: Memory impairment Chapter 5: Disorientation		Criterion E There is evidence from the history, physical examination or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal, or exposure to a toxin, or id due to multiple etiologies	Criterion E Rapid onset and fluctuations of symptoms over the course of the day
Determined by a specific						Criterion F

pathophysiologic al or aetiological process or an unknown cause	Objective evidence from history, physical and neurological examination or laboratory tests of an underlying cerebral or systemic disease (other than psychoactive substance-related) that can be presumed to be responsible for the clinical manifestations in criteria A-D

[1] *The delirium diagnostic criteria used in this thesis*

2.2 Phenomenology

Delirium causes disturbances to attention, awareness, and cognition that manifest in a number of ways.[12,13] Cognitive disturbances include those to memory, orientation, language and visuospatial ability, orientation, and perceptual. Perceptual disturbances that are common in people experiencing delirium and include hallucinations, illusions and delusions. Delirium has a sudden onset that usually last hours to days, although sometimes it continues for weeks or months.[2] These disturbances are often frightening and distressing for both the affected person and their caregivers.[14]

2.2.1 Psychomotor subtypes of delirium

Although delirium is considered one condition, its' clinical presentation varies considerably, most notedly in patterns of psychomotor activity.[15] There are at least three core psychomotor subtypes of delirium: hypoactive, hyperactive and mixed delirium;[16] however, Meagher et al (2011) also reported a small number (6%) of palliative care patients experienced delirium with no psychomotor disturbances ('no subtype').[17] *Hyperactive* delirium is characterised by increased psychomotor activity with heightened states of restlessness, agitation, and arousal.[16] *Hypoactive* delirium is characterised by reduced psychomotor activity, which presents as slowed movement and speech, lethargy and reduced alertness.[18] The mixed sub-type of delirium presents as both increased and decreased psychomotor activity within short time frames.[16,19] In inpatient settings, the hypoactive subtype is the most common (23-78%), followed by mixed (4.6%-27.3%) and hyperactive delirium (1.8%-21.5%).[20]

More recently, two variants- 'catatonic' and 'excited' delirium have also been proposed, representing two extreme ends of the spectrum. The catatonic delirium represents an extreme form of hypoactive delirium, whereas the excited form embodies an extreme form of hyperactive delirium.[21]

There is no validated tool to delineate delirium subtypes and the measurement of motoric subtypes greatly vary, with many models not based on strong empirical data to underpin them. Existing approaches include symptom checklists (e.g Lipowski criteria[22]), motor items from delirium rating scales (e.g Delirium Rating Scale), and electronic approaches to measure motion.[16] These methods differ in the range of hypoactive and hyperactive features used as subtyping criteria, vary in the degree they consider psychological symptoms as well as pure motor symptoms, and use a range of methods to ascertain the included symptoms. Though studies have identified clinically meaningful differences in outcomes in relation to subtypes; findings have been inconsistent, partly due to an inconsistency in motor subtype definitions.[16,23]

The fluctuating nature and varying phenomenology of delirium poses challenges to its recognition and diagnosis, and thus it often goes unrecognised or is misdiagnosed.[24] Some studies have demonstrated that missed delirium is often due to insufficient clinician education and knowledge of the condition.[25] Furthermore, not all clinicians understand that delirium is a medical emergency and many are unaware that it might be the sole manifestation of life-threatening situation such as sepsis.[26] Patients with hypoactive and mixed subtype delirium are most often missed, due to overlapping symptoms with other common conditions, such as depression.[27,28] Clinicians often conflate delirium with hyperactive symptoms and miss the more common occurrence (and increased seriousness) of hypoactive delirium.[26] Further, since dementia is a lead risk factor for delirium[29] they often co-exist, leading to further difficulties with the distinction of symptoms and diagnosis of each.

2.2.2 Subsyndromal delirium

The DSM-5 diagnosis of delirium requires coexisting symptoms across multiple domains, and yet some patients have only one or a few.[30] This clinical scenario

condition is known as subsyndromal delirium (SSD) and was first described in 1983.[31] SSD has since been defined as the presence of one or more symptoms of delirium, where the patient does not meet the DSM criteria for delirium.[32] Subsyndromal delirium is the more commonly used term in the literature however is addressed under 'attenuated delirium syndrome' in the DSM-5.[2] Elucidating subsyndromal delirium symptoms could potentially ensure early recognition individuals at risk of delirium. A 2013 systematic review reported prevalence and incidence of SSD in older people in a variety of hospital settings to be 23% and 13%, respectively.[32]

2.2.3 Persistent delirium

Persistent delirium is full syndromal delirium (FSD) that persists for longer periods of time. There is no universal definition of persistent delirium or its time frame, and it remains an evolving concept. One definition by Cole (2009) is that persistent delirium is evidence of FSD that commenced at time of admission (or shortly after admission) that continues at the time of discharge or beyond.[33] Literature suggests that persistent delirium is associated with a worse functional recovery and increased mortality and complications, compared to delirium that resolves.[33-35]

2.2.4 The implications of delirium sub-types in its aetiology and pathophysiology

There has been longstanding interest in whether different neuropathological processes leading to specific delirium sub-types. It has also been proposed that specific sub-types of delirium associated with specific neurotransmitter pathways may predict or guide different responses to specific pharmacological treatment.[36]

A systematic review published in 2005 investigated whether there is a difference between delirium sub-types and their aetiology, pathophysiology, outcomes and treatment strategies.[37] Of the 10 included studies, four investigated the relationship

between delirium sub-type and aetiology. Meagher et al. (1998)[38] described three etiological categories: an anticholinergic group, a drug-related group, and another group of infectious illness/metabolic. Drug-related causes showed the highest severity score for delirium, and the anticholinergic causes had the lowest score. Drug-related cases had higher scores than both the anticholinergic and infectious/metabolic group for changes in sleep-wake cycle and fluctuation of symptoms. Findings showed that the anticholinergic group were more likely to fit the hypoactive delirium sub-type and concluded that the etiological cause may influence the different symptom patterns.

A 2018 systematic review[39] explored the relationship between CSF biomarker concentrations and delirium sub-types. Only five studies assessed motor subtype, and of those, only one study showed a trend towards higher homovanallic acid (HVA) in hyperactive delirium that did not reach statistical significance.[40] The authors concluded that there were no clear relationships between any of the biomarkers studied and delirium sub-types.

Robust evidence for a link between delirium sub-types and biomarkers is therefore lacking. Standardised methods of measuring sub-types that include consideration of longitudinal changes would increase the rigour and consistency of future research in this area. While it may eventuate that delirium phenomenology is not associated with its pathophysiology, further exploration of potential associations may provide valuable clues into the pathophysiology of delirium.

2.3 Epidemiology

Knowledge of delirium epidemiology (risk factors, occurrence, and outcomes) is evolving and has been constrained due to the fluctuating clinical nature of delirium and its varying measures and diagnostic criteria.

2.3.1 Risk factors for delirium

Although little is known about the pathophysiological changes that occur during delirium, it is known that delirium is a multifactorial neurocognitive condition resulting from a complex interaction of a myriad of predisposing and precipitating risk factors.[41] Predisposing risk factors for delirium are defined as those present at the time of hospital admission, while precipitating factors are those that develop during hospitalization.[42] The greatest predisposing risk factors for delirium are older age (65 years and older), pre-existing cognitive impairment or dementia, severe illness and hip fracture.[43]

In pre-disposed persons, a relatively minor illness such as a urinary tract infection can precipitate delirium. Conversely, less pre-disposed persons e.g. younger adults with no prior cognitive impairment, require a more serious insult, such as traumatic brain injury, for delirium to result.[44] Although the degree of insult needed to develop delirium depends on the degree of pre-disposition of the person, anyone can experience delirium when sufficient precipitants occur.[44] There are several precipitating and predisposing risk factors for delirium; the most common are shown in Table 2.2.

The use of prediction models generally has proliferated in evidenced-based healthcare because they enable early identification of high-risk individuals for whom prevention strategies can then be offered.[45,46] Prediction models are statistical models that provide estimates of individuals who are at greater risk of developing a particular disease.[47] An accurate and timely delirium prediction model would incorporate the highest impact risk factors into a powerful tool, facilitating early implementation of delirium prevention measures.[48]

Table 2.2 Risk factors for delirium from Validated Predictive Models[8,49-51]

Predisposing factors	Precipitating factors
Older age	Polypharmacy
Dementia	Iatrogenic intervention A. Bladder catheter B. Preoperative medical treatment
Pre-existing cognitive impairment	Physiological and metabolic disturbances 1. Elevated serum urea (dehydration) 2. Elevated BUN/creatinine ratio 3. Abnormal serum albumin 4. Electrolyte disturbance 5. Metabolic acidosis
History of delirium	Infection/sepsis
Activities of daily living (ADL)	Major surgery
Severity of illness	Urgent admission
Comorbidity	Coma
Sensory impairment	Institutionalisation
Sleep deprivation	
History of transient ischaemia/stroke	
Depression	
Alcohol abuse	

Prevalence differs from incidence in that prevalence includes all cases (pre-existing and new cases) in a population, whereas incidence refers to new cases only.[52] Delirium prevalence and incidence varies across patient populations, and there is limited epidemiological data in the Australian setting.[53,54] Table 2.3 displays systematic review data on the prevalence and incidence of delirium in key settings.

Table 2.3 Delirium prevalence, incidence and occurrence according to systematic review data

Author, year	Setting	Number of included studies	Prevalence[1]	Incidence[2]	Occurrence[3]
Koirala, 2020	Inpatient (ICU, acute care hospital, and palliative care/hospice) and community	9	*Point prevalence* 9%-32%	-	-
Watt, 2019	Inpatient palliative care (Non-ICU and non-post-operative) and community	42	*Point prevalence* 6.6%-73% *Prevalence prior to death* 75% (58%-88%)	7%-45%	-
Aitken, 2017	Post-operative	10	-	5%-39%	-
Salluh, 2015	ICU	42	-	-	31.8%
De Lange, 2013	Residential aged care	8	0.5%-34.5%	-	-
Siddiqi, 2006	General medical, outside ICU	50	10%-31%	3%-29%	11%-42%

[1] *Delirium at admission*
[2] *Delirium during admission*
[3] *The term 'occurrence' is used for studies where prevalence or incidence was not clearly defined*
ICU: Intensive care unit

2.3.2 Delirium superimposed on dementia

It can be difficult to distinguish between delirium and dementia as symptoms overlap and they commonly coexist. Delirium generally has an acute onset, with fluctuating symptoms, while dementia tends to develop slowly.[55] Another key difference between the two conditions is that dementia is chronic, progressive and incurable, whereas delirium is mostly reversible through treatment of its causes.[55] Delirium that occurs in people with dementia is referred to as delirium superimposed on dementia (DSD). DSD occurs in between 22% and 89% of hospitalized and community populations aged 65 and older with dementia.[56] Delirium is associated with worsening severity of already existing dementia[57] as well as incident dementia.[58] Shared pathophysiological mechanisms for both delirium and dementia have been proposed, yet the nature of their relationship remains unclear.[59] Dementia and cognitive impairment in people with delirium is therefore even more likely to go unrecognized than in patients without delirium. For example, in older patients with delirium, only 36% of cases with dementia had a recognised diagnosis.[60] Further, in a study where 88% of DSD were not recognised, 75% of nurses could not differentiate between delirium and dementia, despite having received formal education on delirium.[61]

2.4 Delirium pathophysiology

The substantial morbidity and mortality of delirium reflects a crucial and unresolved health burden, yet despite the multiple adverse outcomes, the pathophysiology of delirium remains poorly understood and is largely hypothetical. This section summarises the study of biomarkers as a means to understanding delirium pathophysiology and discusses current hypotheses.

2.4.1 Glucose metabolism

Accumulating research suggests glucose metabolism pathways are disrupted in delirium. Elevated cerebrospinal fluid (CSF) lactate and decreased neuron-specific enolase (NSE) have been reported in people with delirium, suggesting the following hypotheses: 1. disrupted glycolysis, with switching from aerobic to anaerobic glucose metabolism by neuronal cells; 2. suppression of the glycolytic pathway in neurons; or 3. disrupted lactate uptake by neuronal cells.[62] A subsequent study further revealed widespread reduction in glucose metabolism (hypometabolism) during delirium, with an overall improvement in glucose metabolism (but not normalisation), following delirium resolution.[63]

2.4.2 Neuronal ageing

This model proposes that older people are more at risk of developing delirium due to age-related cerebral changes in stress-regulating pathways. According to this model, aging causes the immune cells in the central nervous system (CNS) to undergo excessive production of pro-inflammatory cytokines in response to peripheral stimulation, providing a possible pathway for CNS dysfunction and consequent delirium.[21]

2.4.3 Oxidative stress

This hypothesis proposes that oxidative stress (reactive oxygen and nitrogen species e.g. nitric oxide) and/or antioxidant deficiencies may increase cerebral tissue damage, leading to cognitive decline/irreversible cerebral degeneration and behavioural symptoms seen in people with persistent delirium.[21]

2.4.4 Neurotransmitter disruption

Acetylcholinergic neurotransmission is involved in several elements of brain functioning affected in delirium, such as attention, arousal, sleep and perception. This hypothesis relates to deficits in central cholinergic functioning may underlie clinical presentations of delirium.[21]

Studies measuring serum anticholinergic activity (SAA) in people with delirium have reported inconsistent results. One longitudinal study in patients with hip fracture found raised SAA levels in the delirium group; however, the temporal profile of SAA was confounded by predisposing factors such as cognitive impairment and infection. The authors concluded that it is highly unlikely that SAA is independently associated with the presence of delirium.[64]

Elevated levels of CSF homovanillic acid (HVA), the main metabolite of dopamine, has also been associated with psychotic features seen in delirium,[40] and elevated levels of CSF 5-hydroxyindole aceticacid, a metabolite of serotonin, has also been reported in people with delirium.[65] It has further been proposed that decreased tryptophan and increased melatonin may result in decreased serotonin in people with delirium.[66]

2.4.5 Circadian cycle dysregulation

During delirium, signalling pathways and functions of the suprachiasmatic nucleus (SCN) or pineal gland may be disrupted, and changes in hepatic enzyme activity and reduced oral intake make stimulate enterochromaffin cells to produce melatonin.[67] Melatonin (*N-acetyl-5-methoxytryptamine*) is a hormone involved in the maintenance of circadian rhythms and sleep–wake cycles which is produced by the pineal gland, in response to darkness.[68] Disruptions to the 24-hour circadian cycle and usual sleep-wake cycle have long been linked to the development of delirium.

2.4.6 Neuroendocrine dysregulation

This theory suggests that delirium represents an aberrant response to stress, both in the Hypothalamic-Pituitary-Adrenal (HPA) axis and the immune system.[69,70] Abnormally high levels of glucocorticoid in response to acute stress such as trauma or surgery, leads to neuronal injury which may in turn trigger and/or sustain delirium.[21]

2.4.7 Neuro-inflammation

Altered neurotransmitter levels are commonly implicated in delirium, and an animal model suggests that inflammatory changes may be central to the pathophysiology of delirium.[71] Higher serum levels of interleukin (IL)-6 and IL-8[72] and raised S100 calcium-binding protein B (S100B)[73] have been reported in people with delirium. Low levels of anti-inflammatory markers, such as insulin-like growth factor 1, have also been reported.[74]

2.4.8 Systems Integration Hypothesis

A newly proposed theory, the systems integration failure hypothesis by Maldonado (2017) ties together some key hypotheses outlined above (Neuronal aging, Neuro-inflammation, Oxidative stress, Neuroendocrine dysregulation and Circadian dysregulation) into one complex pathway, to explain how the pathophysiologic theories interact, causing various clinically observed delirium phenotypes.[21] This hypothesis proposes that "alterations in neurotransmitter function combined with a failure of the complex, highly organized and interconnected brain systems lead to a failure in the CNS's functional integration and appropriate processing of information and response mechanisms." (Maldonado, 2017, p.23)[21] This theory suggests that most of the available hypotheses on delirium pathophysiology are complementary, intersecting and not mutually exclusive.

2.5 Delirium prevention

2.5.1 Multicomponent interventions

There is now sufficient evidence to suggest that targeted multicomponent non-pharmacological interventions are effective in reducing incidence of delirium.[75-78] These interventions vary from simple single component interventions such as physical environment therapy to complex multicomponent interventions that target several risk factors (e.g the Hospital Elder Life Programme (HELP).[79] There also are interventions which combine non-pharmacological interventions with formal proactive geriatric assessment, which have been evaluated inpatient settings.[80,81]

A meta-analysis of seven studies among elderly inpatients found a significant reduction in the incidence of delirium with multicomponent interventions compared to usual care.[77] Interventions included physiotherapy, reorientation, family involvement in care, attention to sensory deprivation, and education/training. A Cochrane review of 39 studies by Siddiqi et al. (2016)[78] also found a reduction in the incidence of delirium compared to usual care in hospitalised, non-ICU patients. Interventions included education/training, physiotherapy, reorientation, early mobilisation, identification and treatment of underlying causes, sleep hygiene, pain control, bladder and bowel care, nutrition/hydration, attention to sensory deprivation and oxygen delivery.[78]

The Hospital Elder Life Program (HELP) is the one of the earliest and most studied multicomponent intervention aimed at reducing delirium incidence through targeting physical and cognitive activity, sleep enhancement, vision, hearing and hydration.[44] There is no formal data which directly identifies the biological mechanism that mediates these interventions, though from first principles they are interventions which may maintain or optimise elements of homeostasis. An RCT of 852 patients

documented the effectiveness of the HELP program for prevention to delirium. The intervention group (N=426 vs 426 in usual care), showed a significant reduction in delirium incidence from 15.0% in the usual care group to 9.9%.[44]

A recent systematic review examined the adaptations made to the HELP model and the evidence for its effectiveness. The meta-analysis showed significant reductions in delirium incidence (53% lower in the intervention group) and falls (42% lower), with a non-significant trend towards reduced length of stay.[82].

Although these multicomponent non-pharmacological interventions have shown to be effective in the prevention of delirium, there is insufficient high-quality evidence for of non-pharmacological interventions for reducing the severity of delirium or duration of delirium once it has developed.[43,76,83]

2.6 Delirium treatment

There are currently no pharmacological treatments proven or registered for the treatment of delirium. Little is known about treatment targets for delirium, and more pathophysiological research is required to accelerate our understanding and find a treatment. A number of pharmacological interventions have been trialed for both delirium prevention and treatment; this section summarises the evidence for interventions aimed at managing delirium.

2.6.1 Pharmacological interventions

Antipsychotics

Despite the wide use of antipsychotic medication for delirium, particularly in palliative care, data is inconsistent and there is limited evidence for its effectiveness in the treatment or prevention of delirium. Because of this uncertainty, both the National Institute for Health and Clinical Excellence (NICE) guidelines and the Australian

Delirium Clinical Care Standard recommends limited and cautious use of antipsychotics as a short-term treatment option for delirium if a person is distressed or is a risk to themselves or others and only when non-pharmacological interventions have failed or are deemed inappropriate.[84,85]

The therapeutic effects of antipsychotics in delirium remain unknown, but it is thought that they may be mediated through their ability to reduce psychotic symptoms or affect sedation. There are two types of antipsychotics: typical antipsychotics, (e.g. haloperidol) and atypical antipsychotics, (e.g. risperidone),[86] both which target the dopaminergic pathway, supporting the neurotransmitter hypothesis of delirium.[87]

Two recent systematic reviews of RCTs evaluating the effectiveness of antipsychotics for the prevention[88] and treatment[89] of delirium in hospitalised adults showed no evidence for supporting the use of antipsychotics for either treatment or prevention of delirium.

Melatonin

Sleep-wake cycle disturbance has been identified as a prominent symptom in people with delirium, supporting the hypothesis that a circadian rhythm disorder contributes to delirium pathophysiology.[90] Melatonin supplementation may be effective in the treatment of these disturbances and may mediate a reduction in delirium by decreasing the breakdown of serotonin and tryptophan.[91]

Melatonin has been trialled as prophylaxis against delirium with the aim of preserving the sleep-wake cycle, however results vary. A 2016 meta-analysis of 4 RCTs with 669 patients evaluating the effect of exogenous melatonin on delirium prevention, showed a tendency to decrease delirium incidence, but significance was not reached between the groups. In a subgroup analysis of the elderly patients in medical wards, melatonin

supplementation reduced incidence of delirium by 75 %, but no difference was seen in the effects on sleep–wake disturbances.[92]

More recently, in ICU, Nishikimi et al. (2018) trialed Ramelteon, a melatonin antagonist, in 45 patients versus 43 patients in the placebo group.[93] Occurrence and duration of delirium were significantly decreased in the Ramelteon groups. The Ramelteon group of nonintubated patients also showed significantly fewer awakenings during the night and a higher proportion of nights without awakenings.

Dexmedetomidine sedation

Dexmedetomidine is a highly selective Alpha(α) 2-adrenoreceptor agonist which has also been shown to have anti-inflammatory properties, enhancing macrophage phagocytosis and bacterial clearance.[94] α2-adrenoreceptor agonists have shown to improve sleep by establishing a more natural sleep-like state in critically ill patients and therefore may also improve delirium outcomes by addressing the sleep-circadian cycle hypothesis.[95] Dexmedetomidine is increasingly used for sedation in mechanically ventilated patients with delirium in the ICU, but overall evidence for its impact on delirium outcomes is unclear.

A meta-analysis of 18 studies with 3309 patients analysed whether dexmedetomidine could reduce incidence of post-operative delirium (POD) in adult surgical patients. The group treated with dexmedetomidine showed significantly decreased risk of POD, which was also confirmed in a subgroup analysis for cardiac and non-cardiac surgical patients.[96]

An earlier meta-analysis of 20 studies with 2612 patients looked at the effects of dexmedetomidine on neurocognitive function, which included delirium. Dexmedetomidine was associated with a significantly lower risk of

postoperative/postanaesthesia neurocognitive dysfunction. However, there was no significant difference in subgroup analyses when delirium was the outcome.[97]

2.7 Summary

Despite the prevalence and impact of delirium, knowledge of its pathophysiology is largely hypothetical. Developing understanding of the pathophysiological pathways of delirium would inform the future development and testing of new and more targeted therapeutic interventions. Systematic and thorough investigation into improving the methodology of delirium biomarker studies will lay the groundwork for these advances.

This doctoral research project undertook a detailed examination of the clinical and biological correlates of delirium, towards the goal of improving understanding of delirium pathophysiology. Chapter three reports a systematic review on delirium and advanced cancer biomarkers, the first study of the doctoral research project. The study was undertaken to answer the research question: 'What is the overlap between the biomarkers of delirium and the biomarkers of advanced cancer-related syndromes and prognosis?

2.8 References

1. Adamis D, Treloar A, Martin FC, Macdonald AJ. A brief review of the history of delirium as a mental disorder. *History of Psychiatry.* 2007;18(4):459-469.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).* Arlington, VA: American Psychiatric Publisher; 2013.
3. Tucker G. The diagnosis of delirium and DSM-IV. *Dementia and Geriatric Cognitive Disorders.* 1999;10(5):359-363.
4. Smith MJ, Breitbart WS, Platt MM. A critique of instruments and methods to detect, diagnose, and rate delirium. *Journal of Pain and Symptom Management.* 1995;10(1):35-77.
5. Blazer DG, van Nieuwenhuizen AO. Evidence for the diagnostic criteria of delirium: an update. *Current Opinion in Psychiatry.* 2012;25(3):239-243.
6. European Delirium Association. The DSM-5 criteria, level of arousal and delirium diagnosis: inclusiveness is safer. *BMC Medicine.* 2014;12(1):141.
7. World Health Organisation. International Statistical Classification of Diseases and Related Health Problems 10th Revision. 2016.
8. National Institute for Health and Clinical Excellence (NICE). Delirium: diagnosis, prevention and management. 2010; http://www.nice.org.uk/nicemedia/live/13060/49908/49908.pdf. Accessed July 13th, 2020.
9. Tieges Z, Evans JJ, Neufeld KJ, MacLullich AM. The neuropsychology of delirium: advancing the science of delirium assessment. *International Journal of Geriatric Psychiatry.* 2018;33(11):1501-1511.
10. Morandi A, Pandharipande P, Trabucchi M, et al. Understanding international differences in terminology for delirium and other types of acute brain dysfunction in critically ill patients. *Intensive Care Medicine.* 2008;34(10):1907.
11. Slooter AJ, Otte WM, Devlin JW, et al. Updated nomenclature of delirium and acute encephalopathy: statement of ten Societies. *Intensive Care Medicine.* 2020:1-3.
12. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. *Arlington: American Psychiatric Publishing.* 2013.
13. Meagher D, Adamis D, Trzepacz P, Leonard M. Features of subsyndromal and persistent delirium. *The British Journal of Psychiatry.* 2012;200(1):37-44.
14. Williams ST, Dhesi JK, Partridge JS. Distress in delirium: causes, assessment and management. *European Geriatric Medicine.* 2020:1-8.
15. Adamis D, McCarthy G, O'Mahony E, Meagher DJJogp, neurology. Motor disturbances in elderly medical inpatients and their relationship to delirium. *Journal of Geriatric Psychiatry and Neurology.* 2017;30(4):214-219.
16. Meagher D. Motor subtypes of delirium: past, present and future. *International Review of Psychiatry.* 2009;21(1):59-73.

17. Meagher DJ, Leonard M, Donnelly S, Conroy M, Adamis D, Trzepacz PT. A longitudinal study of motor subtypes in delirium: relationship with other phenomenology, etiology, medication exposure and prognosis. *Journal of Psychosomatic Research.* 2011;71(6):395-403.

18. Boettger S, Breitbart W. Phenomenology of the subtypes of delirium: phenomenological differences between hyperactive and hypoactive delirium. *Palliative & Supportive Care.* 2011;9(2):129-135.

19. Lipowski Z. *Acute confusional states.* New York: Oxford University Press 1990.

20. Koirala B, Hansen BR, Hosie A, et al. Delirium point prevalence studies in inpatient settings: A systematic review and meta-analysis. *Journal of Clinical Nursing.* 2020.

21. Maldonado JR. Delirium pathophysiology: An updated hypothesis of the etiology of acute brain failure. *International Journal of Geriatric Psychiatry.* 2017;33(11):1428-1457.

22. Lipowski ZJ. Delirium in the elderly patient. *New England Journal of Medicine.* 1989;320(9):578-582.

23. Meagher DJ, Moran M, Raju B, et al. Motor symptoms in 100 patients with delirium versus control subjects: comparison of subtyping methods. *Psychosomatics.* 2008;49(4):300-308.

24. de la Cruz M, Fan J, Yennu S, et al. The frequency of missed delirium in patients referred to palliative care in a comprehensive cancer center. *Supportive Care in Cancer.* 2015;23(8):2427-2433.

25. Akechi T, Ishiguro C, Okuyama T, et al. Delirium training program for nurses. *Psychosomatics.* 2010;51(2):106-111.

26. Inouye SK. The dilemma of delirium: clinical and research controversies regarding diagnosis and evaluation of delirium in hospitalized elderly medical patients. *The American Journal of Medicine.* 1994;97(3):278-288.

27. Spiller JA, Keen JC. Hypoactive delirium: assessing the extent of the problem for inpatient specialist palliative care. *Palliative Medicine.* 2006;20(1):17-23.

28. Kishi Y, Kato M, Okuyama T, et al. Delirium: patient characteristics that predict a missed diagnosis at psychiatric consultation. *General Hospital Psychiatry.* 2007;29(5):442-445.

29. Ahmed S, Leurent B, Sampson EL. Risk factors for incident delirium among older people in acute hospital medical units: a systematic review and meta-analysis. *Age and Ageing.* 2014;43(3):326-333.

30. Cole M, McCusker J, Dendukuri N, Han L. The prognostic significance of subsyndromal delirium in elderly medical inpatients. *Journal of the American Geriatrics Society.* 2003;51(6):754-760.

31. Lipowski Z. Transient cognitive disorders (delirium, acute confusional sates) in the elderly. *Psychosomatic Medicine and Liaison Psychiatry*: Springer; 1983:289-306.

32. Cole MG, Ciampi A, Belzile E, Dubuc-Sarrasin M. Subsyndromal delirium in older people: a systematic review of frequency, risk factors, course and outcomes. *International Journal of Geriatric Psychiatry.* 2013;11(4):534-543.

33. Cole MG, Ciampi A, Belzile E, Zhong L. Persistent delirium in older hospital patients: a systematic review of frequency and prognosis. *Age and Ageing.* 2009;38(1):19-26.

34. Patel SB, Poston JT, Pohlman A, Hall JB, Kress JP. Rapidly reversible, sedation-related delirium versus persistent delirium in the intensive care unit. *American Journal of Respiratory and Critical Care Medicine.* 2014;189(6):658-665.

35. Kiely DK, Marcantonio ER, Inouye SK, et al. Persistent delirium predicts greater mortality. *Journal of the American Geriatrics Society.* 2009;57(1):55-61.

36. Ross CA. CNS arousal systems: possible role in delirium. *International Psychogeriatrics.* 1991;3(2):353-371.

37. de Rooij SE, Schuurmans MJ, Mast Rvd, Levi M. Clinical subtypes of delirium and their relevance for daily clinical practice: a systematic review. *International Journal of Geriatric Psychiatry.* 2005;20(7):609-615.

38. Meagher DJ, O'Hanlon D, O'Mahony E, Casey PR, Trzepacz PT. Relationship between etiology and phenomenologic profile in delirium. *Journal of Geriatric Psychiatry and Neurology.* 1998;11(3):146-149.

39. Hall RJ, Watne LO, Cunningham E, et al. CSF biomarkers in delirium: a systematic review. *International Journal of Geriatric Psychiatry.* 2018;33(11):1479-1500.

40. Ramirez-Bermudez J, Ruiz-Chow A, Perez-Neri I, et al. Cerebrospinal fluid homovanillic acid is correlated to psychotic features in neurological patients with delirium. *General Hospital Psychiatry.* 2008;30(4):337-343.

41. Inouye S. Predisposing and precipitating factors for delirium in hospitalized older patients. *Dementia and Geriatric Cognitive Disorders.* 1999;10(5):393-400.

42. Inouye S, Charpentier P. Precipitating factors for delirium in hospitalized elderly persons. *Jama.* 1996.

43. National Institute for Health and Clinical Excellence. Delirium: diagnosis, prevention and management. 2010; https://www.nice.org.uk/guidance/cg103. Accessed June 3, 2020.

44. Inouye SK, Bogardus Jr ST, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. *The New England Journal of Medicine.* 1999;340(9):669-676.

45. Adams ST, Leveson SH. Clinical prediction rules. *BMJ (Online).* 2012;344:d8312.

46. Reilly BM, Evans AT. Translating clinical research into clinical practice: impact of using prediction rules to make decisions. *Annals of Internal Medicine.* 2006;144(3):201-209.

47. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. *European Heart Journal.* 2014;35(29):1925-1931.

48. Lindroth H, Bratzke L, Purvis S, et al. Systematic review of prediction models for delirium in the older adult inpatient. *BMJ open.* 2018;8(4):e019223.

49. Clegg A, Young JB. Which medications to avoid in people at risk of delirium: a systematic review. *Age and Ageing.* 2011;40(1):23-29.

50. Van den Boogaard M, Pickkers P, Slooter A, et al. Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients: observational multicentre study. *BMJ (Online).* 2012;344:e420.

51. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *The Lancet.* 2014;383(9920):911-922.

52. Centers for Disease Control and Prevention. Lesson 3: Measures of Risk. 2012; https://www.cdc.gov/csels/dsepd/ss1978/lesson3/section2.html. Accessed 27 July 2020.

53. Travers C, Byrne G, Pachana N, Klein K, Gray L. Prospective observational study of dementia and delirium in the acute hospital setting. *Internal Medicine Journal.* 2013;43(3):262-269.

54. Tropea J, Slee JA, Brand CA, Gray L, Snell T. Clinical practice guidelines for the management of delirium in older people in Australia. *Australias Ageing.* 2008;27(3):150-156.

55. National Institute for Health and Clinical Excellence. Delirium in adults 2014; https://www.nice.org.uk/guidance/qs63. Accessed August 11, 2020.

56. Fick DM, Agostini JV, Inouye SK. Delirium superimposed on dementia: a systematic review. *Journal of the American Geriatrics Society.* 2002;50(10):1723-1732.

57. Fong T, Jones R, Shi P, et al. Delirium accelerates cognitive decline in Alzheimer disease. *Neurology.* 2009;72(18):1570-1575.

58. Davis DH, Muniz Terrera G, Keage H, et al. Delirium is a strong risk factor for dementia in the oldest-old: a population-based cohort study. *Brain.* 2012;135(9):2809-2816.

59. Fong TG, Vasunilashorn SM, Libermann T, Marcantonio ER, Inouye SK. Delirium and Alzheimer's Disease: A Proposed Model for Shared Pathophysiology. *International Journal of Geriatric Psychiatry.* 2019;34(6):781.

60. Jackson TA, MacLullich AM, Gladman JR, Lord JM, Sheehan B. Undiagnosed long-term cognitive impairment in acutely hospitalised older medical patients with delirium: a prospective cohort study. *Age and Ageing.* 2016;45(4):493-499.

61. Fick D, Foreman M. Consequences of not recognizing delirium superimposed on dementia in hospitalized elderly individuals. *Journal of Gerontological Nursing.* 2000;26(1):30-40.

62. Caplan GA, Kvelde T, Lai C, Yap SL, Lin C, Hill MA. Cerebrospinal fluid in long-lasting delirium compared with Alzheimer's dementia. *Journals of Gerontology Series A-Medical Sciences.* 2010;65(10):1130-1136.

63. Haggstrom L, Nelson J, Wegner E, Caplan G. 2-18F-fluoro-2-deoxyglucose positron emission tomography in delirium. *Journal of Cerebral Blood Flow & Metabolism.* 2017;37(11):3556-3567.

64. van Munster BC, Thomas C, Kreisel SH, et al. Longitudinal assessment of serum anticholinergic activity in delirium of the elderly. *Journal of Psychiatric Research.* 2012;46(10):1339-1345.

65. Koponen H, Leinonen E, Lepola U, Riekkinen P. A long-term follow-up study of cerebrospinal fluid somatostatin in delirium. *Acta Psychiatrica Scandinavica.* 1994;89(5):329-334.

66. van der Mast RC, Fekkes D, Moleman P, Pepplinkhuizen L. Is postoperative delirium related to reduced plasma tryptophan? *The Lancet.* 1991;338(8771):851-852.

67. Uchida K, Aoki T, Ishizuka B. Postoperative Delirium and Plasma Melatonin. *Medical Hypotheses.* 1999;53(2):103-106.

68. Shigeta H, Yasui A, Nimura Y, et al. Postoperative delirium and melatonin levels in elderly patients. *The American Journal of Surgery.* 2001;182(5):449-454.

69. Olsson T. Activity in the hypothalamic-pituitary-adrenal axis and delirium. *Dementia and Geriatric Cognitive Disorders.* 1999;10(5):345-349.

70. MacLullich A, Ferguson K, Miller T, de Rooij S, Cunningham C. Unravelling the pathophysiology of delirium: a focus on the role of aberrant stress responses. *Journal of Psychosomatic Research.* 2008;65(3):229-238.

71. Fiskum G, Danilov C, Mehrabian Z, et al. Postischemic oxidative stress promotes mitochondrial metabolic failure in neurons and astrocytes. *Annals of the New York Academy of Sciences.* 2008;1147(1):129-138.

72. Van Munster BC, Korevaar JC, Zwinderman AH, Levi M, Wiersinga WJ, De Rooij SE. Time-course of cytokines during delirium in elderly patients with hip fractures. *Journal of the American Geriatrics Society.* 2008;56(9):1704-1709.

73. van Munster BC, Korevaar JC, Korse CM, Bonfrer JM, Zwinderman AH, de Rooij SE. Serum S100B in elderly patients with and without delirium. *International Journal of Geriatric Psychiatry.* 2010;25(3):234-239.

74. Adamis D, Lunn M, Martin FC, et al. Cytokines and IGF-I in delirious and non-delirious acutely ill older medical inpatients. *Age and Ageing.* 2009;38(3):326-251.

75. Hshieh TT, Yue J, Oh E, et al. Effectiveness of multicomponent nonpharmacological delirium interventions: a meta-analysis. *JAMA internal medicine.* 2015;175(4):512-520.

76. Abraha I, Trotta F, Rimland JM, et al. Efficacy of non-pharmacological interventions to prevent and treat delirium in older patients: a systematic

overview. The SENATOR project ONTOP series. *PLoS ONE.* 2015;10(6):e0123090.

77. Martinez F, Tobar C, Hill N. Preventing delirium: should non-pharmacological, multicomponent interventions be used? A systematic review and meta-analysis of the literature. *Age and Ageing.* 2015;44(2):196-204.

78. Siddiqi N, Harrison JK, Clegg A, et al. Interventions for preventing delirium in hospitalised non-ICU patients. *Cochrane Database of Systematic Reviews.* 2016(3).

79. Inouye SK, Baker DI, Fugal P, Bradley EH, Project HD. Dissemination of the hospital elder life program: implementation, adaptation, and successes. *Journal of the American Geriatrics Society.* 2006;54(10):1492-1499.

80. Marcantonio ER, Flacker JM, Wright RJ, Resnick NM. Reducing delirium after hip fracture: a randomized trial. *Journal of the American Geriatrics Society.* 2001;49(5):516-522.

81. Milisen K, Foreman MD, Abraham IL, et al. A nurse-led interdisciplinary intervention program for delirium in elderly hip-fracture patients. *Journal of the American Geriatrics Society.* 2001;49(5):523-532.

82. Hshieh TT, Yang T, Gartaganis SL, Yue J, Inouye SK. Hospital elder life program: systematic review and meta-analysis of effectiveness. *The American Journal of Geriatric Psychiatry.* 2018;26(10):1015-1033.

83. Bannon L, McGaughey J, Verghis R, Clarke M, McAuley DF, Blackwood B. The effectiveness of non-pharmacological interventions in reducing the incidence and duration of delirium in critically ill patients: a systematic review and meta-analysis. *Intensive Care Medicine.* 2019;45(1):1-12.

84. Australian Commission on Safety and Quality in Health Care. Delirium Clinical Care Standard. 2016; https://www.safetyandquality.gov.au/our-work/clinical-care-standards/delirium-clinical-care-standard. Accessed August 11, 2020.

85. National Institute for Health and Clinical Excellence. Delirium in adults. 2014; https://www.nice.org.uk/guidance/qs63/chapter/Quality-statement-3-Use-of-antipsychotic-medication-for-people-who-are-distressed. Accessed June 17, 2020.

86. Yoon H-J, Park K-M, Choi W-J, et al. Efficacy and safety of haloperidol versus atypical antipsychotic medications in the treatment of delirium. *BMC Psychiatry.* 2013;13(1):240.

87. Burry L, Mehta S, Williamson DR, et al. Pharmacological interventions for the treatment of delirium in critically ill patients. *The Cochrane Database of Systematic Reviews.* 2015;2015(6).

88. Oh ES, Needham DM, Nikooie R, et al. Antipsychotics for preventing delirium in hospitalized adults: a systematic review. *Annals of Internal Medicine.* 2019;171(7):474-484.

89. Nikooie R, Neufeld KJ, Oh ES, et al. Antipsychotics for treating delirium in hospitalized adults: a systematic review. *Annals of Internal Medicine.* 2019;171(7):485-495.

90. de Jonghe A, Korevaar JC, van Munster BC, de Rooij SE. Effectiveness of melatonin treatment on circadian rhythm disturbances in dementia. Are there implications for delirium? A systematic review. *International Journal of Geriatric Psychiatry.* 2010;25(12):1201-1208.

91. Lewis MC, Barnett SR. Postoperative delirium: the tryptophan dyregulation model. *Medical Hypotheses.* 2004;63(3):402-406.

92. Chen S, Shi L, Liang F, et al. Exogenous melatonin for delirium prevention: a meta-analysis of randomized controlled trials. *Molecular Neurobiology.* 2016;53(6):4046-4053.

93. Nishikimi M, Numaguchi A, Takahashi K, et al. Effect of administration of ramelteon, a melatonin receptor agonist, on the duration of stay in the ICU: a single-center randomized placebo-controlled trial. *Critical Care Medicine.* 2018;46(7):1099.

94. Pandharipande PP, Sanders RD, Girard TD, et al. Effect of dexmedetomidine versus lorazepam on outcome in patients with sepsis: an a priori-designed analysis of the MENDS randomized controlled trial. *Critical Care.* 2010;14(2):R38.

95. Nelson LE, Lu J, Guo T, Saper CB, Franks NP, Maze M. The α2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. *Anesthesiology: The Journal of the American Society of Anesthesiologists.* 2003;98(2):428-436.

96. Duan X, Coburn M, Rossaint R, Sanders R, Waesberghe J, Kowark A. Efficacy of perioperative dexmedetomidine on postoperative delirium: systematic review and meta-analysis with trial sequential analysis of randomised controlled trials. *British Journal of Anaesthesia.* 2018;121(2):384-397.

97. Li B, Wang H, Wu H, Gao C. Neurocognitive dysfunction risk alleviation with the use of dexmedetomidine in perioperative conditions or as ICU sedation: a meta-analysis. *Medicine.* 2015;94(14).

Chapter 3: A systematic review of the overlap of biomarkers in delirium and advanced cancer-related syndromes

3.1 Chapter preface

Given the prevalence of delirium in advanced cancer, it was important to compare the biomarkers in delirium and advanced cancer, considering there is potential overlap in the pathophysiological mechanisms. A systematic review was therefore conducted as the initial step in this doctoral project, to explore the overlap of the biomarkers in delirium and specific advanced cancer-related syndromes and prognosis.

The study reported in this chapter was published in *BMC Psychiatry* in 2020. Chapter three contains an edited version of the publication, which is provided in its published form in Appendix 1.1.

Publication reference

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3.2 Introduction

The pathophysiology of delirium is poorly understood, and largely hypothetical. Current hypotheses include: neuronal ageing, neuroinflammation, oxidative stress, neuroendocrine dysregulation, disruption to the circadian rhythm, and neurotransmitter dysregulation.[1,2] A reduction in glucose metabolism seen in people with delirium is a model with developing evidence.[3,4] Collectively, the biological correlates of delirium are referred to as 'delirium biomarkers'. Biomarkers are most commonly studied to investigate their correlation with a disease in order to better understand its underlying pathophysiology, and subsequently inform prevention and treatment strategies for that disease. A challenge for the field of delirium research is that correlation may exist between biomarkers of delirium and those of the patient's disease or injury which placed them at increased risk of delirium, or which precipitated it (for example sepsis or hip fracture). Such correlation should be factored into delirium biomarker research, yet rarely has been.

To date, there has been limited empirical consideration of the distinction between delirium pathophysiology and that of the underlying disease, for example, cancer, where the mechanisms are also common in advanced cancer syndromes. This review used cancer as an exemplar of a condition with its own biological drivers in which delirium is common and for which the pathophysiology may be inter-related or overlapping. The rationale for exploring cancer was two-fold: Firstly, a condition that did not purely impact the brain, was ideal to consider the biomarker aspects which might overlap due to a broad range of mechanisms. Cancer is a medical comorbidity that is not necessarily associated with cognitive issues nor known to have specific shared pathophysiology. Secondly, biomarker research in advanced cancer (and delirium) is a reasonably developed field so the opportunity to explore overlap existed

more readily. Better understanding of the interplay between delirium pathophysiology and that of correlated conditions and diseases, for example, cancer (the focus of this review), is crucial to develop more effective prevention and treatment of delirium.

We therefore conducted a systematic review of the literature to explore the overlap between biomarkers that have been studied in delirium and biomarkers that have been studied in cancer-related syndromes.

3.2.1 Aim

The aim of the systematic review was to identify biomarkers associated with delirium and with specific clinical situations in advanced cancer (namely prognosis; specific clinical syndromes of cognitive impairment, anorexia cachexia, cancer pain, cancer-related fatigue, and sickness behavior); and to evaluate the nature and extent of overlap of the findings.

3.3 Methods

3.3.1 Design

A systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[5]

3.3.2 Search method

In July 2017, two separate searches were conducted in MEDLINE, PubMed, Embase, CINAHL, CENTRAL, and Web of Science. The first was for literature of delirium biomarkers; the second was for literature of biomarkers in advanced cancer-related syndromes. Primary terms for the delirium search were: ‘delirium’ and ‘biomarker’. Search terms for the cancer search were: ‘cancer’, ‘neoplasms’, ‘metastasis’, ‘fatigue’, ‘sickness behavior’, ‘cancer pain’, ‘cachexia’, and ‘prognosis’. Additional terms which encompassed commonly researched biomarkers were also included**.** Filters in

Medline were: 1: Humans; 2. English language and 3. Published from 1980 onward (when delirium was first included in the *DSM, Third Edition (DSM-III)*). Search terms and filters were tailored to each subsequent database, as required. The full search strategy for MEDLINE can be found in Appendix 2. Reference lists of included studies and relevant systematic reviews and meta-analyses identified in the search were examined for additional eligible studies.

3.3.3 Inclusion and exclusion criteria

We included English language studies published in peer-reviewed journals that reported body fluid biomarkers in adult participants with delirium or an advanced cancer-related syndrome of interest. Studies were excluded if they reported delirium tremens only; did not measure delirium using a validated tool; the sample had less than 75% of participants with advanced cancer; measured tissue, genetic or animal biomarkers, or were conducted post-mortem. Protocols and ongoing studies were also excluded. Based on the expert knowledge of the authors in both delirium and cancer, the advanced cancer-related syndromes and prognosis were chosen based on the potential biological plausibility that the pathophysiological mechanisms could overlap with that of delirium. We limited the search to advanced cancer as this is the cancer population with the highest prevalence of both delirium and the cancer-related syndromes of interest. Delirium, based on current biological understanding, is likely a systemic disease not purely an organ specific disease, and hence tissue markers were excluded as these are targeted to organ specific conditions (e.g. cancer).

3.3.4 Study selection, data extraction and management

Search results were imported into Endnote X7 software, duplicates removed and then exported into Covidence.[TM6] Two reviewers per search (IAD and AH: delirium search, IAD and MA: cancer search) independently applied eligibility criteria for both

searches and examined title and abstracts. Exclusions were documented only for articles that required full-text to make a formal decision. Inter-reviewer disagreement on included studies was discussed to resolve any discrepancies, with the third reviewer consulted when required. Data extraction was conducted by the doctoral researcher (IAD) using Excel (2016) with two other reviewers (MA and AH) providing input and oversight. Data extraction was guided by the REporting recommendations for tumor MARKer prognostic studies (REMARK) checklist.[7]

3.3.5 Quality assessment

In the absence of a gold standard risk of bias assessment for biomarker studies, the REMARK checklist,[7] a tumor marker reporting guideline, was chosen to assess the methodological quality of the included studies. The REMARK checklist was selected due to the extensive detail contained in the guideline, particularly in the assay procedures, compared to other guidelines that could have been chosen. One reviewer (IAD) applied an adaptation of the REMARK checklist, with 10% verification by two other reviewers (MA and AH).

3.3.6 Data synthesis

All biomarkers in every article from each database were analysed. Each individual biomarker was recorded in Excel and categorized into 'delirium studies' and 'cancer studies'. The initial analysis involved all biomarkers that had been explored in delirium and advanced cancer studies. The synthesis of these articles was structured according to the biomarker type, the biological material used, the assay used, and the numbers and proportions of participants who had both delirium and advanced cancer. Following this, we decided only to include the biomarkers that had been studied in both delirium and an advanced cancer syndrome. Of these studies, we included all biomarkers that

had been studied in both a delirium study and an advanced cancer study. This is how we defined an 'overlap' of biomarkers.

The heterogeneity of data precluded performing a meta-analysis; we therefore reported the data using a narrative synthesis approach using text and tabular summaries.

3.4 Results

The delirium search yielded 3342 articles and the cancer syndromes search 4081, giving a total of 7423 articles. An additional 25 articles were found through the hand search. After removal of 1817 duplicates and 5120 articles through title and abstract screening, we reviewed 511 full text papers and subsequently excluded 288. After initial analysis, a further 72 were excluded as they did not report a biomarker studied in delirium and advanced cancer. This resulted in a total of 151 articles included in this review: 71 reported biomarkers studied in delirium, and 80 reported biomarkers studied in a cancer syndrome or prognosis (Figure 3.1).

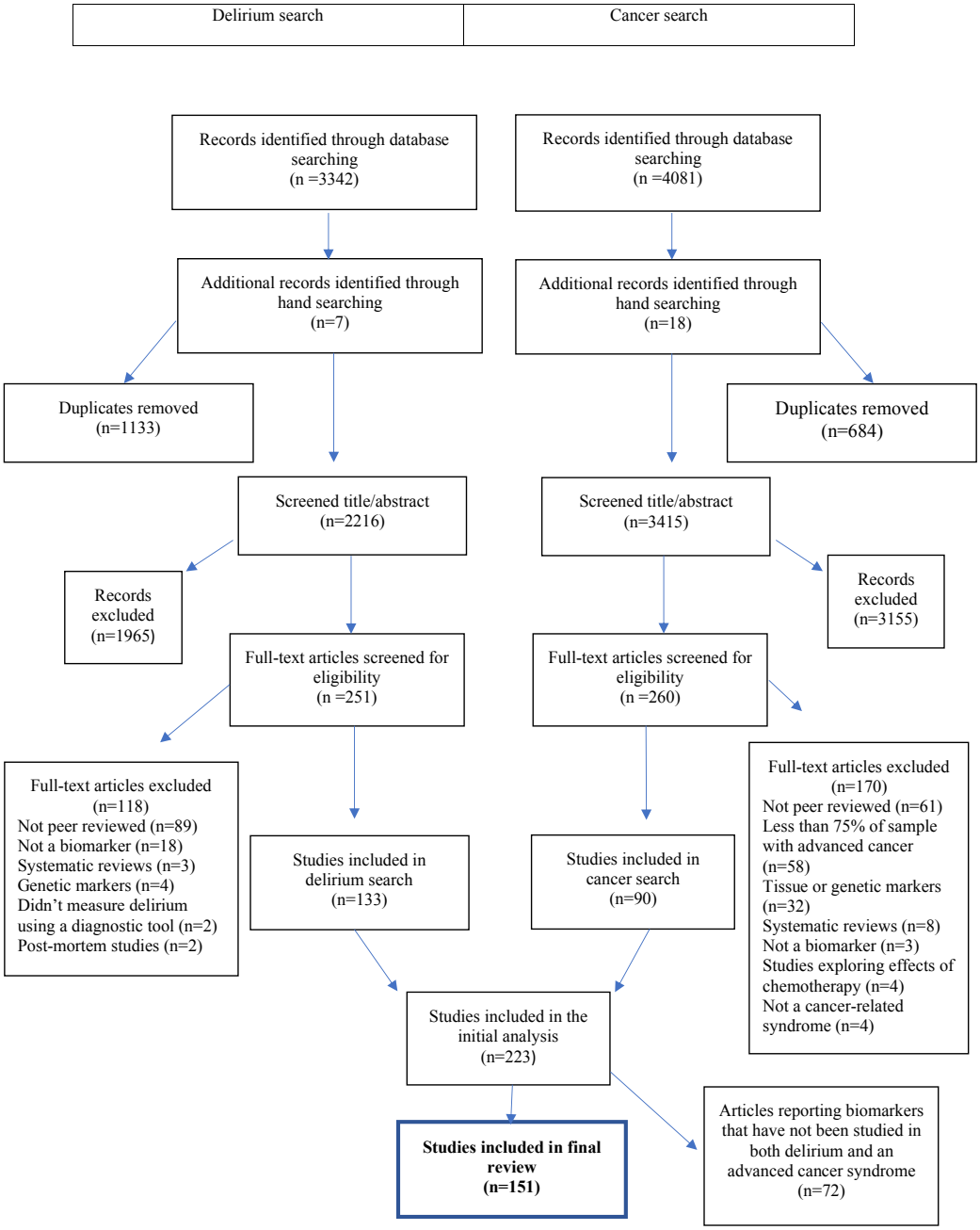

Figure 3.1 PRISMA flow diagram of search results

3.4.1 Study characteristics

The 151 studies were conducted between 1985 and 2017 in Europe (n=86), Asia (n=33), The Americas (n=27), Australia (n=2), and multiple regions (n=3). Studies were set in a large range of settings, with the most common in general hospital settings (n=111; 73%). Thirty-nine studies (26%) did not report the setting. Sample sizes ranged from 7-2456, with relatively even numbers of male and female participants (55.4% male). Ninety nine articles reported a mean age, with an overall weighted mean age of 69.3 years. Of the 37 articles that reported the median age of participants, the overall median age was 54.5 years. The overall age of participants in the remaining 15 articles was not possible to determine (Table 3.1 and 3.2).

Table 3.1 Participant characteristics- delirium studies

Author and year	Country	Setting	Aims	Participants			
				N	Male, n (%)	Mean age; SD; (range)	Comorbidities
Egberts *et al.* (2017)	The Netherlands	NR	To compare mean NLR levels of patients with and without delirium who were acutely admitted to a geriatric ward	Total participants (n=86); with delirium (n=13); no delirium (n=73)	In the delirium group: 4 (30.8%); in the no delirium group: 28 (38.4%)	In the delirium group: 81.2 ± 6.6; in the no delirium group: 79.9 ± 6.5 (range NR)	NR
Kozak *et al.* (2017)	Turkey	Non-intensive stroke unit	To investigate whether the occurrence of delirium in patients with acute ischemic stroke (AIS) is associated with serum TNF-alpha, IL-1b, BDNF and NSE on admission	Total participants (n=60); with ischemic stroke and delirium (n=11); with acute ischemic stroke but no delirium (n=49)	29 (48.3%)	66.15 ± 12.53 (range 31-89)	Cardiovascular Diabetes
Tomasi *et al.* (2017)	Brazil	Respiratory Care Unit	Hypothesis: In non-severe septic patients, blood biomarkers of inflammation, endothelial activation, coagulation, and brain function would be different when compared to patients with and without brain dysfunction	Total participants (n=38); with CAP-induced sepsis (n=20); patients with sepsis acquired encephalopathy (n=10); non-sepsis patients with delirium (n=8)	Total cohort: 19 (50%); in patients with delirium: 6 (75%)	Median age of total cohort: 60 (29-88); median age of delirium patients: 57 (38-88)	Cardiovascular Respiratory Diabetes
Vasunilashorn *et al.* (2017)	USA	Two academic medical centers	To examine associations between CRP measured preoperatively and on postoperative day 2 and delirium incidence, duration, and feature severity	Total participants (n=560); with delirium (n=134); no delirium (n=426)	In the delirium group: 53 (39.5%); in the no delirium group: 181 (42.4%)	In the delirium group: 77.5 ± 5.0; in the no delirium group: 76.4 ± 5.2 (range NR)	Cardiovascular Connective tissue disease
Chu *et al.* (2016)	China	The orthopaedic ward of a medical centre	To investigate the association between IGF-1 levels and the incidence of delirium in a homogeneous and well-defined population	Total participants (n=103); with delirium (n=23); no delirium (n=80)	76 (64.4%)	81.74 ± 3.98 (range NR)	NR

Dillon *et al.* (2016)	USA	University teaching hospital	To identify the top candidate protein marking for delirium using plasma obtained at 4 serial time points from older patients undergoing major non-cardiac surgery	Total participants (n=566); in the pooled cohort (n=150; with delirium (n=150); no delirium (n=150))	In the pooled cohort: with delirium: 75 (50%); in the no delirium group: 75 (50%)	In the pooled cohort: delirium group: 77.6 ± 4.7; in the no delirium group: 77.2 ± 4.5 (range NR)	Vascular
Guo *et al.* (2016)	China	Department of Anaesthesiology and Critical Care Medicine	To investigate the prevalence and perioperative risk factors of POD, including medical history, comorbidities and clinical laboratory data, in elderly patients after THA for hip fracture	Total participants (n=572); with POD (n=120); no POD (n=452)	In the delirium group: 36 (30%); in the no delirium group: 170 (37.6%)	Median age in the delirium group: 82 (76-86); in the no delirium group: 76 (72-80)	Cardiovascular Neurological
Karlicic *et al.* (2016)	Serbia	Psychiatric ICU	To examine the relation between the markers of inflammation and lethal outcome in patients diagnosed with delirium and hospitalized in the intensive psychiatric care unit	Total participants (n=120); delirious patients who survived (n=80); Delirious patients who died (n=40)	In the delirium group who survived: 68 (85%); in the deceased group: 29 (72.5%)	In delirium patients who survived: 46.8 ± 1.6; in the deceased group: 57.3 ± 13.2 (range NR)	Respiratory Urinary
Neerland *et al.* (2016)	UK and Norway	University hospital	To examine whether delirium in individuals with hip fracture is associated with high CRP, IL-6, and sIL-6R levels in the CSF	Total participants (n=149); with delirium (n=71); no delirium (n=78)	In the delirium group: 21 (29.5%); in the no delirium group: 16 (20.5%)	Median age in the delirium group: 85 (IQR 80-89); in the no delirium group: 83 (IQR 71-88)	NR
Shen *et al.* (2016)	China	General surgery	To investigate potential serum predictive factors including IGF-1 for POD in elderly patients after open abdominal surgery	Total participants (n=140); with POD (n=36); no POD (n=104)	In the delirium group: 17 (47.2%); in the no delirium group: 43 (41.3%)	In the delirium group: 73.8 ± 5.9; in the no delirium group: 68.8 ± 7.0 (range NR)	Cardiovascular Diabetes Obstructive sleep apnea

Sun *et al.* (2016)	China	NR	To elucidate the pathogenesis of POD by observing the kinetics of inflammation, stress, and dementia markers in elderly oral cancer patients with POD	Total participants (n=112); with POD (n=56); no POD (n=56)	In the delirium group: 27 (48.2%); in the no delirium group: 23 (41%)	In the delirium group: 73.2 ± 6.5; in the no delirium group: 72.7 ± 8.3 (range NR)	NR
Yen *et al.* (2016)	USA	University Medical Center	To assess preoperative serum IGF-I levels as a predictor of incident delirium in non-demented elderly elective knee arthroplasty patients	Total participants (n=98); with delirium (n=22); no delirium (n=76)	In the delirium group: 9 (40.9%); in the no delirium group: 38 (50%)	In the delirium group: 72.5 ± 4.4; in the no delirium group: 73.7 ± 5.2	Dementia Cardiovascular Diabetes Obstructive sleep apnea Benign prostatic hypertrophy Incontinence Digestive
Avila-Funes *et al.* (2015)	Mexico	Tertiary care hospital	To investigate the association between serum E2 levels and incidence of delirium in a sample of hospitalized elderly women	Total participants (n=141); with delirium (n=23); no delirium (n=118)	0%- all women	77.8 ± 5.6 (range NR)	Dementia Cardiovascular Diabetes Cancer
Brum *et al.* (2015)	Brazil	Hospital cancer center	To evaluate the role of BDNF and TNF-a serum levels as disease markers of delirium in oncology inpatients	Total participants (n=70); oncology inpatients with delirium (n=17); oncology patients without delirium (n=28) and non-oncology healthy controls (n=25)	In oncology inpatients with delirium: 10 (26%); oncology patients without delirium: 13 (34%) and	65.19 ± 8.29 (range 41-89)	NR

					non-oncology healthy controls: 15 (40%)		
Egberts *et al.* (2015)	The Netherlands	Internal Medicine and Geriatrics	To investigate the levels of the potential biomarkers neopterin, IL-6 and IGF-1 in elderly patients with and without a delirium	Total participants (n=86); with delirium (n=23); no delirium (n=63)	In the delirium group: 10 (43.5%); in the no delirium group: 30 (47.6%)	Median age in the delirium group: 87.0 (84-88); in the no delirium group: 81.0 (75-85)	NR
Foroughan *et al.* (2015)	Iran	General hospital-unspecified	To investigate the occurrence of delirium and identify the associated risk factors in a sample of hospitalized elderly in Southwestern Iran	Total participants (n=200); with delirium (n=44); no delirium (n=156)	In the delirium group: 28 (42.4%); in the no delirium group: 38 (57.6%)	In the delirium group: 78.5 ± 8.2; in the no delirium group: 70.7 ± 6 (range NR)	Dementia Cardiovascular Diabetes Cancer
Skrede *et al.* (2015)	Norway	University teaching hospital	To investigate the relationship between MCP-1, measured in serum preoperatively and postoperatively, and the development of delirium in a population of elderly hip fracture patients	Total participants (n=19); pre-op delirium (n=5); POD (n=9); no delirium (n=10)	5 (26.3%)	Median age: 83 (79-91)	NR
Vasunilashorn *et al.* (2015)	USA	3 academic medical centers	To examine the relationship between 12 cytokines (measured at 4 time points) and delirium among older adults undergoing major elective surgery	Total participants (n=566): discovery cohort (39 delirium cases) and a replication cohort (36 delirium cases); and a pooled cohort which combined discovery and replication (n=75); Patients with no delirium and no sub-syndromal delirium on any postoperative day. Discovery cohort (n=39); replication cohort	In the discovery delirium cohort: 18 (46%); in the no delirium discovery cohort: 18 (46%); in the replication delirium cohort: 23 (63.8%) and in the no	Discovery cohort: with delirium: 77.3 ± 5.0; without delirium: 76.8 ± 4.7. Replication cohort: with delirium: 78.0 ± 4.4; without delirium: 77.6 ± 4.2 (range NR)	Vascular

				(n=36); and pooled cohort (n=75)	delirium replication cohort: 23 (63.8%)		
Alexander *et al.* (2014)	USA	ICU	To determine the association between inflammatory markers, APOE, APOE genotype, and the occurrence, duration, and outcome of delirium in ICU patients	Total participants (n=77); delirium present (n=35); no delirium (n=18)	In the delirium group: 17 (48.5%); in non-delirium group: 8 (44.4%)	Delirium group: 47.2 ± 17.4; no delirium group: 46.4 ± 18.3 (range NR)	Respiratory Acute brain dysfunction
Baranyi *et al.* (2014)	Germany	Department of cardiac surgery	To investigate the impact of sIL-2R as a biomarker of delirium after cardiac surgery with CPB.	Total participants(n=34); POD (n=11); no delirium (n=23)	22 (64.7%)	68.2 ± 9.7 (range NR)	NR
Cape *et al.* (2014)	UK and the Netherlands	Two university teaching hospitals	To investigate 5 biomarkers known to be involved in the neuro-inflammatory process in rodents	Total participants (n=43); with delirium (n=19); with no delirium (n=24)	In the delirium group: 5 (26.3%); in the no delirium group: 6 (25%)	In the delirium group: 81.3 ± 6.0; in the no delirium group: 81.3 ± 8.6 (range NR)	Dementia
Capri *et al.* (2014)	Italy	General hospital-unspecified	To further investigate predictive factors of POD assessing pre-operative-inflammaging related-cytokines plasma level	Total participants (n=74); with POD (n=37); no POD (n=37)	In the delirium group: 20 (54%); in the no delirium group: 17 (45.9%)	In the delirium group: 79.2 ± 6.7; in the no delirium group: 76.4 ± 6.7 (range NR)	NR
Chen *et al.* (2014)	China	General hospital-unspecified	To investigate the ability of plasma leptin level to predict delirium and prolonged delirium in elderly patients after hip fracture surgery	Total participants (n=372); with delirium (n=70); without delirium (n=116); healthy controls (n=186)	47 (25.3%)	Total cohort: 76.7 ± 8.0 (range NR)	NR
Hatta *et al.* (2014)	Japan	4 university hospitals and 1 general hospital	To investigate whether a change in inflammatory status, indicated by blood natural killer (NK) cell activity, predicts delirium	Total participants (n=29); patients developing delirium (n=9); no delirium (n=20)	In the delirium group: 5 (56%); in the no delirium group: 6 (30%)	In the delirium group: 77.2 ± 6.5; in the no delirium group: 81.5 ± 7.5	Dementia Cardiovascular

Kazmierski *et al.* (2014)	Poland	The cardiac surgical ICU	Primary: to assess whether patients with MCI referred for coronary artery bypass graft (CABG) surgery are at a greater risk of development of POD. Secondary aim: to investigate the putative associations between MCI and cortisol levels, as well as inflammatory and nutritional factors	Total participants (n=113); with delirium (n=41); no delirium (n=72)	In the delirium group: 29 (70.7%); in the no delirium group: 61 (84.7%)	Median age in the delirium group: 68.8 (IQR 64-74); in the no delirium group: 61.5 (IQR 58-67.5)	Dementia Cardiovascular Diabetes Depression
Ritchie *et al.* (2014)	UK	Medical Acute Admissions Unit	To describe the association between CRP and the incidence and severity of delirium in a large sample of elderly patients admitted to an acute hospital, and to determine if there was any interaction between CRP and delirium by diagnosis as a proxy for upstream etiologies	Total participants (n=710); with delirium (n=87); no delirium (n=623)	In the delirium group: 33 (37.9%); in the no delirium group: 258 (41.4%)	In the delirium group: 86.7 ± 7.26; mean age in the no delirium group: 82.5 ± 7.29 (range in total cohort 70-101)	Cardiovascular Musculoskeletal Infection Metabolic
Ritter *et al.* (2014)	Brazil	ICU in University teaching hospital	To test the hypothesis that an association between systemic inflammatory mediators and the occurrence of delirium will differ between septic and non-septic patients	Total participants (n=78); with delirium (n=31): out of the delirious cohort 18 (58%) of them had sepsis on admission; patients without delirium (n=47)- 21 (44%) of this cohort had sepsis at ICU admission	In the delirium group: 20 (64%); in the no delirium group: 34 (72%)	Median age in the delirium group: 56 (43-75); in the no delirium group: 57 (42-66)	Sepsis
Zhang *et al.* (2014)	China	ICU- teaching hospital	To examine CRP on ICU entry was associated with subsequent development of delirium	Total participants (n=223); with delirium (n=54); no delirium (n=169)	In the delirium group: 37 (68.5%); in the no delirium group: 104 (61.5%)	In the delirium group: 64.5± 18.1; in no delirium group: 54.9 ± 16.3 (range NR)	NR

Cerejeira *et al.* (2013)	Portugal	Orthopaedics	To determine the response of plasma cortisol and IGF-1 following surgical trauma, and their relationship with the innate immune response and POD	Total participants (n=101); with delirium (n=37); no delirium (n=64)	In the delirium group: 15 (40.5%); in the no delirium group: 35 (54.7%)	In the delirium group: 73.65 ± 5.87 (64-89); in the no delirium group: 72.69 ± 6.53 (60-87)	NR
Colkesen *et al.* (2013)	Turkey	ICU	To examine the association between serum cortisol levels and occurrence of delirium after ACS	Total (n=52); with delirium (n=25); no delirium (n=27)	In the delirium group: 13 (52%); in the no delirium group: 15 (55%)	In the delirium group: 66 ± 6; in the no delirium group: 62 ± 9 (range NR)	Cardiovascular
Kazmierski *et al.* (2013)	Poland	Cardiac surgical ICU	Primary: To investigate the association between preoperative and postoperative plasma cortisol concentrations and the development of POD. Secondary: To assess whether any association between cortisol and delirium is stress related or mediated by way of MDD or cognitive impairment	Total participants (n=113); with delirium (n=41); no delirium (n=72)	90 (79.65%)	Median age: 64 (IQR 59-71)	Cardiovascular Diabetes Depression
Kazmierski *et al.* (2013)b	Poland	Cardiac surgical ICU	Primary: to investigate the independent association between raised pro-inflammatory cytokine levels (IL-2 and TNF- a) and delirium diagnosed after CABG surgery. Secondary aim: to establish whether any association between raised cytokine levels and delirium is related to surgical and anesthetic procedures or mediated by pre-existing conditions associated with raised cytokine levels, such as	Total participants (n=113); with delirium (n=41); no delirium (n=72)	In the delirium group: 29 (70.7%); in the no delirium group: 61 (84.7%)	Median age in the delirium group: 68.8 (IQR 64-74); in the no delirium group: 61.5 (IQR 58-67.5)	Dementia Depression

			MDD, cognitive impairment, or aging				
Liu *et al.* (2013)	China	University teaching hospital	To investigate the association of serum IL-6 levels with the occurrence of delirium in elderly patients after major non-cardiac surgery	Total participants (338); with delirium (n=50); no delirium (n=288)	In the delirium group: 27 (54%); in the no delirium group: 163 (56.6%)	In the delirium group: 74 ± 6; in the no delirium group: 71±7 (range NR)	Cardiovascular Respiratory Diabetes Sepsis Intestinal obstruction Renal function lesion
Plaschke *et al.* (2013)	Germany	University teaching hospital	To explore the role of pro- and anti-inflammatory cytokines in POD in two studies	Total participants (n=151); Cardiac ICU: with delirium (n=32); no delirium (n=82); Non-cardiac ICU: with delirium (n=17); no delirium (n=20)	In the delirium group: 21 (65.6%); no delirium group: 67 (81.7%)	Cardiac ICU: with delirium: 73.3 ± 6.0; without delirium: 67.3 ± 9.3. Non-cardiac ICU: with delirium: 64.4 ± 13.3; without delirium: 64.6 ± 10.0	NR
Skrobik *et al.* (2013)	Canada	ICU	To compare biological and drug treatment characteristics in patients with coma and/or delirium while in the ICU	Total participants (n=99); with delirium (n=64); with coma (n=59); no coma and no delirium (n=12)	In the delirium group: 31 (48.4%); in the coma group: 55 (55.4%); in the no coma and no delirium group: 7 (58.3%)	In the delirium group: 62.0 ± 13.9; in the coma group: 63.2 ± 14.2; in the no delirium and no coma group: 55.2 ± 15.7 (range NR)	Hepatic dysfunction Renal dysfunction

Westhoff *et al.* (2013)	The Netherlands	Teaching hospital	To study the hypothesis by analysing a range of pro- and anti-inflammatory markers in CSF in elderly patients undergoing emergency hip surgery	Total participants (n=61); with delirium (n=23); no delirium (n=38)	In the delirium group: 7 (30.4%); in the no delirium group: 12 (31.5%)	In the delirium group: 84.6 ± 5.2; in the no delirium group: 82.9 ± 4.5 (range NR)	NR
Bakker *et al.* (2012)	The Netherlands	The Department of Cardiothoracic Surgery	To identify preoperative and operative characteristics that enable the prediction of delirium after cardiac surgery in elderly patients	Total participants (n=201); with delirium (n=63); no delirium (n=138)	In the delirium group: 37 (59%); in the non-delirium group: 84 (61%)	Delirium group: 76.7 ± 3.9; in the no delirium group: 75.9 ± 3.7 (range NR)	Cardiovascular Diabetes
Baranyi *et al.* (2012)	Germany	Department of cardiac surgery	To investigate the impact of intra- and postoperative albumin levels as a biomarker of delirium after cardiac surgery with CPB	Total participants (n=34); POD (n=11); no delirium (n=23)	22 (64.7%)	68.2 ± 9.7 (range NR)	NR
Cerejeira *et al.* (2012)	Portugal	General hospital orthopedic ward	To clarify whether delirium is associated with an unbalanced inflammatory response or a dysfunctional interaction between the cholinergic and immune systems	Total participants (n=101); with delirium (n=37); no delirium (n=64)	In the delirium group: 15 (40.5%); in the no delirium group: 35 (54.7%)	73 ± 6.3 (range 60–89)	NR
Girard *et al.* (2012)	USA	General hospital-unspecified	To assess the associations between a priori-selected markers of inflammation and coagulation and delirium during critical illness	Total participants (n=138); with delirium (n=107); no delirium (n=31)	69 (50%)	Median age: 66	Cardiovascular Respiratory Sepsis Stroke/intracranial haemorrhage Renal Failure
Osse *et al.* (2012)	The Netherlands	University hospital	To examine the association between plasma levels of pterins and amino acids and POD	Total participants (n=125); with delirium (n=58); no delirium (n=67)	In the delirium group: 34 (58.6%); in the no delirium	In the delirium group: 76.7 ± 3.9; and in the no delirium	Cardiovascular

					group: 48 (71.6%)	group: 75.1 ± 3.1 (range NR)	Diabetes
Bisschop *et al.* (2011)	The Netherlands	Department of Orthopedic Surgery or Traumatology	To evaluate a possible relationship between glucose, cortisol, insulin, and delirium	Total participants (n=143); with delirium (n=70); no delirium (n=73)	In delirium group: 17 (24%); in the no delirium group: 26 (36%)	Delirium group: 85.1 ± 6.7; in the no delirium group: 82.6 ± 6.9 (range NR)	Cardiovascular Preadmission cognitive impairment Diabetes
Holmes *et al.* (2011)	UK	Memory assessment services	To determine if raised serum TNF-a or IL-6 are associated with the presence of sickness behaviour symptoms, independent of the development of delirium, in a prospective cohort study of participants with AD	Total participants with mild to severe AD (n=222); with delirium (n=197); without delirium (n=25)	102 (34%)	82.8 ± 0.4	NR
Lee *et al.* (2011)	Korea	Orthopaedic surgery	To identify predictive factors of delirium, including risk factors and prodromal symptoms	Total participants (n=65); with delirium (n=18); no delirium (n=47)	In the delirium group: 8 (44.4%); in the no delirium group: 14 (29.7%)	In the delirium group: 81.7 ± 6.35 (69-94); in the no delirium group: 75.0 ± 7.83 (65-90)	NR
McGrane *et al.* (2011)	USA	Two tertiary care centers	To test the hypothesis that systemic inflammation, as measured by the inflammatory biomarkers procalcitonin and CRP, is associated with a longer duration of brain dysfunction in mechanically ventilated patients	Total participants (n=87)	44 (50%)	Median age: 60 (IQR 49-66)	Sepsis
Morandi *et al.* (2011)	USA	General hospital-unspecified	To prospectively test the hypothesis that low IGF-1 concentrations early during critical illness would be associated with delirium in	Total mechanically ventilated medical ICU patients in entire sample (n=110); patients included in primary analysis=62)	In the entire sample: 57 (52%); in the patients included in the primary	Median age in the entire sample: 65 (IQR 52-74); in the patients included in the	Cardiovascular Respiratory

			mechanically ventilated medical ICU patients		analysis: 35 (57%)	primary analysis: 66 (53-76)	Sepsis
Van der Boogaard *et al.* (2011)a	The Netherlands	ICU	To examine plasma biomarkers in delirious and non-delirious patients and the role of these biomarkers on long-term cognitive function	Total participants (n=100); with delirium (n=50); no delirium (n=50)	In the delirium group: 27 (46%); in the no delirium group: 26 (40%)	In the delirium group: 72 (95% CI 38-86); in the no delirium group: 68 (95% CI 31-84)	NR
Van der Boogaard *et al.* (2011)b	The Netherlands	ICU	To explore whether biomarkers associated with delirium could be detected in urinary protein profiles of hyperactive delirium compared to matched non-delirium ICU- patients	Total participants (n=20); with hyperactive delirium (n=10); no delirium (n=10)	In the delirium group: 7 (70%); in the no delirium group: 6 (60%)	Median age in the delirium group: 75 (IQR 70-78); in the no delirium group: 75 (IQR 68-78)	NR
Burkhart *et al.* (2010)	Switzerland	University teaching hospital	To identify modifiable risk factors associated with the development of POD in elderly patients after elective cardiac surgery to be able to design follow-up studies aimed at the prevention of delirium by optimizing perioperative management	Total participants (n=113); with delirium (n=35); without delirium (n=78)	77 (68%)	74.3 ± 5.51 (range NR)	Cardiovascular Diabetes Renal insufficiency
Mu *et al.* (2010)	China	General hospital-unspecified	To examine the association between serum cortisol level and occurrence of early POD in patients undergoing CABG surgery	Total participants (n=243); with delirium (n=123); no delirium (n=120)	In the delirium group: 101 (82.1%); in the no delirium group: 99 (82.5%)	In the delirium group: 63.6 ± 7.7; in the no delirium group: 58.3 ± 8.0 (range NR)	Cardiovascular Respiratory Sepsis
Pearson *et al.* (2010)	UK	NR	To test the hypothesis that delirium is associated with higher CSF and plasma	Total participants (n=20); with delirium (n=7); no delirium (n=13)	In the delirium group: 1 (14.2%); in the	In the delirium group: 81.4 ± 7.2; in the no	Cardiovascular

			cortisol levels in older patients with acute hip fracture		no delirium group: 4 (30.7%)	delirium group: 80.5 ± 8.7; (range of total cohort 62-93)	Respiratory Diabetes Rheumatoid arthritis
Plaschke *et al.* (2010)	Germany	Cardiac surgical ICU	To analyse whether the BIS, cortisol, and IL-6 were different in delirious patients as compared to non-delirious ones after cardiac surgery	Total participants (n=114); with delirium (n=32); no delirium (n=82)	89 (78%)	In the delirium group: 73.3 ± 6.0; in the no delirium group: 67.3 ± 9.3 (range NR)	Cardiovascular Diabetes
Tsruta *et al.* (2010)	Japan	University teaching hospital-Advanced Medical Emergency & Critical Care Center	To investigate the prevalence and associated factors of delirium in critically ill patients during an ICU stay	Total participants (n=103); with delirium (n=21); no delirium (n=82)	In the delirium group: 13 (62%); in the no delirium group: 51 (62%)	In the delirium group: 70 ± 17; in the no delirium group: 64 ± 19 (range NR)	Cardiovascular Respiratory Digestive Trauma/burns Acute poisoning
Van Munster *et al.* (2010)	The Netherlands	Department of Orthopedic Surgery /Traumatology of an Academic Medical Centre	To investigate the levels of cortisol in a large sample and compare the levels cortisol, IL-6 and IL-8 and S100B in one study among elderly patients with hip fracture with and without delirium	Total participants (n=120); with delirium (n=62); without delirium (n=58)	In the delirium group: 16 (26%); in the no delirium group: 23 (40%)	In the delirium group: 84.8 ± 6.9; in the no delirium group: 82.9 ± 7.9 (range NR)	NR
Adamis *et al.* (2009)	UK	Elderly care unit	To investigate the relationship of serum cytokines, IGF-I, severity of illness, cognition, possession of APOE epsilon 4 genotype, gender and age on (i) the presence of delirium and (ii) on its severity	Total participants(n=67); with delirium (n=28); no delirium (n=39)	19 (28.3%)	84.2 ± 6.3 (70–94)	Dementia Cardiovascular Respiratory

							Urinary tract infection Falls Cellulitis
Van Munster *et al.* (2009)	The Netherlands	Academic Medical Centre	(1) to compare changes before and after surgery of S100B and NSE levels in serum in patients with and without POD, and to investigate the difference in serum levels before, during and after delirium; (2) to study the serum levels of S100B and NSE in different subtypes of delirium	Total participants (n=120); patients with delirium (n=62); no delirium (n=58)	In the delirium group: 16 (26%); in the no delirium group: 23 (40%)	In the delirium group: 84.8 ± 6.9; in the no delirium group: 82.9 ± 7.0	NR
Lemstra *et al.* (2008)	The Netherlands	Teaching hospital	To investigate the association of cytokine levels and incident delirium in a homogeneous and well-defined population	Total participants (n=68); with POD (n=18); no POD (n=50)	In the delirium group: 8 (44.4%); in the no delirium group: 13 (26%)	NR	Neurological Respiratory Endocrine Psychiatric
Pfister *et al.* (2008)	Switzerland	ICU	To test the hypothesis that cerebral perfusion and selected serum markers of inflammation and delirium differ in septic patients with and without sepsis-associated delirium	Total participants (n=16); with sepsis-associated delirium (n=12); Patients with no sepsis-related delirium (n=4)	14 (62%)	Median age: 74.5 (18-90)	NR
Rudolph *et al.* (2008)	USA	An academic medical center	To determine if a difference exists in the postoperative pattern of change in a priori determined classes of inflammatory markers in matched patients with and without delirium after cardiac surgery	Total participants (n=42); with delirium (n=12); no delirium (n=30)	In the delirium group: 11 (92%); in the no delirium group: 9 (75%)	In the delirium group: 74.7 ± 7.0; in the no delirium group: 73.9 ± 8.4 (range NR)	Cardiovascular Diabetes

Van Munster *et al.* (2008)	The Netherlands	Department of Orthopedic Surgery /Traumatology of an Academic Medical Centre	To compare the time-course of cytokine expression in elderly patients with hip fracture with and without POD and investigate the possible associations between cytokines and different subtypes of delirium	Total participants (n=98); with delirium (n=50); no delirium (n=48)	In the delirium group: 13 (26%); in the no delirium group: 18 (37.5%)	In the delirium group: 84.6 ± 7.1; in the no delirium group: 83.2 ± 6.7 (range NR)	NR
Adamis *et al.* (2007)	UK	Elderly care unit	To investigate the relationship between physical illness severity and delirium, and the relationship between putative marker of predisposition and perpetuation (APOE epsilon4 allele APOE4, CRP and cytokines) of delirium	Total participants n=164; consented for laboratory tests (n=116); delirium present on first assessment (n=42); subsequently (n=5); no delirium (n=117)	54 (32.9%)	84.6 ± 6.57 (70-104)	Dementia
de Rooij *et al.* (2007)	The Netherlands	General hospital-unspecified	To compare the expression patterns of pro- and anti-inflammatory cytokines in patients with and without delirium	Total participants (n=185); with delirium (n=64); no delirium (n=121)	In the delirium group: 22 (34%); in the no delirium group: 54 (45%)	In the delirium group: 81.2± 7.1; in the no delirium group: 77.3 ± 8.0 (range NR)	Cardiovascular Cancer Infectious disease Water/electrolyte disturbances
Plaschke *et al.* (2007)	Germany	ICU	To examine whether measurement of SAA level is a reliable indicator of delirium in ICU patients, and whether there is a significant relationship between SAA and quantitative EEG data and the clinical diagnosis of delirium using the CAM-ICU	Total participants (n=37); with delirium (n=17); without delirium (n=20)	In the delirium group: 12 (70.5%); in the no delirium group: 15 (75%)	In the delirium group: 62.7 ± 13.2; in the no delirium group: 64.5 ± 9.9	Cardiovascular Digestive Pancreas/liver failure
White *et al.* (2005)	UK	Emergency medical admissions	To investigate the activities of plasma esterases (drug	Total participants (n=283); with delirium	177 (41.3%)	82.4 ± 0.3	Dementia

			metabolising enzymes) in delirium	(n=105); no delirium (n=178)			
Wilson *et al.* (2005)	UK	Acute medical ward	To determine if low base line IGF-1 levels is a risk factor for incident delirium in patients aged 75 and over admitted to an acute medical ward	Total participants (n=100); with delirium (n=12); no delirium (n=88)	31 (31%)	84.5 ± 4.2 (range NR)	Depression
Beloosesky *et al.* (2004)	Israel	NR	To determine the kinetics of CRP, fibrinogen and ESR in aged patients with hip fractures, over a month after surgery and to examine the relationship of these parameters to cognition, post-operative complications, functional level after 1 month and 6-month post-operative mortality	Total participants (n=32); delirium present (n=10); no delirium (n=22)	9 (28.1%)	85.1 ± 4.8 years (77–97)	Cardiovascular Respiratory Diabetes Digestive Urinary
Robertsson *et al.* (2001)	Sweden	A hospital neuropsychiatric diagnostic unit	To determine activity in the HPA in demented patients by measuring their basal serum cortisol levels and performing DST and to ascertain whether the stress regulating system was more disturbed in the patients with delirium than in those without delirium	Total participants (n=172); with delirium (n=67); no delirium (n=105)	NR	69.8 ± 6.9 (52-79)	Dementia
Van der Mast *et al.* (2000)	The Netherlands	Thorax centre of a University Hospital	To examine the interrelationships between the plasma levels of amino acids, physical condition, and POD in patients undergoing elective cardiac surgery	Total participants (n=296); with POD (n=40); no POD (n=256)	192 (65%)	63 ± 11 (range 26–83)	Cardiovascular
Van der Mast *et al.* (1999)	The Netherlands	NR	To investigate the incidence of delirium after various types of cardiac	Total participants (n=296); with delirium	192 (65%)	63 ± 11 (26–83)	NR

			surgery, and associated preoperative predictors	(n=40); no delirium (n=256)			
Gustafson *et al.* (1993)	Finland	Stroke unit	To investigate the relationships between the activity of HPA axis and ACS in patients with acute supratenrorial ischemic stroke	Total participants (n=155); with a supratentorial cerebral infarction (n=83); healthy control group (n=72)	Of the stroke patients: 52 (63%); healthy control NR	Stroke patients: 74.8 ± 8 (44-89); healthy controls: 69.2 ± 10	Dementia Cardiovascular Diabetes Stroke
McIntosh *et al.* (1985)	USA	The Boston Veterans Administration Hospital	To measure the levels of plasma cortisol and B-endorphin in patients who underwent elective surgery in order to determine whether there is a relation between circulating levels of these hormones and POD	Total participants (n=7); with delirium (n=3); no delirium (n=4)	7 (100%)	Mean age NR; (42-65)	NR

Abbreviations: *ACS: Acute confusional state; AD: Alzheimer's disease; APOE: Apolipoprotein E; BDNF: Brain-derived neurotrophic factor; BIS: Bispectral Index; CNS: Central nervous system; CPB: Cardiopulmonary bypass; CRP: C-reactive protein; CSF: Cerebrospinal fluid; DST: Dexamethasone suppression test; E2: Estradiol; EEG: Electroencephalography; HPA: Hypothalamic- Pituitary-Adrenal axis; ICU: Intensive care unit; IGF: Insulin-like growth factor; IL-: Interleukin; IQR: Interquartile range; MCI: Mild cognitive impairment; MCP: Monocyte chemoattractant protein; MDD: Major depressive disorder; NLR: Neutrophil/Lympthocyte ratio; NR: Not reported; NSE: Neuron-Specific Enolase; POD: Post-operative delirium; S100b: Calcium binding protein B; SAA: Serum anticholinergic activity; sIL-: Soluble interkeukin; THA: Total hip arthroplasty; TNF-a: Tumor necrosis factor- alpha*

Table 3.2 Participant characteristics- cancer studies

Author and year	Country	Setting	Aims	Participants					
				N	Male, n (%)	Mean age; SD; (range)	Type of cancer	Advanced cancer (%)	Cancer stage
Amano *et al*. (2017) [1]	Japan	Palliative care	To investigate the association between CRP level, symptoms, and ADL in advanced cancer patients receiving palliative care	Total participants with advanced cancer (n=1702)	1003 (58.9%)	68.4 ± 12.7 (range NR)	Mixed	100%	NR
Fogelman *et al*. (2017)	USA	NR	To identify which symptoms or serum markers can best predict weight loss in patients with locally advanced or metastatic pancreatic cancer	Total participants with baseline serum for analysis (n=69); with cancer (n=63); healthy controls with no cancer diagnosis (n=6)	In the weight loss group: 14 (32.6%); in the no weight loss group: 29 (67.4%)	In the weight loss group (at diagnosis): 61.5 ± 9.4 (45.9-78; in the no-weight loss group (at diagnosis): 62.9±11.4 (36-86)	Pancreatic cancer	100%	NR
Luo *et al*. (2017)	Korea	NR	Aim of cohort study: To evaluate the effect of elevated plasma fibrinogen levels for predicting the prognosis of advanced-stage EOC compared with serum CA-125 levels and systemic inflammatory	Total participants with advanced cancer (n=217)	0 (0%)	Median age: 54.4 (range 25–84)	Ovarian	100%	3 (1.4%) stage IIIA, 15 (6.9%) stage IIIB, 149 (68.7%) stage IIIC, and 50 (23%) stage IV.

[1] Secondary analysis of Amano, 2016

			biomarkers, such as NLR and PLR						
Paulsen *et al*. (2017)	Norway	NR	To examine the relationship between inflammatory biomarkers (cytokines and markers of the inflammatory response) and PROMs of pain, appetite and fatigue in patients with advanced cancer receiving opioids	Total participants with cancer (n=49)	25 (51%)	63.9 (CI 61.2-66.8)	Mixed	96%	NR
Amano *et al*. (2016)	Japan	Palliative care	To investigate the clinical implications of CRP as a prognostic marker in advanced cancer patients in palliative settings	Total participants with advanced cancer (n=1511)	895 (59%)	Mean age in group one (CRP<1): 68.8 ± 13.4; mean age in group two (CRP ≤ 1): 69.1 ± 12.1; mean age in group 3 (CRP ≤ 5): 68.4 ± 12.6 and mean age in group 4 (CRP ≤ 10); 66.3 ± 13.4 (range NR)	Mixed	100%	NR
Bye *et al*. (2016)	Norway	University Hospital-unspecified	To study changes in inflammatory biomarkers and energy intake in an	Total participants (n=60); with cancer	15 (75%)	Median age: 67.5 (range 35-79)	Pancreatic	100%	6 (30 %) patients had locally advanced

			unselected cohort of pancreatic cancer patients with and without cachexia as they approached the terminal stage of disease	(n=20); healthy controls (n=40)					cancer, 13 (65 %) had metastatic disease and one (5%) had recurrent disease after an earlier pancreatic resection.
Mitsunga *et al*. (2016)	Japan	Cancer centre	To establish a classification using CRP level to stratify the aggressiveness of treatment-naive advanced prostate cancer in patients undergoing first-line chemotherapy	Total participants with cancer (n=421); Retrospective cohort (n=280); prospective cohort (n=141)	In the retrospective cohort: 122 (43.6%); in the prospective cohort: 75 (53.2%)	Median age in the retrospective cohort: 63 (IQR 57-70); median age in the prospective cohort: 67 (IQR 62-74)	Pancreatic cancer	100%	Prospective cohort: 21.3% stage III, 78.7% stage IV; Retrospective cohort: 11.8% stage III; 88.2% stage IV
Morgado *et al*. (2016)	Argentina	NR	To evaluate the relationship between weight loss and several parameters of skeletal muscle function	Total participants with cancer and fatigue (n=49); Arm A: patients with ≥5% weight loss in the last 6 months (n=27); Arm B: advanced cancer patients without weight loss (n = 22)	In the weight loss group: 20 (74.1%); in the weight-stable group: 11 (50%)	Mean age in the weight loss group: 62 (39-85); in the weight-stable group: 60 (24-79)	Mixed	100%	NR

Rodrigues *et al*. (2016)	Brazil	NR	To characterize the incidence of fatigue in the context of advanced cancer not influenced by cancer treatment and to assess the clinical and laboratory factors associated with this symptom	Total participants with advanced cancer (n=51); no control	24 (47.1%)	Median age 64 (33-85)	Mixed	100%	NR
Srdic *et al*. (2016)	Croatia	University hospital-Department for Respiratory Diseases	Primary aim: To obtain prevalence of cancer cachexia and sarcopenia in patients with advanced lung cancer using criteria for definition and diagnosis. Secondary aim: To assess determinants for chemotherapy toxicity and prognostic factors for survival	Total participants with advanced cancer (n=100); with cancer cachexia (n=69); no cachexia (n=31)	67 (67%)	Mean age: 64 (IQR 41-87)	NSCLC	100%	34 % stage IIIB 66% stage IV
Wu *et al*. (2016)	China	Department of Colorectal Surgery	To examine the correlations of NLR and PLR with chemotherapy sensitivity and prognosis	Total participants with advanced cancer (n=55)	35 (64%)	28 (51%) of patients were < 60 years old; 27 (49%) of patients were ≥ 60 years old.	Lung	100%	14 (35%) stage IV; 13 (30%) stage IIIB and 6 (15%) stage IIIA
Bilir *et al*. (2015)	Turkey	University medical oncology centre	To investigate the possible etiologic factors of cachexia	Total participants (n=80); with cancer cachexia (n=46); healthy	In the cachexia group: 36 (78.2%); in the control group: 24 (70.5%).	In the cachexia group: mean age: 60.9 ± 14; in the control	Mixed	100%	NR

				participants with no known chronic disease or weight loss (n=34)		group: 57.8 ± 12 (range NR)			
Miura *et al*. (2015)	Japan	Cancer centre	To characterize IL-6 related factors in patients who were scheduled to undergo first-line chemotherapy for treatment-naïve advanced pancreatic cancer	Total participants with advanced cancer (n=79)	677 (58.4%)	In the <60 group: 342 participants (29.5%); in the 65-74 range: 340 participants (29.3%); in the ≥ 75 age group: 477 participants (41.2%)	Pancreatic cancer	100%	35.5% stage III cancer, 64.5% stage IV
Miura *et al*. (2015)b	Japan	Palliative care	To clarify the value of the GPS as a prognostic score in advanced cancer patients receiving palliative care services	Total participants with advanced cancer (n=1160)	677 (58.4%)	In the <65 group age group: 342 participants (29.5%); in the 65-74 range: 340 participants (29.3%); in the ≥ 75 age group: 477 participants (41.2%)	Mixed	100%	NR
Barrera *et al*. (2014)	Mexico	University Medical Oncology Clinic	To associate the plasma levels of several cytokines with clinical characteristics and prognosis in patients with advanced NSCLC	Total participants (n=135); with advanced cancer (n=110); healthy	47 (42.5%)	58.5 ± 16.4	NSCLC	100%	12.5% stage IIIB, remaining 87.5% stage IV

				controls (n=25)					
Blakely *et al*. (2014)	USA	Palliative surgery	To determine if preoperative CRP is associated with patient outcomes following palliative surgery	Total participants (n=50); patients with normal CRP (n=23); patients with elevated CRP levels (n=27)	In the normal CRP group: 11(47.8%); in the elevated CRP group: 15 (55.5%)	In the normal CRP group: mean age: 63 ± 13 (44-93); in the elevated CRP group: 63 ± 15.4 (23-88)	Mixed	100%	NR
Fujiwara *et al*. (2014)	Japan	University hospital-unspecified	To investigate the difference in serum metabolite levels between pancreatic cancer patients with and without cachexia and to explore the pattern and intra-day variations in metabolite levels using metabolomics	Total participants with advanced cancer (n=21); with cachexia (n=9); without cachexia (n=12)	In the cachexia group: 8 (8.8%); in the non-cachexia group: 8 (66.6%)	Median age in cachexia group: 66.5 (range 36-77); in the no-cachexia group: 68.5 (range 39-76) years	Pancreatic	100%	10 (48%) stage IVA and 11 (52%) stage IVB
Lindemann *et al*. (2014)	Australia	NR	To evaluate the influence of elevated CRP levels as well as hypoalbuminemia on the further survival in patients with advanced inoperable cancer affecting specifically the esophagus	Total participants with advanced cancer (n=218)	185 (84.9%)	67 ± 11.84 years (21–93)	Esophageal	100%	NR
Mondello *et al*. (2014)	Italy	Oncology-hospital	To investigate the role of leptin, ghrelin and	Total participants (n=170); with	74 (52.8%)	Mean age in the cancer	Mixed	100%	25% stage III, 75% stage IV

			obestatin as diagnostic and predictive markers of cachexia in oncologic patients. Their impact on patient survival was also evaluated	advanced cancer (n=140); healthy controls (n=30)		group: 61.8 ± 14.3; in the control group: 59.6 ± 12.2 (range NR)			
Moriwaki *et al*. (2014)	Japan	NR	To evaluate the prognostic value of GPS in Biliary tract cancer patients with good ECOG PS undergoing chemotherapy	Total participants with advanced cancer (n=62)	33 (53%)	Median age: 68 (44-85)	Biliary tract cancer	100%	NR
Szkandera *et al*. (2014)	Austria	Oncology	To validate the prognostic significance of pre-treatment plasma CRP levels on CSS in a large cohort of 474 pancreatic cancer patients	Total participants with cancer (n=474)	256 (54%)	Mean age at diagnosis: 64.6 ± 10.4 (range NR)	Pancreatic cancer	77.3%	1% stage I, 3.8% stage IIA, 17.9% stage IIB, 7% stage III, 70.3% stage IV
Zhang *et al*. (2014)	China	University hospital-oncology	To determine if there was a significant correlation between CRF and chemotherapy-associated adverse effects and plasma levels of TNF-α and IL-1 as well as urinary 17-HCS before and after chemotherapy	Total participants with cancer (n=200)	118 (59%)	64 (32%) of patients were < 40 years old; 85 (42.5%) were between 40-60 years old; and 51 (25.5%) were > 60	Mixed	79%	13.5% stage II, 56.5% stage III, 22.5% stage IV
Jafri *et al*. (2013)	USA	NR	To see ALI at the time of diagnosis can predict survival outcomes in patients with newly	Total participants with advanced	116 (67%)	Median age: 57 (34-88)	NSCLC	100%	All stage IV

			diagnosed metastatic NSCLC	cancer (n=173)					
Laird *et al*. (2013)	Switzerland, Germany, Denmark, UK, Iceland, Italy, Norway, and Sweden.	Multiple centres (e.g., hospital inpatients, hospital outpatients, hospices/specialist palliative care units)	To examine the relationship of pain, other key symptoms, and systemic inflammation in a large international cohort of patients with advanced cancer	Total participants with advanced cancer (n=1466)	739 (50%)	Median age: 62 (IQR 54-70)	Mixed	100%	NR
Laird *et al*. (2013)b	Switzerland, Germany, Denmark, Australia, UK, Iceland, Austria, Italy, Norway, Sweden, and Canada.	Multiple (hospital inpatients, hospital outpatients, hospices/specialist palliative care units)	1) to compare the prognostic value of established clinical factors with the systemic inflammation-based mGPS; 2) to assess whether performance status in combination with mGPS is more powerful than either alone; and 3) to assess both of these aspects in a test sample before validation in an independent sample	Total participants with cancer (n=2456)	In the test sample: 931 (51%); in the validation sample: 237 (53%)	Median age in the test sample: 63 (IQR 54-71); in the validation sample: 64 (IQR 56-71)	Mixed	100%	NR
Paiva *et al*. (2013)	Brazil	Palliative care	Primary aim: To evaluate the prevalence of CRF among advanced cancer patients undergoing their first consult in palliative care and to access its impact on QOL. Secondary aim: To investigate	Total participants with cancer (n=223); with cancer-related fatigue (n=55); without cancer-related	112 (50.7%)	60.4 ± 12.6 (21-86)	Mixed	100%	NR

			the association of CRF with known and possible predictors, as well as to determine the prognostic impact of CRF and its relationship with the inflammatory marker CRP was evaluated	fatigue (n=168)					
Suh *et al*. (2013)	Korea	3 hospice and palliative care centre	To investigate whether plasma levels of IL-6 or TNF-α could predict survival in patients with far advanced cancer	Total participants with advanced cancer (n=98)	52 (53.1%)	52 (53%) of patients were ≥ 65 years old; 46 (47%) of patients were < 65 years' old	Mixed	100%	NR
De Raaf *et al*. (2012)	The Netherlands	Palliative care	To determine in both advanced cancer patients and cancer survivors: 1) which inflammatory markers are related to physical fatigue and mental fatigue, and 2) whether inflammatory markers that are associated with fatigue are related to each other	Total participants (n=92); with advanced cancer (n=45); cancer survivors (n=47)	In the cancer group: 18 (40%); in the cancer survivor group: 19 (40%)	Mean age in the cancer group: 58 (22-81); in the cancer survivor group: 57 (36-77)	Mixed	100%	NR
Gioulbasanis *et al*. (2012)	Greece	Oncology-university hospital	To investigate the possible association between baseline IL-8 plasma levels and nutritional status, and to evaluate the predictive and prognostic value of	Total participants with cancer (n=114)	101 (88.6%)	Median age: 67.5 ± 5.4 (range NR)	NSCLC	100%	All stage IV

			IL-8 in patients with NSCLC						
Gulen *et al*. (2012)	Turkey	NR (control group from Chest Diseases Outpatient Clinic)	To investigate the relationship of adipokines and systemic inflammation in weight-losing advanced-stage NSCLC patients	Total participants (n=88); with cancer (n=63); further divided into subgroups as those with a >5% weight loss in preceding 6 months (n=33) and those who had not (n=30); healthy controls (n=25)	All male (100%)	Mean age for the cancer group: 65.63 ± 9.87 and for the control group: 63.52 ± 11.54 (range of total cohort 52-84)	NSCLC	100%	43% stage III and 57% stage IV
Heitzer *et al*. (2012)	Austria	NR	Primary aim: To identify biological, measurable biomarkers in serum correlating with pain intensity in patients with cancer. Secondary aim: to assess cytokine serum level differences between patients and healthy controls and to evaluate possible relationships between pain entities, pain intensity, gender, location of the	Total participants (n=65); with cancer pain (n=45); healthy individuals without pain (n=20)	17 (44.7%)	63.1 ± 11.5 (43-89)	Mixed	100%	NR

			primary tumour, and the patients' cytokine baseline concentrations						
Minton *et al*. (2012)	Norway, UK, Austria, Germany, Switzerland, Italy, Canada, and Australia	Palliative care, hospices, general oncology and medical wards	To identify factors independently associated with fatigue and to determine the prevalence of severe fatigue in a diverse group of palliative care cancer patients across a variety of settings and in different countries.	Total participants with cancer in the fatigue subset analysis (n=720)	In the fatigue group: 162 (50%); 233 (56%) in the no fatigue group	Mean age in the fatigue group: 63.4; mean age in the no fatigue group: 62.5 (range NR)	Mixed	100%	NR
Partridge *et al*. (2012)	UK	Palliative care	To examine whether mGPS is of use in cancer patients near the end of life	Total participants with biomarkers recorded (n=102); in mGPS 0 group (n=16); in mGPS 1 group: (n=20); in mGPS 2 (n=66)	In the mGPS 0 group: 8 (17.4%); in the mGPS 1 group: 9 (19.6%); in the mGPS2 group: 29 (63%).	Median age in the mGPS 0 group: 73; in the mGPS 1 group: 76; and in the mGPS 2 group: 71.	Mixed	100%	NR
Pond *et al*. (2012)	Russia and USA	NR	To evaluate and compare the prognostic abilities of the prognostic classifiers and to investigate the ability of CRP to enhance their prognostic abilities	Total participants (n=220)	100%	NR	Prostate	100%	NR

Wang *et al*. (2012)	China	University hospital-cancer centre	To compare the prognostic value of pre-therapy CRP-based prognostic scores such as the mGPS and PI with those based on the cellular components of the systemic inflammatory response such as the NLR, PLR and PNI in patients with pancreatic cancer	Total participants with cancer (n=177)	120 (67.7%)	125 patients were < 65 years old; 53 patients were ≥ 65 years' old	Pancreatic cancer	79%	21% stage I and II, 79% stage III and IV
Aydin *et al*. (2011)	Turkey	Thoracic Surgery Department	To investigate the prognostic value of serum CRP, pre-albumin, and transferrin levels in patients with advanced stage esophageal cancer treated with stent placement	Total participants (n=61)	29 (47.5%)	63.9 ± 13.5 (range 34-94)	Esophageal cancer	100%	NR
Dev *et al*. (2011)	USA	Supportive Care Clinic at University Cancer Centre	To assess the relationship between opioid use and serum cortisol and testosterone levels and explore the association of cortisol with symptoms as measured by the ESAS in patients with advanced cancer	Total patients with advanced cancer (n=77)	48 (62%)	Median age: 63 (51.5-69)	Mixed	100%	NR
Gioulbasanis *et al*. (2011)	Greece	Oncology-university hospital	To evaluate the correlation of MNA with laboratory markers of inflammation/cache	Total participants (n=115); group A with no nutritional	In group A: 24 (88.9%); in group B: 50 (84.7%);	Median age: 66 (32-86)	Lung cancer	100%	NR

			xia in patients with metastatic lung cancer	sufficiency (n=27); group B with a risk of malnutrition (n=59); group C with malnutrition (n=29)	group C: 27 (93.1%)				
Hwang *et al*. (2011)	Korea	Oncology-university hospital	To evaluate the relationships between carcinomatosis peritonei, liver metastasis, bone metastasis, ECOG PS, albumin, CRP, GPS, and PFS, and OS in patients with recurrent or metastatic gastric cancer receiving first-line palliative chemotherapy	Total participants with cancer (n=402)	293 (72.9%)	203 (50.5%) of patients were < 60 years of age; 199 (49.5%) were ≥ 60	Gastric adenocarcinoma	77.6%	NR
Kwak *et al*. (2011)	Korea	Four hospice-palliative care centres	To examine fatigue and serum levels of IL-6 and TNF-α in terminally ill Korean cancer patients without clinical evidence of acute inflammation to clarify the roles of inflammatory cytokines in fatigue	Total participants with advanced cancer (n=90); no control	48 (53%)	64.3 ± 12.7 (range NR)	Mixed	100%	NR
Lee *et al*. (2011)	Korea	Emergency	To investigate the relationship between serum CRP levels and the short-term mortality of advanced cancer in ED patients	Total participants with advanced cancer (n=126)	92 (73%)	65.1 ± 11.3 (range NR)	Mixed	100%	NR

Scheede-Bergdahl *et al*. (2011)	Canada	Nutrition and Performance Laboratory	To investigate the clinical relevance of plasma levels of four pro-inflammatory cytokines in advanced cancer patients to further establish their potential in the diagnostic definition of cancer cachexia	Total participants with advanced cancer (n=83)	47 (56.6%)	61.8 ± 12.9 (34-85)	GI or NSCLC	100%: 41% locally advanced and 59.0% metastatic	NR
Vlachostergios *et al*. (2011)	Greece	University hospital-oncology	To investigate the potential correlations of IGF-I with known clinical and biochemical predictors of adverse clinical outcome, including inflammatory response and weight loss, and examined their clinical relevance about TTP and OS in patients with metastatic NSCLC	Total participants with advanced cancer (n=77)	66 (85.7%)	49 (63.6%) of patients were ≤ 70 years old; 28 (36.4%) were > 70 years' old	NSCLC	100%	NR
Diakowska *et al*. (2010)	Poland	NR	To investigate the differences in serum leptin concentrations adjusted to gender and body mass in all these conditions as compared to healthy participants with reference to the severity of background inflammatory response	Total participants (n=218); with cancer and cachexia (n=84); with cancer and no cachexia (n=51); with non-malignant cancer and cachexia (n=20); non-	In cancer cachexia group: 65 (77.3%); in non-cachexic cancer patients: 43 (84.3%); in non-malignant cachexia controls: 7 (23.3%)	In cancer cachexia group: 63.3 (35-86); in non-cachexic cancer patients: 63.7 (24-83); in non-malignant cachexia controls: 65.2 (51-	Esophageal cancer	84%	3 (2.2%) stage I, 18 (13.3%) stage II, 33 (24.4%) stage III and 81 (60%) stage IV

				malignant cancer and non-cachectic (n=63)	and in non-malignant non-cachectic group: 37 58.7%)	84) and in non-malignant non-cachectic group: 60.5 (47-82)			
Meek *et al*. (2010)	UK	Oncology-hospital	To examine the relationship between IGF-1, IGFBP-3, weight loss and the systemic inflammatory response in patients with inoperable NSCLC	Total participants with advanced cancer (n=56)	34 (60.7%)	11 patients <60 years old and 45 patients ≥ 60 years' old	NSCLC	100%	51.7% stage III, 46.4% stage IV
Ishizuka *et al*. (2009)	Japan	University hospital-Gastroenterological surgery	To evaluate the influence of the mGPS for prediction of mortality in these patients	Total participants with advanced cancer (n=112)	67 (59.8%)	74 participants were ≤ 70 years old; and 38 > 70 years' old	Colorectal Cancer	100%	2.7% stage IIB, 1.7% stage III and 95.6% stage IV
Karapanagiotou *et al*. (2009)	Greece	NR	To detect the role of ghrelin in cachexia and systemic inflammation of advanced NSCLC patients as well as its role as a diagnostic and prognostic tool	Total participants (n=161); NSCLC patients with weight loss (n=75); NSCLC patients without weight loss (n=26); healthy controls (n=60)	In weight-loss group: 21 (84%); in the non-weight loss group: 62 (81.6%)	In the cachectic cancer group mean age: 59.9 ± 11.8; in the non-cachectic cancer group: 55.9 ± 10.7; in the control group: 52.1 ± 12.3	NSCLC	100%	23 (23%) stage IIIB and 78 (77%) stage IV
Paddison *et al*. (2009)	USA	Palliative care	To investigate whether routinely	Total participants	18 (40.9%)	66 ± 8.3 (range NR)	NSCLC	100%	All either Stage IIIB

			collected cellular immune data were associated with the severity of fatigue reported by advanced lung cancer patients	with advanced cancer (n=44)					with effusion or Stage IV (stage % NR)
Takahashi *et al*. (2009)	Japan	Medical university	To examine plasma cytokine and hormone levels prospectively in cachectic cancer patients and healthy volunteers	Total participants (n=26); cachectic cancer patients (n=16); healthy hospital personnel who had undergone no changes in body weight over the previous 6 months, had no acute or chronic disease, and were receiving no regular medication (n=10)	12 (75%)	63 ± 11 (range NR)	Mixed	100%	100% stage IV
Inagaki *et al*. (2008)	Japan	NR	To investigate associations between plasma IL-6 levels and fatigue in terminally ill cancer patients	Total participants with advanced cancer (n=46); clinically fatigued patients (n=27);	28 (60.8%)	58.4 ± 10.5 (range NR)	Mixed	100%	NR

				without fatigue (n=19)					
Karapanagiotou *et al*. (2008)	Greece	NR	To examine the diagnostic and prognostic role of leptin, adiponectin and resistin in advanced NSCLC, their association with cancer-related weight loss and the potential effect of chemotherapy on their serum levels	Total participants (n=152); with advanced cancer (n=101); healthy controls (n=51)	In the cancer group: 83 (82%); in the control group: 26 (51%)	In the cancer group: 64.2 ± 10.4; in the healthy controls: 55.5 ± 8.9	NSCLC	100%	23 (23%) stage IIIB and 78 (77%) stage IV
Sharma *et al*. (2008)	Australia	General hospital-unspecified	1) To confirm the prognostic value of the GPS in advanced colorectal cancer, and 2) to explore a predictive pattern of plasma cytokines and their gene polymorphisms for clinical outcome; and 3) to investigate which cytokines contribute to GPS	Total participants with advanced cancer (n=52)	33 (64%)	11 (21%) of patients were ≤ 60; 41 (79%) were >60 years old	Colorectal cancer	100%	100% stage IV
Weryńska *et al*. (2008)	Poland	NR	To evaluate serum leptin concentrations in the groups of lung cancer patients with and without cachexia when compared to healthy controls, and to explore the correlations between serum	Total participants with advanced cancer (n=40); with cachexia (n=20); no cachexia (n=20)	In the cancer group: 25 (62.5%); in the control group: 5 (33.3%)	Mean age in the cancer group: 61 (50–75); mean age in the control group: 44 (28-77)	NSCLC	100%	15% stage IIIA, 30% stage IIIB, 35% stage IV

			leptin concentration level and the antropometric indicators of cancer cachexia: body mass, arm circumference and skin triceps fold thickness						
Demiray *et al*. (2007)	Turkey	Oncology	To investigate the role of serum leptin and resistin levels in the pathogenesis of cancer cachexia to evaluate whether these peptides are effective in predicting cachexia and to investigate their effects on the quality of life of the patients	Total participants (n=87); with advanced cancer (n=67); healthy individuals without a known chronic disease (n=20)	In the cancer group: 62 (92.5%); in the control group: 16 (80%).	Mean age in the cancer group: 62.9 ± 8.7; in the control group: 63.1 ± 6.2 (range NR)	NSCLC	100%	Stage IIIB and stage IV (doesn't specify % of stage)
Ravasco *et al*. (2007)	Portugal	NR	To investigate the influence of inflammatory cytokines, pro-cachectic, immunomodulatory, and pro-angiogenic on REE, weight, and nutritional intake and to explore potential interactions between their circulating concentrations and colorectal cancer stage/histologic differentiation and response to radiotherapy	Total participants with cancer (n=101)	80 (79.2%)	65 ± 12 (37-88)	Colorectal adenocarcinoma	85%	6.9% stage I, 7.9% stage II, 50.4% stage III, 34.6% stage IV

Richey *et al*. (2007)	USA	Patients were recruited from Head and Neck Tumor Board conferences and outpatient clinics	Primary objective: To more completely characterize cancer cachexia in HNSCC in terms of associated clinical variables, serum cytokines, measures of inflammation and anaemia, and cachexia factors. Secondary objective: To investigate tumour cytokine and cachexia factor expression	Total participants with cancer (n=24); cachectic patients (n=11); non-cachectic patients (n=13)	In the cachectic group: 8 (73%); in the non-cachectic group: 2 (15%)	Mean age in the cachectic group: 57 ± 12; mean age in the non-cachectic group: 58 ± 9 (range NR)	HNSCC	70.8%	70.8% stage IV- other stages NR
Suh *et al*. (2007)	Korea	Palliative care	To prove serum CRP level as a predictor of survival time, considering patient's symptoms, physical examination findings, and various serological variables in terminally ill cancer patients with a prospective cohort design	Total participants with advanced cancer (n=44)	25 (56.8%)	Median age: 68 years (30–87)	Mixed	100%	NR
Al Murri *et al*. (2006)	UK	Oncology centre	To examine the relationship between the GPS and survival in patients with metastatic breast cancer	Total participants with metastatic breast cancer (n=96)	All female (0%)	21 (21.8%) patients were ≤ 50 years old; 75 (78.1%) were >50 years of age (range NR)	Breast	100%	NR

Kayacan *et al*. (2006)	Turkey	NR	To determine the role TNF-α and IL-6, implicated for cancer cachexia development in inoperable NSCLC patients.	Total participants (n=56); with cancer (n=44; 23 cachectic and 21 non-cachectic); healthy smokers for the control (n=12)	51 (91%)	In the cachexia group: 59.9 ± 11.8; in the non-cachectic group: 55.9 ± 10.7; in the control group: 52.1 ± 12.3	NSCLC	100%	In the cachexia group: 18 (60.9%) stage IV and 4 (17.4%) stage IIIb. In the non-cachexia group: 10 (47.6%) stage IV and 6 (28.6%) stage IIIb.
Ramsey *et al*. (2006)	UK	Specialist renal cancer unit	To examine the value of the GPS, compared with established scoring systems, for predicting cancer-specific survival in patients with metastatic renal cancer	Total participants with advanced cancer (n=119)	85 (70.8%)	56 (47%) of patients were ≤ 60 years of age; 63 (52.9%) were > 60 years' old	Renal cancer	100%	NR
Di Nisio *et al*. (2005)	The Netherlands	NR	To evaluate: 1) the prognostic value for survival of circulating levels of IL-6, IL-10, IFN-a, and P-selectin in all the 141 patients at the time of entry into the study; 2) the association between these circulating markers and prognosis in the group of patients treated with	Total participants with advanced cancer (n=141)	83 (58.8%)	62.3 (38.4-85.7)	Mixed	100%	NR

			LMWH; and 3) whether the beneficial survival effects observed in the MALT study were related to the influence of LMWH on plasma levels of soluble P-selectin or cytokines						
Rich *et al*. (2005)	France	General hospital-unspecified	To evaluate the role of circulating cytokines in the production of symptoms in cancer patients	Total participants with advanced cancer (n=80); with near normal circadian rhythm (n=40); with dampened circadian rhythm (n=40)	In group 1 (good rhythm): 23 (57.5%); group 2 (dampened rhythm): 29 (72.5%)	Median age in group 1 (good rhythm): 59.5 (42-76); median age in group 2 (dampened rhythm): 60 (36-74)	Colorectal cancer	100%	NR
Bolukbas *et al*. (2004)	Turkey	Hospital-oncology department	Primary aim: to evaluate the serum leptin concentration in patients with advanced gastrointestinal cancer and to determine the factors such as gender, age and BMI which may be related with this peptide. Secondary aim: to find out the relationship of leptin with weight loss and to compare the serum leptin	Total participants (n=69); with advanced gastrointestinal cancer (n=44); healthy controls with stable weight (n=25)	In the cancer group: 29 (66%); in the non-cancer group: 12 (48%)	Median age in the gastric cancer group: 58 (range 34-80); in the colorectal cancer group: 59 (range 33-80); in the malignant group: 58 (range 33-80); and in the control group: 38	Gastrointestinal	100%	100% stage III

			concentrations in distinct type of gastrointestinal cancers			(range 22-67)			
De Vita *et al*. (2004)	Italy	NR	To evaluate IL-6 serum levels and their prognostic significance in patients with advanced GI cancer	Total participants with advanced cancer (n=68)	46 (67.6%)	34 (50%) of patients were ≤ 60 years of age; 34 (50%) were > 60 years' old	Gastric (n=30) and colorectal (n=38)	100%	10.2% stage III, 89.7% stage IV
Dulger *et al*. (2004)	The Netherlands	NR	To investigate the serum levels of leptin, TNF-α , IL-1b, IL-6, insulin, and growth hormone in patients with upper GI cancer and cachexia.	Total participants (n=54); with cancer cachexia (n=19); with cancer and no cachexia (n=20); healthy controls (n=15)	25 (64%)	Median age: 53.72 (28-76)	Esophogeal	100%	All stage IV
Elahi *et al*. (2004)	UK	Hospital-department of Clinical Biochemistry	To examine the relationship between the combination of hypoalbuminemia and an elevated circulating concentration of CRP and survival in patients with advanced GI cancer	Total participants with advanced cancer (n=165)	105 (64%)	110 (67%) of patients were < 70 years old and 55 (33%) of patients were > 70 years' old	Gastric: 66 (40%) and colorectal: 99 (60%) cancer	100%	NR
Jamieson *et al*. (2004)	UK	Palliative care	To examine the relationship between adiponectin and the systemic inflammatory	Total participants (n=33); with advanced cancer (n=20);	In the cancer group: 12 (65%); in the control	Median age in the cancer group: 64 (43-79); in the control	NSCLC	100%	NR

			response in weight-losing patients with NSCLC	healthy controls (n=13)	group: 6 (46%)	group: 65 (46-74)			
Songur *et al*. (2004)	Turkey	NR	To initiate a prospective clinical protocol for investigation of serum levels of IL-6 in advanced NSCLC patients and analyzed the influence on malnutrition and survival	Total participants (n=91); with advanced cancer (n=71); healthy controls (n=20)	65 (91.5%)	38 patients < 60 years old; 33 patients ≥ 60 years' old	NSCLC	100%	48% stage III, 52% stage IV
Scott *et al*. (2003)	UK	NR	To examine the relationships between weight loss, the systemic inflammatory response and quality of life in patients with inoperable NSCLC.	Total participants with advanced cancer (n=106); weight-loss group (n=45); weight-stable group (n=61)	62 (58.4%)	Median age: 69 (43-87)	NSCLC	100%	73.6% stage III, 26.4% stage IV
Aleman *et al*. (2002)	Spain	NR	To analyse the relation of serum leptin levels with the nutritional status and the inflammatory response in patients with advanced NSCLC	Total participants (n=106); with advanced cancer (n=76); without cancer (n=30)	67 (88%)	Median age: 62.5 years (36–75)	NSCLC	100%	7.8% stage IIIA, 39.4% stage IIIB, 52.6% stage IV
Orditura *et al*. (2002)	Italy	NR	To determine if IL-8 serum levels may have prognostic significance in patients with advanced NSCLC	Total participants (n=85); with advanced cancer (n=60); healthy	49 (81.6%)	28 patients were ≤ 60 years old, and 32 patients > 60 years	NSCLC	100%	46.7% stage III, 53.3% stage IV

				controls (n=25)					
Scott *et al*. (2002)	UK	NR	To examine the relationship between the magnitude of the systemic inflammatory response and weight loss, PS and survival in patients with inoperable NSCLC	Total participants with cancer (n=106)	62 (58.4%)	Median age: 69 (43-87)	NSCLC	100%	73.6% stage III, 26.4% stage IV
Jatoi *et al*. (2001)	USA	NR	1) To investigate whether circulating concentrations of NPY and leptin differ among cancer patients with advanced disease compared with normative values derived from a healthy control population, and 2) To explore whether serum concentrations of NPY, leptin, and/or CCK8 may be able to serve as correlates of anorexia severity in patients with advanced cancer	NI	48 (66%)	62 (range 42-84)	NR	100%	NR
Mantovani *et al*. (2001)	Italy	NR	To examine the correlation between serum levels of leptin, IL-6 and TNF-α in a population of non-cachectic but	Total participants (n=58); with advanced cancer (n=29); healthy	In the cancer group: 14 (48.2%); in the control group: 13 (44.8%)	Mean age in the cancer group: 55 (41-77); in the control	Mixed	100%	1 (3.4%) stage IIIA, 28 (96.6%) stage IV

			advanced-stage cancer patients at various sites and to determine the correlation between leptin and pro-inflammatory cytokines and the most relevant clinical parameters of patients, such as BMI and PS.	controls (n=29);		group: 45 (20-80)			
Mantovani *et al*. (2000)	Italy	NR	To determine whether there is a relationship between the production and/or release of pro-inflammatory cytokines and leptin at the source cell level	Total participants (n=32); with advanced cancer (n=16); healthy controls (n=16)	8 (50%)	58.3 (range 41–71)	Mixed	100%	10 patients (62.5%) with stage IV, and 6 (37.5% with stage III
Nenova *et al*. (2000)	Bulgaria	NR	To investigate the serum levels of TNF-α cytokine in advanced carcinoma patients and to attempt an evaluation of its prognostic significance and its relation to cancer cachexia	Total participants (n=87); with advanced cancer (n=71); clinically healthy controls (n=16)	20 (28.1%)	Average age 53.6 ± 1.8 years	Mixed	100%	100% stage IV
O'Gorman *et al*. (1999)	UK	NR	To examine the temporal relationship between weight loss, appetite, performance status, and acute-phase protein response in	Total participants with cancer (n=50); with weight loss after 6-8 weeks of observation (n=16); with	35 (70%)	Median age: 68 (44-78)	Mixed	100%	NR

			patients with GI cancer	weight gain after 6-8 weeks (n=9); and patients who were stable after 6-8 weeks (n=25)					
Okada *et al*. (1998)	Japan	NR	To investigate the relationship between serum IL-6 levels and the clinical status of pancreatic cancer	Total participants (n=100); with pancreatic cancer (n=55); patients with chronic pancreatitis (n=25); normal healthy adults (n=20)	38 (69%)	61.2 ± 7.3 (range NR)	Pancreatic cancer	91%	9.9% stage II, 30.1% stage II, 60% stage IV
Wallace *et al*. (1998)	UK	NR	NR	Total participants (n=54); with advanced cancer (n=27); healthy controls (n=27)	In the cancer group: 14 (82.3%); in the control group: 14 (51.8%)	Median age in the cancer group: 62 (range 48-74); median age in the control group: 59 (range 49-67)	Gastrointestinal	100%	NR
Maltoni *et al*. (1997)	Italy	Palliative care centres	To better define the prognosis of terminal patients by evaluating the prognostic capacity of certain easily detectable biological parameters	Total participants with advanced cancer (n=530)	300 (57.8%)	226 (43.5%) of patients were ≤ 65 years old; 293 (56.5%) were > 65 years' old	Mixed	100%	NR

Simons *et al*. (1997)	The Netherlands	NR	To investigate the relationship between total plasma leptin, weight loss, body composition, appetite and REE in a group of male lung-cancer patients	Total participants with cancer and weight loss of 10% pre-illness (n=21)	All male (100%)	Median age: 69 (56-82)	Lung	76%	23.8 stage III, 52.3% stage IV

Abbreviations: *ADL: Activities of daily living; BMI: Body Mass Index; CCS: Cancer-specific survival; CRF: Cancer-related fatigue; CRP: C-reactive protein; ECOG: The Eastern Cooperative Oncology Group; ED: Emergency department; EOC: Endothelial ovarian cancer; ESAS: Edmonton Symptom Assessment System; GI: Gastrointestinal; GPS: Glasgow Prognostic Score; IFN: Interferon; IGF: Insulin-like growth factor; IGFBP: Insulin-like growth factor binding protein; IL-: Interleukin; LMWH: Low molecular weight heparin; mGPS: Modified Glasgow Prognostic Score; MNA: Mini nutritional assessment; NLR: Neutrophil/Lymphocyte ratio; NPY: Neuropeptide Y; NR: Not reported; NSCLC: Non-small-cell lung carcinoma; OS: Overall survival; PFS: Progression free survival; PI: Prognostic index; PLR: Platelet/Lymphocyte ratio; PNI: Prognostic nutritional index; PROM: Patient-reported outcome measures; PS: Performance status; QOL: Quality of life; TNF: Tumor necrosis factor*

Blood biomarkers were examined in 138 studies, 4 studies examined biomarkers in cerebrospinal fluid (CSF), 3 in urine, and 16 (11%) did not report the type of biological material. Of the studies that reported the assay technique, diverse assays were used (n=20), with Enzyme-linked immunosorbent assay (ELISA) being the most common (n=62; 58%). Forty-four studies (29%) did not report the specific assay used. Of these, 21 studies (48%) were routinely measured biomarkers (Tables 3.3 and 3.4).

3.4.2 Delirium and advanced cancer biomarkers

A total of 41 biomarkers were found to be common in both delirium and advanced cancer syndrome studies. The five most commonly studied biomarkers were C-reactive protein (CRP) (n=79), interleukin (IL)-6 (n=58), tumor necrosis factor alpha (TNF- α) (n=42) IL-10 (n=21) and IL-8 (n=24). Of these, 24 biomarkers had a positive association with delirium, cancer prognosis or a cancer syndrome in at least one study. No cancer studies reported having any participants with delirium, and of the delirium studies, six reported participants with cancer. Figure 3.2 illustrates two main populations identified from this systematic review, with the centre showing the 'true overlap' defined as studies that included participants with both delirium and cancer (n=6 studies).

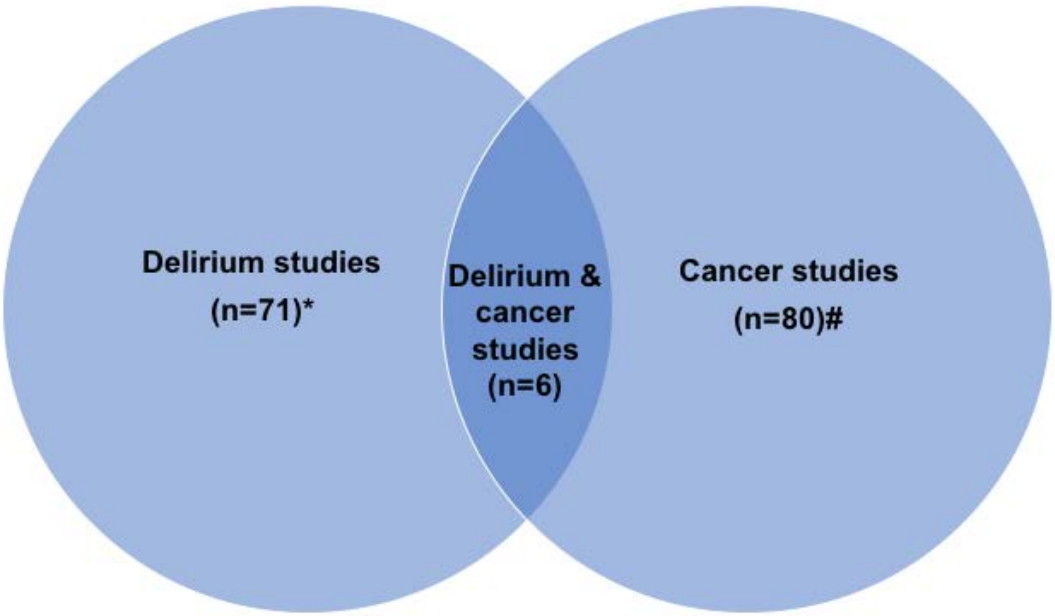

Figure 3.2 Conceptual model illustrating the 'true overlap' of delirium and advanced cancer biomarker studies

** Cancer as a comorbidity not measured/reported; # Delirium as a concurrent illness or comorbidity not measured/reported*

In two of these studies, all participants in the study had cancer; in another, 64.2% of participants had cancer; in the remaining three studies, less than 30% of all participants had cancer. In three of the studies, 100% of participants who had delirium also had cancer, in another two, 26% and 27% of the delirium cohorts had cancer, and in the remaining study 14% of the delirium participants had cancer (Table 3.3). Although only six delirium studies reported co-existing cancer, there is still uncertainty as to how many participants in both groups of studies had both delirium and cancer. The two most common biomarkers in these six studies that reported a positive association with delirium were CRP (n=3) and IL-6 (n=3). It is unclear however whether these biomarkers were predominantly associated with delirium or the cancer, as three of the six studies grouped the delirium participants together, irrespective of their cancer comorbidity.

Table 3.3 Characteristics of assays and main findings of included delirium studies*

Author and year	Participants		Endpoints	Biomarkers studied	Biological material	Assay method	Covariates accounted for in multivariate analysis	Results	
	Total (N)	Sample						Positive association with at least one delirium endpoint**	Negative association
Egberts et al. (2017)[8]	86	Aged ≥65 admitted to geriatrics	Delirium presence	CRP, NLR	Blood	Flow cytometry	Age, gender, the CCI score, CRP level, and WBC counts	NLR	CRP
Kozak et al. (2017)[9]	60	Patients with acute ischemic stroke	Delirium presence	TNF-α, IL-1β, IL-18, BDNF, NSE	Serum	ELISA	No multivariate analysis	None	TNF-α, IL-1β, IL-18, BDNF, NSE
Tomasi et al. (2017)[10]	38	Patients with sepsis-associated delirium and non-sepsis associated delirium[a]	Delirium presence	IL-6, IL-8, IL-10, BDNF, VCAM-1, ICAM-1, MPO, cathepsin, PDGF-AA, PDGF-AB/BB, RANTES, PAI, NCAM	Plasma	ELISA	No multivariate analysis	IL-6, IL-10, RANTES, VCAM-1, ICAM-1, PDGF-AB/BB	IL-8, MPO, BDNF, NCAM, PDGF-AA, PAI, Cathepsin D
Vasunilashorn et al. (2017)[11]	560	Patients ≥70 undergoing major non-cardiac surgery[a]	-Delirium incidence -Delirium duration -Delirium severity	CRP	Plasma	ELISA	Age, sex, surgical procedure, anesthesia route, CCI and POST-OP infectious complications	CRP	None
Chu et al. (2016)[12]	103	Patients aged ≥70	Delirium incidence	IGF-1	Serum	ELISA	MMSE and age	None	IGF-1

		admitted for acute or elective vertebral, knee, or hip surgery							
Dillon et al. (2016)[13]	Entire sample (n-566); pooled sample (n=150)	Dementia-free adults ≥70 years old undergoing major scheduled non-cardiac surgery[a]	Delirium incidence	Proteomics[b]	Plasma	ELISA	No multivariate analysis	CRP (PRE-OP, PACU, POD2)	CRP (PO1MO)
Guo et al. (2016)[14]	572	Aged ≥65 with hip fractures undergoing THA[a]	-Delirium presence -Delirium prevalence	CRP, Alb, Hb	Blood	NR	NR	CRP, Alb, Hb	None
Karlicic et al. (2016)[15]	120	Patients with delirium in the psychiatric ICU	Lethal outcome	CRP	NR	NR	Age, pneumonia and CRP	CRP	None
Neerland et al. (2016)[16]	149	Patients with acute hip fracture	Delirium presence	CRP, IL-6, sIL-6R	CSF	ELISA	No multivariate analysis	CRP[b]	sIL-6R, IL-6
Shen et al. (2016)[17]	140	Patients ≥65 undergoing elective gastrointestinal tumor resection[a]	-Delirium incidence -Delirium severity	IGF-1, CRP, IL-6	Serum	ELISA	NR	IGF-1, CRP, IL-6	None
Sun et al. (2016)[18]	112	Oral cancer patients[a]	Delirium incidence	IL-6, CRP, PCT, cortisol, AB1-40	Blood	ELISA	No multivariate analysis	IL-6, CRP, PCT, cortisol, AB1-40	None

Yen et al. (2016)[19]	98	Patients undergoing elective knee replacement surgery	Delirium incidence	IGF-1	Serum	ELISA	Obstructive sleep apnea, IGF-1 and diabetes	None	IGF-1
Avila-Funes et al. (2015)[20]	141	Patients aged ≥70 admitted to tertiary care hospital	Delirium incidence	Cortisol, E2	Blood	Radioimmunoassay	Age, BMI, comorbidity, MMSE, previous history of delirium, BUN/Cr ratio, and cortisol levels	E2	Cortisol
Brum et al. (2015)[21]	70	Oncology inpatients[a]	Delirium presence	BDNF, TNF-α	Serum	ELISA + Flow cytometry	No multivariate analysis	None	BDNF, TNF-α
Egberts et al. (2015)[22]	86	Patients admitted to Internal Medicine and Geriatrics[a]	Delirium presence	NP, IL-6, IGF-1	Plasma	HPLC	Age, gender and the CCI, and those including NP were adjusted for age, gender, CCI, tertiles of eGFR and CRP	NP, IL-6, IGF-1	None
Foroughan et al. (2015)[23]	200	Elderly patients admitted to general hospital	Delirium presence	CRP, Hb	Blood	NR	NR	CRP, Hb	None
Skrede et al. (2015)[24]	10	Patients with hip fracture	Delirium incidence	MCP-1	Serum	ELISA	No multivariate analysis	MCP-1	None
Vasunilashorn et al. (2015)[25]	566	Patients ≥70 undergoing major non-	Delirium incidence	IL-1B, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IFN-	Plasma	Luminex assay	No multivariate analysis	IL-1B, IL-2, IL-6, IL-8, IL-12, VEGF, IL-5, TNF-α	GM-CSF, IFN-γ, IL-10, IL-4

		cardiac surgery[a]		γ, GM-CSF, TNF-α, VEGF					
Alexander et al. (2014)[26]	77	ICU patients requiring mechanical ventilation	-Delirium presence -Delirium duration	IL-6, IL-8, IL-10, APOE	Serum	ELISA	Age, sex, APACHE III, CCI, 24-hour propofol dose, 24-hour narcotic dose, and 24-hour benzodiazepine dose.	APOE	IL-10, IL-8, IL-6
Baranyi et al. (2014)[27]	34	Patients undergoing surgery for CPB[a]	Delirium incidence	sIL-2R	Serum	ELISA	No multivariate analysis	sIL-2R	None
Cape et al. (2014)[28]	43	Patients >60 years old with hip fracture	-Delirium incidence -Delirium prevalence	IL-1β, IFN-γ, GFAP, IGF-1, IL-1RA	CSF	ELISA	Presence of prior dementia	IL-1β, IL-1RA[c]	GFAP, IFN-γ, IGF-1
Capri et al. (2014)[29]	351	Patients admitted for any kind of emergency or elective surgery[a]	Delirium presence	IL-1β, IL-2, IL-6, IL-8, IL-10, TNF-α	Plasma	ELISA	Age, comorbidity, ADL, IADL, HADS and pre-op benzodiazepines intake	IL-6, IL-2	IL-8, IL-10, IL-1β (UDL), TNF-α (UDL)
Chen et al. (2014)[30]	372	Patients aged ≥65 who underwent surgery for a femoral neck fracture or an intertrochanteric fracture[a]	Delirium presence	LP	Plasma	ELISA	Age, ASA, type of surgery and plasma leptin level	LP	None

Hatta et al. (2014)[31]	29	Patients aged 65-89 admitted to hospital due to an emergency	Delirium incidence	NK cell activity, IL-1β	Blood	ELISA	No multivariate analysis	NK cell activity	IL-1β
Kazmierski et al. (2014)a[32]	113	ICU patients scheduled for CABG surgery with CPB	Delirium incidence	Cortisol, IL-2, TNF-α, HCY, cobalamin	Serum	CLIA	NR	Cortisol, IL-2, TNF-α, HCY	Cobalamin
Kazmierski et al. (2014)b[33]	113	ICU patients scheduled for CABG surgery with CPB	Delirium incidence	IL-2, TNF-α	Plasma	CLIA	NR	Il-2, TNF-α	None
Ritchie et al. (2014)[34]	710	Patients admitted to a Medical Acute Admission Unit	-Delirium incidence -Delirium severity	CRP	NR	NR	NR	CRP	None
Ritter et al. (2014)[35]	78	ICU patients	Delirium presence	TNF-α, STNFR-1, STNFR2, APN, IL-1β, IL-6, IL-10	Plasma	ELISA	Sedation and sepsis	STNFR-1, STNFR2, IL-1β	TNF-α, IL-6, IL-10
Zhang et al. (2014)[36]	223	ICU patients	Delirium presence	CRP	Plasma	i-CHROMATM	Age, sex, APACHE II, intubation status, living alone, physical restraint, alcohol drinking, smoking, type of medical condition, and hospital LOS before ICU admission	CRP	None

Cerejeira et al. (2013)[37]	101	Patients ≥60 years without dementia undergoing elective hip arthroplasty[a]	Delirium incidence	Cortisol, IGF-1, CRP, IL-6, IL-8, IL-10	Plasma	ELISA	No multivariate analysis	Cortisol	CRP, IL-6, IL-8, IL-10, IGF-1
Colkesen et al. (2013)[38]	52	Patients with ACS admitted to coronary ICU[a]	Delirium presence	Cortisol, troponin I, MB-CK	Serum	CLIA	NR	Cortisol	Troponin I, MB-CK
Kazmierski et al. (2013)[39]	113	ICU patients scheduled for CABG surgery with CPB	Delirium incidence	Cortisol, IL-2	Plasma	CLIA	NR	Cortisol[d], IL-2	None
Liu et al. (2013)[40]	338	Patients aged ≥60 undergoing major non-cardiac surgery[a]	Delirium incidence	IL-6	Blood	ELISA	Age, education, history of coronary artery disease, alcoholism, PRE-OP ASA ≥ 3, PRE-OP NYHA ≥ 2, PRE-OP MMSE score ≤ 24, PRE-OP serum IL-6 ≥ 7.5 ph/ml, POST-OP serum IL-6, POST-OP VAS pain level	IL-6	None
Plaschke et al. (2013)[41]	114	1. Patients following heart surgery[a]	Delirium incidence	IL-6	Plasma	ELISA	No multivariate analysis	None	IL-6

		2. Patients on the non-cardiac ICU[a]							
Skrobik et al. (2013)[42]	99	ICU patients[a]	Drug-induced coma and delirium	TNF-α, IL-1β, IL-1RA, IL-6, IL-8, IL-10, IL-17, MIP-1B, MCP-1	Blood	BCA	Fentanyl, midazolam, CYP3A4/5, P-gp inhibitors	IL-6	TNF-α, IL-17, IL-8, MCP-1, IL-1RA, MIP-1B, IL-10, IL-1β
Westhoff et al. (2013)[43]	61	Patients ≥75 admitted for surgical repair of acute hip fracture[a]	Delirium incidence	EGF, eotaxin, FGF-2, Flt-3L, Fractalkine, G-CSF, GM- CSF, IFN-a2, IFN-γ, IL-1RA, IL-1α, IL-1β, IL-2, sIL-2Ra, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12p40, IL-12p70, IL-13, IL-15, IL-17, IP-10, MCP-1, MCP-3, MDC, MIP-1α, MIP-1β, PDGF-AA, PDGF-AB/BB, RANTES, sCD40L, TGF-α, TNF-α, TNF-β, VEGF	Blood + CSF	Lumbar punctures and Luminex assays	No multivariate analysis	Flt-3L, IL-1RA, IL-6	EGF, eotaxin, FGF-2, Fractalkine, G-CSF, GM-CSF, IFN-a2, IFN-γ, IL-1α, IL-1β, IL-2, sIL-2Ra, IL-3, IL-4, IL-5, IL-7, IL-8, IL-9, IL-10, IL-12p40, IL-12p70, IL-13, IL-15, IL-17, IP-10, MCP-1, MCP-3, MDC, MIP-1α, MIP-1β, PDGF-AA, PDGF-

									AB/BB, RANTES, sCD40L, TGF-α, TNF-α, TNF-β, VEGF
Bakker et al. (2012)[44]	201	Patients undergoing cardiac surgery	Delirium incidence	Cre	Plasma	NR	NR	Cre	None
Baranyi et al. (2012)[45]	34	Patients undergoing surgery for cardiopulmonary bypass[a]	Delirium incidence	Alb, CRP	Serum	NR	No multivariate analysis	Alb	CRP
Cerejeira et al. (2012)[46]	101	Patients aged ≥60 undergoing elective total hip arthroplasty[a]	Delirium incidence	IL-8, IL-1β, IL-6, IL-10, TNF-α, CRP, AChE, BuChE	Blood	ELISA (Multiplex assay)	No multivariate analysis	AChE, BuCHE	CRP, IL-1β, TNF-α, IL-6, IL-10
Girard et al. (2012)[47]	138	Mechanically ventilated ICU patients[a]	Delirium incidence	CRP, MMP-9, MPO, NGAL, sTNFR1, D-dimer, protein C, PAI-1, VWF	Plasma	ELISA	Age, severity of illness, and severe sepsis	MMP-9, Protein C, sTNF-R1	CRP, MPO, NGAL, D-dimer, PAI-1, VWF
Osse et al. (2012)[48]	125	Patients ≥70 undergoing elective cardiac surgery	Delirium incidence	NP, BH4, HVA, Glu, Ser, Gly, Cit, Tau, Arg, Met, Try, Tyr, Phe, Leu, Ile, Val, Try:LNAA, Tyr:LNAA, Phe:LNAA, Phe:tyr, Cit:arg, Tau:Ser 9 met	Plasma	HPLC	BH4, total biopterin, HVA, ratios of Trp:LNAA, tyr:LNAA, phe:LNAA, phe:Tyr, Cit:Arg, TSM ratio; baseline CRP, plasma	NP, HVA	BH4, Glu, Ser, Gly, Cit, Tau, Arg, Met, Try, Tyr, Phe, Leu, Ile, Val, Try:LNAA,

							urea, cre, age, sex, type of surgery, acute cardiac surgical risk factors, EuroSCORE, MMSE, pre-op anxiety and depression, and chronic medical comorbidity		Tyr:LNAA, Phe:LNAA, Phe:tyr, Cit:arg, Tau:Ser 9 met
Bisschop et al. (2011)[49]	143	Patients undergoing surgery for hip fracture	-Delirium presence -Delirium severity	Cortisol, insulin, glucose	Blood	NR	Sex, age, pre-existing cognitive impairment, pre-existing functional impairment, cortisol, glucose, insulin, insulin:glucose	Cortisol	Glucose, insulin
Holmes et al. (2011)[50]	222	Patients with mild to severe AD	-Presence of sickness behaviour -Delirium incidence	IL-6, TNF-α, CRP	Blood	ELISA	Baseline ADAS score, age, gender, and the presence of delirium	None	Il-6, TNF-α, CRP
Lee et al. (2011)[51]	65	Patients ≥65 who had undergone hip surgery[a]	Delirium incidence	CRP	Blood	NR	No multivariate analysis	None	CRP
McGrane et al. (2011)[52]	87	Mechanically ventilated, medical and surgical ICU patients[a]	Delirium/coma-free days	PCT, CRP	Blood	TRACE Assay analysis	Age, APACHE II, sedation group (dexmedetomidine vs. lorazepam), and sepsis	PCT	CRP

Morandi et al. (2011)[53]	110[e]	Mechanically ventilated medical ICU patients	Delirium presence	IGF-1	Blood	Radioimmunoassay	Age, severe sepsis and APACHE II		IGF-1
Van der Boogaard et al. (2011)a[54]	100	ICU patients[a]	Delirium presence	TNF-α, IL-1β, IL-6, IL-8, IL-17, IL-18, MIF, IL-1RA, IL-10, MCP-1, HNP-1, CRP, PCT, Ab1-42, Ab1-40, S100B, cortisol	Plasma	Luminex assay, immunologic detection, and an immunometric assay	NR	Delirium vs non-delirium: IL-8[f], IL-10[g], Ratio A$\beta_{1-42/40}$, TNF-α, IL-6, MIF, IL-1RA, MCP-1, PCT, cortisol, ABN-42 Inflamed delirium vs non-inflamed delirium: IL-8, TNF-α, IL-18, IL-1RA, MCP-1, PCT, CRP, ratio A$\beta_{1-40/N-40}$, ratio A$\beta_{N-42/40}$,	Delirium vs non-delirium: IL-1B, IL-17, IL-18, HNP, CRP, S100B, Tau, Ratio Tau/Aβ_{1-42}, Aβ_{1-42}, Aβ_{1-40}, Aβ_{N-42}, Aβ_{N-40}, Ratio A$\beta_{N-42/40}$, Ratio A$\beta_{1-42/N-42}$, Ratio A$\beta_{1-40/N-40}$ Inflamed delirium vs non-inflamed delirium: IL-1β, IL-6, MIF, IL-10, cortisol, ABN-42, IL-1B, IL-17, HNP, S100B, Tau, tau/AB1-42, Ratio

									Tau/Aβ_{1-42}, Aβ_{1-42}, Ratio A$\beta_{1-42/N-42}$Aβ_{1-40}, Ratio A$\beta_{1-42/40}$, Aβ_{N-42}, Aβ_{N-40}
Van der Boogaard et al. (2011)b[55]	20	ICU patients	Delirium presence	Proteomics[h]	Urine + Blood	NR	No multivariate analysis		CRP, Cre
Burkhart et al. (2010)[56]	113	Patients aged ≥65 undergoing elective cardiac surgery with CPB	Delirium presence	CRP	NR	NR	EuroSCORE, Leucocytes, CRP max, Fentanyl intraoperatively, duration of mechanical ventilation, packed RBC, and treated PONV	CRP	None
Mu et al. (2010)[57]	243	Patients undergoing elective CABG surgery	Delirium incidence	Cortisol	Serum	CLIA	Age, history of diabetes mellitus, pre-op LVEF, PRE-OP NYHA, pre-op EuroSCORE score, duration of surgery, post-op APACHE II, serum cortisol, post-op LVEF, post-op complications (within 1 day)	Cortisol	None

Pearson et al. (2010)[58]	20	Patients ≥60 with acute hip fracture awaiting surgery[a]	Delirium presence	Cortisol	CSF + serum	ELISA	No multivariate analysis	Cortisol	None
Plaschke et al. (2010)[59]	114[i]	Patients undergoing elective CABG[a]	Delirium incidence	Cortisol, IL-6	Plasma	ELISA	No multivariate analysis	IL-6, cortisol	None
Tsruta et al. (2010)[60]	103	ICU patients[a]	-Delirium incidence -Delirium prevalence	CRP	Serum	Immunotur bidimetry	Age, APACHE II, coexistence of infection, use of a mechanical ventilator and length of ICU stay	CRP	None
Van Munster et al. (2010)[61]	120	Patients ≥65 admitted for hip fracture surgery	Delirium presence	Cortisol, IL-6, IL-8, S100B	Plasma	CBA	Age, infection, pre-existent cognitive and functional impairment	Cortisol, S100B, IL-6, IL-8	None
Adamis et al. (2009)[62]	67	Patients aged ≥70 admitted to elderly care unit	-Delirium incidence -Delirium severity	APOE, IL-1α, IL-1β, IL-1RA, IL-6, TNF-α, IGF-1, IFN-γ, LIF	Serum	ELISA	No Multivariate analysis	IGF-1, IFN-γ, IL-1RA,	APOE, IL-1α, IL-1β, IL-6, TNF-α, LIF
Van Munster et al. (2009)[63]	120	Patients ≥65 admitted for hip fracture surgery	Delirium incidence	S100B, NSE	Blood	ECLIA	No multivariate analysis	S100B	NSE
Lemstra et al. (2008) (88)	68	Patients undergoing surgery for hip fracture	Delirium incidence	CRP, IL-6, IGF-1	Blood	ELISA	No multivariate analysis	None	CRP, IL-6, IGF-1
Pfister et al. (2008)[64]	16[j]	Patients with sepsis	Sepsis-related delirium presence	CRP, IL-6, S-100B, cortisol	Serum	Solid-phase enzyme-labelled chemilumin escent	No multivariate analysis	CRP, S100B, Cortisol	IL-6

						sequential immunometric assay			
Rudolph et al. (2008)[65]	42	Patients undergoing cardiac surgery	Delirium incidence	IL-1β, IL-1RA, IL-6, IFN-a, TNF-α, TNF-R1, TNF-R2, IL-2, IL-2R, IL-7, IL-12p40_p70, IL-15, IFN-γ, IP-10, IL-4, IL-5, IL-10, IL-13, MIP-1a, MIP-1b, MIG, Eotaxin, RANTES, CCL-2, IL-8, GM-CSF, IL-17, DR5	Serum	ELISA	No multivariate analysis	MIP-1a, MIP-1b, MIG, Eotaxin, RANTES, CCL-2	IL-1β, IL-1RA, IL-6, IFN-a, TNF-α, TNF-R1, TNF-R2, IL-2, IL-2R, IL-7, IL-12p40_p70, IL-15, IFN-γ, IP-10, IL-4, IL-5, IL-10, IL-13, IL-8, GM-CSF, IL-17, DR5
Van Munster et al. (2008)[66]	98	Patients ≥65 admitted for hip fracture surgery	Delirium presence	IL-6, IL-8, IL-12 (TNF-α, IL-1β, and IL-10 excluded from analysis)	Plasma	CBA	No multivariate analysis	Il-6, IL-8	IL-12
Adamis et al. (2007)[67]	164	Acutely ill patients admitted to elderly care unit	-Delirium presence -Delirium resolution	APOE, IL-1α, IL-1β, IL-1RA, IL-6, TNF-α, IGF-1, IFN-γ, LIF, CRP	Serum	ELISA	LogAPACHE II, DRS, CRP, Gender, TNF-α, IFN-g, IGF-I, IL-1RA, and possession of APOE epsilon 4 allele	IGF-1, APOE, IFNγ	IL-6, IL-1α, IL-1β, IL-1RA, TNF-α, LIF, CRP
de Rooij et al. (2007)[68]	185	Patients aged ≥65 admitted to the Department	Delirium presence	IL-1β, IL-6, IL-8, IL-10, TNF-α, CRP	Serum	CBA	Age, cognitive impairment, and infection	IL-6, IL-8	IL-1β, IL-10, TNF-α, CRP

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Plaschke et al. (2007)[69]	37	ICU patients	Delirium presence	SAA, IL-6	Blood	ELISA	No multivariate analysis for IL-6	None	SAA, IL-6
White et al. (2005)[70]	283	Patients ≥75 from emergency medical admissions	-Delirium prevalence -Delirium incidence	CRP, Alb, AChE, BuChE, Aspirin esterase, Benzoylcholinesterase	Plasma	ELISA	No multivariate analysis	CRP, Alb, AChE, BuChE, Aspirin esterase, Benzoylcholinesterase	None
Wilson et al. (2005)[71]	100	Patients ≥75 suffering from significant physical illness	Delirium incidence	IGF-1	Plasma	CLIA	Depression, IGF-1 levels and IQCODE scores	IGF-1	None
Beloosesky et al. (2004)[72]	32	Patients undergoing surgery for hip fracture	-Cognition -Post-operative complications (including delirium) -Post-operative function -Mortality	CRP, FBG	Blood	Nephelometric assay	Unclear	CRP	FBG
Robertsson et al. (2001)[73]	172	Patients <80 referred to the neuropsychiatric diagnostic unit with suspected dementia	Delirium presence	Cortisol	Serum	NR	Age, severity of dementia and severity of delirium	Cortisol	None
Van der Mast et al. (2000)[74]	296[k]	Patients admitted for elective	Delirium incidence	Try, Ile, Val, Met, Leu, Tyr, Phe, Ser, cortisol	Plasma	HPLC	Plasma amino acids; the ratios of	Trp, Trp:LNAA	Cortisol, Ile, Val, Met, Leu,

		cardiac surgery					Trp/oLNAA, Tyr/oLNAA, and Phe/oLNAA; albumin; cortisol; and thyroid functions.		Tyr, Phe, Ser
Van der Mast et al. (1999)[75]	296	Patients admitted for elective cardiac surgery	Delirium incidence	Alb, cortisol, 5-HT, try, phe, val, leu, Ile, try:tyr:phe	Plasma	HPLC	Age, inclusion as an in-patient, use of nifedipine, MMSE score, GHQ score, DAL score, Albumin, ratio rT3:T3; ratio Phe:oLNAA	Alb, phe:Ile, Phe:Leu, Phe:val, Phe:tyr, Phe:try	Cortisol, 5-HT
Gustafson et al. (1993)[76]	155	Stroke patients	Delirium presence	Cortisol	Plasma	Radioimmunoassay	Intercept, basal plasma cortisol, paresis, age, left-sided brain lesion, sex, anticholinergic medication, post-dexamethasone plasma cortisol	Cortisol	None
McIntosh et al. (1985)[77]	7	Male patients admitted to hospital for elective surgery	Delirium incidence	Cortisol, B-endorphin	Plasma	Radioimmunoassay	No multivariate analysis	Cortisol, B-endorphin	None

** Studies with both delirium and cancer participants are bolded; red coloured biomarkers indicate significance in multivariate analysis*

[a] *Dementia was an exclusion criteria*

[b] *Only CRP is reported from this study*

[c] *Only between incident and prevalent delirium*

[d] *Pre-operative and post-operative cortisol remained significantly increased in delirium, however, after controlling for pre-operative depression, only preoperative cortisol concentration remained significant, irrespective of the cortisol level after surgery.*

[e] *Only 66 included in the primary analysis*
[f] *In inflamed patients only*
[g] *In non-inflamed patients only*
[h] *Only CRP and Cre are reported*
[i] *Same cohort as Plaschke et al. 2007*
[j] *Only 16 were analysed*
[k] *same cohort as Van Der Mast et al. 1999*

Abbreviations: *5HIAA: 5-Hydroxyindoleacetic acid; 5-HT: Serotonin; 6-SMT: 6-sulfatoxymelatonin; 8-Iso PGF2a: 8-iso-prostaglandin F2α; A1A: Alpha-1 antitrypsin; a-1-AGP: a-1-acid glycoprotein; AA: Anticholinergic activity; AB1: Amyloid-B; AChE: Acetylcholinesterase; ACS: Acute Coronary Syndromes; ADAS: Alzheimer's Disease Assessment Scale; ADL: Activities of daily living; Ala: Alanine; Alb: Albumin; AD: Alzheimer's Disease; APACHE: Acute Physiology and Chronic Health Evaluation; APN: Adiponectin; ANG: Angiopoietin; APOA1: Apolipoprotein A1; APOE: Apolipoprotein E; Arg: Arginine; APS: Acute Physiology Score; ASA: American Society of American Society of Anaesteologists Scale; BCA: The bicinchoninic acid assay; BDNF: Brain-Derived Neurotrophic Factor; BH4: Tetrahydrobiopterin; BLI: B-Endorphin-Like Immunoreactivity; BuChE: Butyrylcholinesterase; C3: Complement C3; CABG: Coronary Artery Bypass Graft; CBA: Cytometric bead array immunoassay; CCI: Charlson Comorbidity Index; Cit: Citrulline; CK: Creatine Kinase; CK-MB: Creatine Kinase-MB; CLIA: Chemiluminescence immunoassay; CNTN-1: Contactin-1; CPB: Cardiopulmonary Bypass; Cre: Creatinine; CRP: C-Reactive Protein; E2: Estrodiol; FBG: Fibrinogen; FBLN-1: Fibulin-1; ECLIA: Electrochemiluminescence immunoassay; EGF: Epidermal Growth Factor; FGF-2: Fibroblast Grown Factor; Flt-3L: FMS-like tyrosine kinase 3 ligand; GABA: Gamma-Aminobutyric Acid; G-CSF: Granulocyte Stimulating Factor; GFAP: Glial Fibrillary Acidic Protein; GHQ: General Health Questionnaire; Glu: Glutamic acid; Gly: Glycine; GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor; HADS: Hospital Anxiety and Depression Scale; Hb: Haemoglobin; HCY: Homocysteine; HNP-1: Defensin; HP:Haptoglobin; HPLC: High-performance liquid chromatography; HVA: Homovanillic Acid; IADL: Instrumental activities of daily living; ICU: Intensive care unit; Ile: Isoleycine; ICAM-1: Intercellular Adhesion Molecule 1; IDO: Indoleamine 2, 3-dioxygenase; IFN: Interferon; IGF: Insulin- Like Growth Factor; IL= Interleukin; IL-1RA: Interleukin-1 Receptor Antagonist; Ile: Isoleucine; IP-10: Interferon gamma-induced protein 10; IQCODE: The Informant Questionnaire on Cognitive Decline in the Elderly; KYN: Kynurenine; Leu: Leucine; LIF: Leukaemia Inhibitory Factor; LNAA: Large Neutral Amino Acids; LOS: Length of stay; LP: Leptin; Met: Methionine; MB-CK: MB-isoform of Creatinine Kinase; MCP: Monocyte Chemotactic Protein; MDC: Human Macrophage-derived Chemokine; MIF: Macrophage Migration Inhibitory Factor; MIG: Monokine induced by Gamma Interferon; MIP: Macrophage Inflammatory Protein; MMP-9: Matrix Metalloproteinase- 9; MMSE: Mini-mental state examination; MPO: Myeloperoxidase; MT: Melatonin; NCAM: Neural Cell Adhesion Molecule; NGAL: Neutrophil Gelatinase-Associated Lipocalin; NLR: Neutrophil-Lymphocyte ratio; NK cells: Natural killer cells; NP: Neopterin; NR: Not reported; NSE: Neuron Specific Enolase; Orn: Ornithine; NYHA: New York Heart Association; PACU: Post-anesthesia care unit; PAI-1: Plasminogen activator inhibitor-1; PCT: Procalcitonin; PDGF: Platelet- Derived Growth Factor; Phe: Phenylalanine; pMHPG: Plasma free 3-methoxy-4-hydroxyphenylglycol; pNF-H: The Phosphorylated Neurofilament H; PO1MO: 1 month post-operative; POD2: Post-operative day 2; PONV: Post-operative nausea and vomiting; POST-OP: Post-operative; PRE-OP: Pre-operative; P-tau: Phosphorylated tau; RANTES: Chemokine (C-C motif) ligand 5; RBC: Red blood cell; S100B: s100 calcium-binding protein B; sCD40L: Soluble CD40 ligand; Ser: Serine; sIL-XR: Soluble IL- X receptor; SLI: Somatostatin-Like Immunoreactivity; sTNFR: Soluble Tumor Necrosis Factor Receptor; Tau: Taurine; T-tau: Total tau; TGF-a: Transforming Growth Factor Alpha; THA: Total Hip Arthroplasty; TRACE: Time Resolved Amplified Cryptate Emission; TSH: Thyroid Stimulating Hormone; TNF: Tumor Necrosis Factor; Trp: Tryptophan; TRX: Thioredoxin; Tyr: Tyrosine; UDL: Under detection limit; Val: Valine; VCAM-1: Vascular Cell Adhesion protein 1; VEGF: Vascular Endothelial Growth Factor; vWF: Von Willebrand factor; ZAG: Zinc-a-2-Glycoprotein*

Table 3.4 Characteristics of assays and main findings of included cancer studies*

Author and year	Participants		Endpoints	Biomarkers studied	Biological material	Assay method	Covariates adjusted for in multivariate analysis	Results	
	Total participants (N)	Cases; control						Positive association with at least one endpoint**	Negative association
Amano et al. (2017)[a78]	1702	Advanced cancer patients; no control	-Anorexia -Weight loss -Fatigue -Dyspnea -Dysphasia -Edema -Pressure ulcer -ADL disabilities	CRP	NR	NR	Age, gender, primary tumour site, distant metastasis, chemotherapy, ECOG PS, and setting of care	CRP	None
Demiray et al. (2017)[79]	87	Participants with advanced cancer; healthy participants without a known chronic disease	-Cachexia -Weight loss -PFS -OS	LP, resistin	Serum	ELISA	NR	LP Multivariate results NR	Resistin* Multivariate results NR
Fogelman et al. (2017)[80]	69	Participants with advanced cancer; healthy controls with no cancer diagnosis	Either 10% weight loss or death at 60 days from the start of therapy	APN, bFGF, CXCL-16, FSN, Ghrelin, IGF-1, IL-1β, IL-6, IL-8, Klotho, LP, MCP-4, MK, MSTN, PIF, sTNFR1, sTNFR2, TARC, TNF-	NR	NR	Smoking status, best response, pain, difficulty swallowing	MK, IL-1β, CXCL- 16, IL-6, IL-8, TNF-α Multivariate results NR	APN, bFGF, FSN, Ghrelin, IGF-1, Klotho, LP, MCP-4, MSTN, MK, PIF, sTNFR1, sTNFR2, TARC, VEGF, ZAG

				α, VEGF, ZAG					Multivariate results NR
Luo et al. (2017)[81]	217	Participants with advanced cancer; no control	-PFS -OS	FBG, CA-125, NLR, PLR	Serum + Plasma	NR	NR	FBG	CA-125, NLR, PLR
Paulsen et al. (2017)[82]	49	Participants with cancer; no control	-Pain -Appetite -Fatigue	CRP, ESR, sTNF-R1, IL-1RA, IL-6, MCP-1, IL-18, MIF, TGF-β1	Serum	ELISA (multiplex assay)	Sex, BMI and age	sTNF-r1, MCP-1, MIF, CRP, IL-6, IL-1RA	IL-18, TGF-β 1, ESR
Amano et al. (2016)[83]	1511	Advanced cancer patients; no control	-Survival rate -Mortality rate	CRP	Plasma	Latex-enhanced immunoturbidimetric assay	Age, gender, primary tumor site, distant metastasis, chemotherapy, ECOG PS, and setting of care	CRP	None
Bye et al. (2016)[84]	60	Participants with advanced cancer; healthy controls with normal weight	-Cachexia -Survival	IL-10, IFN-γ, LP, APN, TNF-α, IL-6, IGF-1	Serum	ELISA	No multivariate analysis	IL-6	IL-10, IFN-γ, TNF-α, APN, IGF-1
Mitsunga et al. (2016)[85]	421	Participants with advanced cancer with low, intermediate and high CRP levels	OS	CRP, NLR	Blood	ELISA (Multiplex assay)	**Retrospective cohort:** Sex, age, ECOG-PS, UICC stage, CA 19-9, prognostic CRP classification; **Prospective**	CRP, NLR	None

							cohort: Sex, age, ECOG-PS, UICC stage, CA 19-9, NLR classification, mGPS, prognostic CRP classification		
Morgado et al. (2016)[86]	49	Participants with advanced cancer and fatigue with and without weight loss	-Weight loss -Fatigue	Hb, LDH, Alb, CRP, Cre	Serum + Urine	NR	No multivariate analysis	Alb, CRP	Hb, LDH, Cre
Rodrigues et al. (2016)[87]	51	Participants with advanced cancer; no control	Fatigue	IL-1, IL-6, TNF-α, α-1-AGP, GPS (Alb+CRP)	Blood	NR	No multivariate analysis	TNF-α, GPS (Alb+CRP)	None
Srdic et al. (2016)[88]	100	Participants with advanced cancer with and without cachexia	-Cachexia -Chemotherapy toxicity -Survival	CRP, IL-6, Alb, Hb	NR	The Bromocresol Purple method	NR	CRP, IL-6, Alb, Hb	None
Wu et al. (2016)[89]	55	Participants with advanced cancer; no control	-OS -PFS	NLR, PLR, ALP, LDH	Blood	NR	NR	PLR, NLR, LDH	ALP
Bilir et al. (2015)[90]	80	Participants with advanced cancer and cachexia; healthy controls with no	-OS -Cachexia	Il-1β, IL-1α, IL-6, TNF-α, orexin-A, galanin, TWEAK, TRAF-6, NPY, CRP,	Serum	ELISA	NR	CRP, TRAF-6, Alb, LDH, IL-1a, IL-6, TNF-α, TWEAK, orexin-A, NPY, testosterone	IL-1β, galanin

		known chronic disease or weight loss		Testosterone, Alb, LDH					
Miura et al. (2015)a[91]	79	Participants with advanced cancer; no control	-Body composition -Fatigue	IL-6	Serum	ELISA (multiplex assay)	NR	IL-6	None
Miura et al. (2015)b[92]	1160	Participants with advanced cancer; no control	Survival	mGPS (Alb+CRP)	NR	NR	Primary tumor site, age and gender	mGPS (Alb+CRP)	None
Barrera et al. (2014)[93]	135	Participants with advanced cancer; healthy controls	-QoL (fatigue, PS, hyporexia, BMI) -Survival	IL-31, IL-33, IL-27, IL-29, IL-1β, IL-2, IL-6, IL-8, IL-12p70, IL-17A, IFN-γ, TNF- α, IL-4, IL-10	Plasma	CBA	No multivariate analysis	IL-6, IL-8, IFN-γ, IL-33, IL-10, IL-29[b], IL-12p70[b], IL17a[b]	IL-31, IL-27, IL-1β, IL-2, TNF-α, IL-4
Blakely et al. (2014)[94]	50	Participants with advanced cancer with normal CRP and elevated CRP	-OS -Mortality rate -gastrointestinal obstruction -Pain -Bleeding -Other symptoms (NR) -Major complications	CRP	Serum	NR	NR	CRP	None
Fujiwara et al. (2014)[95]	21	Participants with advanced cancer with and without cachexia	Cachexia	LP, IL-6, TNF-α	Serum	ELISA	No multivariate analysis		LP, IL-6, TNF-α

Lindemann et al. (2014)[96]	218	Participants with advanced cancer; no control	-Survival -Weight loss	CRP, Alb	Plasma	Immune-turbidimetry	No multivariate analysis	CRP, Alb	None
Mondello et al. (2014)[97]	170	Participants with advanced cancer; healthy controls	-Survival -Cachexia	LP, ghrelin, obestatin	Serum	ELISA	Age, ghrelin, obestatin, leptin, metastatic disease and chronic kidney disease	LP, Ghrelin, obestatin	None
Moriwaki et al. (2014)[98]	62	Patients with advanced cancer with GPS 0, GPS 1 or GPS 2	OS	GPS (Alb+CRP), ALP, LDH, Bilirubin, CEA, CA 19-9	NR	NR	GPS, median ALP, median LDH, number of metastatic organs, liver metastasis, peritoneal metastasis, other metastasis	GPS (Alb+CRP)	ALP, Bilirubin, LDH, CEA, CA 19-9
Szkandera et al. (2014)[99]	474	Participants with cancer; no control	Cancer-specific survival	CRP, NLR, PLR	Plasma	NR	Age, gender, tumour grade, tumour stage, administration of chemotherapy, surgical resection, NLR, PLR, bilirubin levels and plasma CRP levels	CRP, NLR	PLR
Zhang et al. (2014)[100]	200	Participants with cancer; no control	-Fatigue -Chemotherapy adverse effects	TNF-α, IL-1 α, IL-1 β, 17-HCS	Plasma + urine	ELISA	No multivariate analysis	TNF-α, IL-1α, IL-1β	17-HCS
Jafri et al. (2013)[101]	173	Participants with advanced	-PFS -OS	ALI (Alb+NLR)	Serum	NR	Sex, race, PS and histology	ALI (Alb+NLR)	None

		cancer with high inflammation and with low inflammation							
Laird et al. (2013)a[102]	1466	Participants with advanced cancer with low and high CRP levels	-Symptoms of the EORTC (pain, appetite loss, cognitive function, dyspnea, fatigue, physical function, role function, social function, QoL, nausea/vomiting, diarrhea, sleep, constipation) -Survival	CRP	Blood	NR	No multivariate analysis	CRP	None
Laird et al. (2013)b[103]	2456	Participants with advanced cancer; no control	-Symptoms of the EORTC (pain, appetite loss, cognitive function, dyspnea, fatigue, physical function, role function, social function, QoL, nausea/vomiting, diarrhea, sleep, constipation) -Survival	mGPS (Alb+CRP)	Blood	NR	NR	mGPS (Alb+CRP)	None
Paiva et al. (2013)[104]	223	Participants with cancer with and without fatigue	-Fatigue -OS	CRP, Hb, LDH, Alb	Blood	NR	Age, KPS, type of treatment, breast cancer, upper gastrointestinal cancer, head	CRP, Hb, LDH, Alb, WBC	None

							and neck cancer, lower gastrointestinal cancer, lung cancer, urologic cancer, and CRP		
Suh et al. (2013)[105]	98	Participants with advanced cancer; no control	Survival	IL-6, TNF-α	Plasma	ELISA (multiplex assay)	Gender (male), fatigue (BFI-K score), ECOG (3-4), IL-6 (high, ≥9.06 pg/mL)	IL-6	TNF-α
De Raaf et al. (2012)[106]	92	Participants with advanced cancer; cancer survivors	Physical and mental fatigue	CRP, IL-1-RA, NP, IL-6 and IL-8	Plasma	CBA	No multivariate analysis	CRP, IL-6, IL-1-ra, NP	IL-8
Gioulbasanis et al. (2012)[107]	114	Participants with advanced cancer with malnutrition, with a risk of malnutrition, and who were well nourished	-Nutritional status (cachexia) -Survival	IL-8	Plasma	CLIA	PS, histology, BMI, gender, age, smoking status, weight loss history	IL-8	None
Gulen et al. (2012)[108]	88	Participants with advanced cancer with and without weight loss; age- and sex-matched controls	Weight loss (>5%)	LP, APN, TNF-α, CRP	Serum	ELISA	No multivariate analysis	LP	APN, TNF-α, CRP

Heitzer et al. (2012)[109]	65	Advanced cancer patients with cancer pain; healthy controls without pain	Pain intensity	IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, TNF-α, TNF-β, IFN-γ, IL-1α, IL-7, IL-13, IL-18, MCP-1, MIP-1a, MIP-1B, OPG	Serum	ELISA	NI	Unclear	Unclear
Minton et al. (2012)[110]	720	Participants with advanced cancer with and without fatigue	Fatigue	CRP, Alb, Hb	Blood	NR	Hb, current treatment with chemo, QOL score, depression, pain dyspnoea, cognitive function, insomnia and loss of appetite	CRP, Alb, Hb	None
Partridge et al. (2012)[111]	102	Patients with advanced cancer with GPS 0, GPS 1 or GPS 2 ; no control	Survival	mGPS (Alb+CRP)	Blood	NR	Sex, primary cancer site, age, Hb and WBC	mGPS (Alb+CRP)	None
Pond et al. (2012)[112]	220	Participants with advanced cancer; no control	-OS -PFS	CRP	NR	NR	NR	CRP	None
Wang et al. (2012)[113]	177	Participants with cancer; no control	Survival	CRP, Alb, mGPS (Alb+CRP), NLR	NR	NR	PS, pretherapeutic weight, WBC, neutrophil count, NLR,	CRP, mGPS (Alb+CRP), NLR	Alb

							CRP, mGPS, PI, the 7th TNM staging, surgery, degree of differentiation, palliate chemotherapy		
Aydin et al. (2011)[114]	61	Advanced cancer patients; no control	Survival	CRP, Alb, TFN	Serum	Nephelometric assay	No multivariate analysis	CRP, Alb, TFN	None
Dev et al. (2011)[115]	77	Participants with advanced cancer; no control	Symptom distress (pain, fatigue, nausea, depression, anxiety, drowsiness, appetite, well-being, dyspnea, sleep)	Cortisol	Serum	NR	NR	Cortisol	None
Gioulbasanis et al. (2011)[116]	115	Participants with advanced cancer with malnutrition, with a risk of malnutrition, and who were well nourished	-Nutritional status (cachexia) -Survival	Alb, CRP, ghrelin, LP, APN, IGF-1	Plasma	Radioimmunoassay	Number of metastatic sites, PS, weight loss <5%, MNA groups, age, and major histological type	CRP, LP, Alb	Ghrelin, APN, IGF-1
Hwang et al. (2011)[117]	402	Participants with cancer; no control	-PFS -OS	Alb, CRP	Serum	Latex turbidimetric immunoassay	Peritoneal metastasis, bone metastasis, albumin, CRP, ECOG PS, GPS	Alb, CRP	None

Kwak et al. (2011)[118]	90	Participants with advanced cancer; no control	Fatigue	IL-6, TNF-α	Blood	NR	BFI score, age, gender, BMI, blood pressure, heart rate, cancer site, previous treatment, comorbidity, medication, pain score, sleep disorder, dyspnea, ECOG PS, WBC, Hb, BUN, creatinine, albumin, AST, ALT, total bilirubin, CRP, IL-6, and TNF-α	None	IL-6, TNF-α
Lee et al. (2011)[119]	126	Participants with advanced cancer; no control	14 day mortality	CRP	Serum	NR	CRP, chemotherapy, age, dyspnea, altered mental status, hypotension, and leukocytosis	CRP	None
Scheede-Bergdahl et al. (2011)[120]	83	Participants with advanced cancer; no control	- Clinical features of cachexia (weakness, loss of appetite, fatigue, QoL, weight loss) -Survival	IL- 6, IL-1β, IL-8, TNF-α	Plasma	BCA	Sex, age, diagnosis, oncological treatment, CCI and medications	IL- 6, IL-1β, IL-8, TNF-α	None
Vlachostergios et al. (2011)[121]	77	Participants with advanced	-TTP -OS	IGF-1, CRP, Alb	Serum	Radioimmu noassay	Sex, current smoker, albumin, IGF-1	IGF-1, CRP, Alb	None

		cancer; no control							
Diakowska et al. (2010)[122]	218	Participants with cancer with and without cachexia; healthy blood donors; and patients with non-malignant diseases of alimentary tract	Cachexia	LP, CRP, IL-1, IL-6, IL-8, TNF-α, Alb, Hb.	Serum	ELISA	NR	LP, IL-6, Alb, TNF-α	IL-1, IL-8, Hb, CRP*
Meek et al. (2010)[123]	56	Participants with advanced cancer; no control	Cancer-specific survival	IGF-1, IGFBP-3, CRP, mGPS (Alb+CRP), LP	Serum	NR	BMI, cancer stage, Hb, WBC, mGPS	mGPS (Alb+CRP)	IGF-1, IGFBP-3, LP, CRP
Ishizuka et al. (2009)[124]	112	Participants with advanced cancer; no control	Mortality	CRP, Alb, mGPS (Alb+CRP), Neutrophil ratio	Serum	NR	Neutrophil ratio, CA 19–9, CRP, albumin, and mGPS	mGPS (Alb+CRP)	None
Karapanagiotou et al. (2009)[125]	161	Participants with advanced cancer; healthy controls	-Weight loss -TTP -OS	Ghrelin, LP	Serum	ELISA	Sex, age, BMI, Ghrelin	Ghrelin Multivariate results NR	LP Multivariate results NR
Paddison et al. (2009)[126]	44	Participants with advanced cancer; healthy controls	Fatigue	Hb, WBC, Neutrophil, Monocyte,Lymphocyte	Blood	NR	Age, gender, time until treatment termination; and fatigue	Hb, WBC, Neutrophil count, monocyte count	None

Takahashi et al. (2009)[127]	26	Participants with cancer cachexia; healthy controls	Anorexia (cachexia and BMI)	TNF-α, IFN-γ, IL-6, IL-1RA, LP, ghrelin	Plasma	ELISA	No multivariate analysis	TNF-α, IL-6, IL-1RA, LP	IFN- γ, ghrelin
Inagaki et al. (2008)[128]	46	Participants with advanced cancer with and without fatigue	Fatigue	IL-6	Plasma	ELISA	Logistic regression: IL-6, gender, weight and clinical fatigue Multiple regression: gender, weight, IL-6 and total score of the CFS	IL-6	None
Karapanagiotou et al. (2008)[129]	152	Participants with advanced cancer; healthy controls	-Weight loss -TTP -OS	LP, APN, resistin	Serum	ELISA	Sex, age, BMI, resistin	Resistin	LP, APN
Sharma et al. (2008)[130]	52	Participants with advanced cancer; no control	-OS -Toxicity	IL-1β, IL-2, IL-4, IL-5, IL-8, IL-6, IL-10, IL-12, GM-CSF, IFN-Y, TNF-α, sIL-6R, sgp130, VEGF, eotaxin, MCP-1, MIP-1α, MIP-1β, Alb, CRP, GPS (Alb+CRP)	Serum	NR	Tumour site (colonic primary), GPS, CEA, and albumin	GPS (Alb+CRP), Hb, Alb	CRP, IL-1β, IL-2, IL-4, IL-5, IL-8, IL-6, IL-10, IL-12, GM-CSF, IFN-Y, TNF-α, sIL-6R, sgp130, VEGF, eotaxin, MCP-1, MIP-1α, MIP-1β
Weryńska et al. (2008)[131]	40	Participants with advanced	-Cachexia -Nutritional status	LP	Serum	ELISA	No multivariate analysis	LP	None

		cancer with and without cachexia							
Ravasco et al. (2007)[132]	101	Participants with cancer; no control	-REE -Weight loss -Nutritional intake	IL-1RA, IL-6, TNF-α, IL-10, IFN-γ, VEGF	Serum	ELISA	Cancer histology and stage, nutritional intake	IL-1RA, IL-6, TNF-α, IFN-γ, VEGF	IL-10
Richey et al. (2007)[133]	24	Participants with cancer with and without cachexia	Cachexia	GPS (Alb+CRP), Alb, IL-1a, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, TNF-α, IFN-γ, VEGF, GM-CSF, MCP-1, MIP-1a, MIP-1B, RANTES, FGF, Hb, CRP, CEA	Serum	Dry-slide method with the VITROS Fusion Series analyser	No multivariate analysis	GPS (Alb+CRP), Alb, CEA	IL-1a, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, TNF-α, IFN-γ, VEGF, GM-CSF, GM-CSF, MCP-1, MIP-1a, MIP-1B, RANTES, FGF, Hb, CRP, CEA
Suh et al. (2007)[134]	44	Participants with advanced cancer; no control	Survival	CRP	Serum	NR	NR	CRP	None
Al Murri et al. (2006)[135]	96	Breast cancer patients; no control	Survival	CRP, Alb, GPS (Alb+CRP)	NR	NR	GPS and treatment	CRP, GPS (Alb + CRP)	None
Kayacan et al. (2006)[136]	56	Participants with advanced cancer with and without cachexia; healthy smokers for the control	-Cachexia -PS -Survival	TNF-α, IL-6	Serum	ELISA	NR	None	TNF-α, IL-6

Ramsey et al. (2006)[137]	119	Participants with advanced cancer; no control	-Cancer-specific survival -Cancer-specific mortality	GPS (Alb+CRP)	NR	NR	GPS, Hb, calcium, WBC, neutrophil count, Alb, CRP	GPS (Alb+CRP)	None
Di Nisio et al. (2005)[138]	141	Participants with advanced cancer; no control	Survival	IL-6, IL-10, IFN-y, P-selectin	Plasma	BCA	Life expectancy, WHO performance status, concomitant treatment, type of carcinoma, and histology	IL-10, IL-6, P-selectin	IFN-y
Rich et al. (2005)[139]	80	Participants with advanced cancer with good and dampened circadian rhythms	-Extent of metastatic disease -PS -QoL	IL-6, TGF-a, TNF-α, cortisol	Serum	ELISA	NR	IL-6, TGF-a, TNF-α	Cortisol
Bolukbas et al. (2004)[140]	69	Participants with advanced cancer; healthy controls with stable weight	Weight loss	LP	Serum	ELISA	NR	LP	None
Dulger et al. (2004)[141]	54	Participants with advanced cancer with and without cachexia; healthy gender- and age-matched adults	Cachexia	TNF-α, IL-1β, IL-6, CRP, LP, GH, TG, insulin, glucose, triglyceride, total protein, ESR	Serum	Solid-phase, two-site chemiluminescent immunometric assays	No multivariate analysis	Alb, total protein, GH, TNF-α, IL-1β, IL-6, insulin, LP, ESR[b], CRP[b]	Glucose, TG

Elahi et al. (2004)[142]	165	Participants with advanced cancer; no control	Survival	Alb, CRP	NR	Fluorescence polarization immunoassay	NR	Alb, CRP	None
Jamieson et al. (2004)[143]	33	Participants with advanced cancer; healthy controls	Weight loss	Hb, Alb, CRP, APN, LP, IL-6	Serum	ELISA	No multivariate analysis	Hb, Alb, CRP, APN, LP, IL-6	None
Songur et al. (2004)[144]	91	Participants with advanced cancer; healthy controls	-Malnutrition -Survival	IL-6, Alb, CRP, TFN, LDH	Serum	NR	NR	IL-6, Alb, CRP, TFN, LDH	None
Scott et al. (2003)[145]	106	Participants with advanced cancer with and without weight loss	Weight loss	Hb, Alb, CRP	Blood	NR	No multivariate analysis	Hb, Alb, CRP	None
Aleman et al. (2002)[146]	106	Patients newly diagnosed with NSCL vs patients with no cancer	-Nutritional status -Survival	IL-6, IL-12, IL-10, IL-2, LP, α -1A, ferritin, CRP, TNF-α, s-TNFR2, s-IL-2R, IFN-γ	Serum	CLIA	NR	IL-6, IL-12, IL-2, sTNFR2, IFN-γ, sIL-2R, LP, α-1A, CRP, ferritin Multivariate results unclear	IL-10, TNF-α Multivariate results unclear
Orditura et al. (2002)[147]	85	Participants with advanced cancer;	-OS -TTF	IL-8, IL-10, IL-2	Serum	ELISA	NR	IL-10, IL-2, IL-8	None

		healthy controls							
Scott et al. (2002)[148]	106	Participants with advanced cancer; no control	Survival	Alb, CRP	Blood	NR	Age, sex, stage, histological type, weight loss, haemoglobin, albumin, CRP, KPS and EORTCV QLQ-C30 subscale	CRP, Alb	None
De Vita et al. (2001)[149]	68	Participants with advanced cancer; no control	-TTP -OS	IL-6	Serum	ELISA	NR	Il-6	None
Jatoi et al. (2001)[150]	73	Participants with advanced cancer; healthy controls	Anorexia and/or weight loss	NPY, LP, CCK-8	Serum	Radioimmunoassay	No multivariate analysis	NPY	LP, CCK-8
Mantovani et al. (2001)[151]	58	Participants with advanced cancer; normal weight healthy controls	-BMI -Cachexia -ECOG PS -Survival	LP, IL-6, TNF-α	Serum	ELISA	No multivariate analysis	Unclear	Unclear
Mantovani et al. (2000)[152]	32	Participants with advanced cancer; normal	Cachectic symptoms (BMI)	LP, IL-1a, IL-6, and TNF-α	Serum	ELISA	No multivariate analysis	Unclear	Unclear

		weight healthy controls							
Nenova et al. (2000)[153]	87	Participants with advanced cancer; healthy controls	-Cachexia -Prognosis	TNF-α	Serum	ELISA	No multivariate analysis	Unclear	Unclear
O'Gorman et al. (1999)[154]	50	Participants with advanced cancer with weight loss or weight gain; weight stable controls	-Weight loss -Appetite -PS -Inflammation	Alb, CRP	Blood	NR	No multivariate analysis	Alb, CRP	None
Okada et al. (1998)[155]	100	Participants with cancer; healthy controls	Weight loss	IL-6	Serum	ELISA	No multivariate analysis	IL-6	None
Wallace et al. (1998)[156]	54	Participants with advanced cancer; healthy controls	Weight loss	LP	Serum	Radioimmunoassay	No multivariate analysis	LP	None
Maltoni et al. (1997)[157]	530	Participants with advanced cancer; no control	Survival	Neutrophil, lymphocyte & monocyte %, basophil + eosinophil %, Hb, TFN, Alb, total WBC, Pseudocholinesterase, proteinuria, TFN,	Blood	NR	No multivariate analysis	Neutrophil %, lymphocyte %, total WBC, CHE, Alb	basophil + eosinophil %, Hb, TFN

				transport iron					
Simons et al. (1997)[158]	21	Participants with cancer and weight loss; no control	-Weight loss -Body composition -Appetite -REE	LP	Plasma	ELISA	No multivariate analysis	LP	None

Note: Cancer prognosis was not separated from the other syndromes in the table
** Red coloured biomarkers indicate significance in multivariate analysis*
[a] *Secondary analysis of Amano, 2016*
[b] *In cancer vs no cancer only*

***Abbreviations**: 17-HCS= 17-hydroxycorticosteroids; α-1-AGP: a-1-acid glycoprotein; α-1A: alpha-1 antitrypsin; Alb: Albumin; ADL: Activities of daily living; ALP:Alkaline phosphatase; APN: Adiponectin; APOA2: Apolipoprotein A2; BCA: The bicinchoninic acid assay; bFGF: Basic fibroblast growth factor; CA 19-9- Cancer antigen; CBA: Cytometric bead array immunoassay; CCK: Cholecystokinin; CEA: Carcinoembryonic antigen; CK: Creatine Kinase; CLIA: Chemiluminescence immunoassay; Cre: Creatinine; CRP: C-Reactive Protein; CXCL: Soluble CXC chemokine ligand; EORTC: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; ESR: Erythrocyte sedimentation rate; FBG: Fibrinogen; FSN: Follistatin; GH: Growth Hormone; GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor; HA: Hyaluronic Acid; Hb: Haemoglobin; IGF: Insulin-Like Growth Factor; IGFBP: Insulin-like Growth Factor Binding Protein; IL: Interleukin; IFN: Interferon; LDH: Lactate Dehydrogenase; LP: Leptin; MCP: Monocyte Chemotactic Protein; MIP: Macrophage Inflammatory Protein; MK: Midkine; NI: Not enough information; NR: Not reported; MSTN: Myostatin; NLR: Neutrophil-lymphocyte ratio; NP: Neopterin; NPY: Neuropeptide Y; OPG: Osteoprotegrin; OS: Overall survival; PFS: Progression free survival; PLR: Platelet-lymphocyte ratio; PS: Performance status; QoL: Quality of life; RANTES: Chemokine (C-C motif) ligand 5; REE: Resting energy expenditure; sTNFR: SolubleTumor Necrosis Factor Receptor; Sgp130= Soluble glycoprotein 130; TARC: Thymus and Activation-Regulated Chemokine; TFN: Transferrin; TG: Triglyceride; TNF: Tumor Necrosis Factor; TRAF-6: Tumor Necrosis Factor Receptor associated factor-6; TTF: Time to treatment failure; TWEAK: TTP: Time to disease progression; TNF-like weak inducer of apoptosis; VEGF: Vascular Endothelial Growth Factor; ZAG: Zn-alpha2 glycoprotein*

3.4.3 Quality assessment

The quality assessment showed a large variability in the reporting of included studies. 150 (99%) studies had a clear aim statement which included their outcome of interest. One study did not report a clear aims statement.[156] One hundred and nineteen studies (79%) did not explicitly state the hypothesis; however, in most (n=94; 62%) the hypothesis could be interpreted by the study aim. All but one study (99%) stated the participant population in detail. No study reported all elements of the assay methods in the REMARK checklist. One hundred and thirty one studies (87%) did not report whether assays were blinded to the study endpoint, however 59 (45%) of those studies were objective assessments. Further, 14 studies (9%) reported a power calculation to justify their sample size. Most (n=125; 83%) of studies defined all clinical endpoints examined. Ninety seven (64%) studies undertook multivariate analysis, and of these 67 (69%) described the multivariate model and the covariates included in the model, and 23 (23%) explained the rationale for inclusion of the covariates in the models. Furthermore, 27 delirium studies (38%) did not report the reason for admission. Of the 44 studies that did report the reason for admission, these were predominantly for surgery- elective and acute (n=40). Most studies in the non-surgical population did not report a reason for admission, with the exception of 4 studies where the medical condition of interest occurred on admission (e.g stroke).

The methodological quality of the assay procedures of all studies is depicted in Figure 3.3, with reporting of type of biological material mostly provided but much lower frequency of reporting for other critical descriptors.

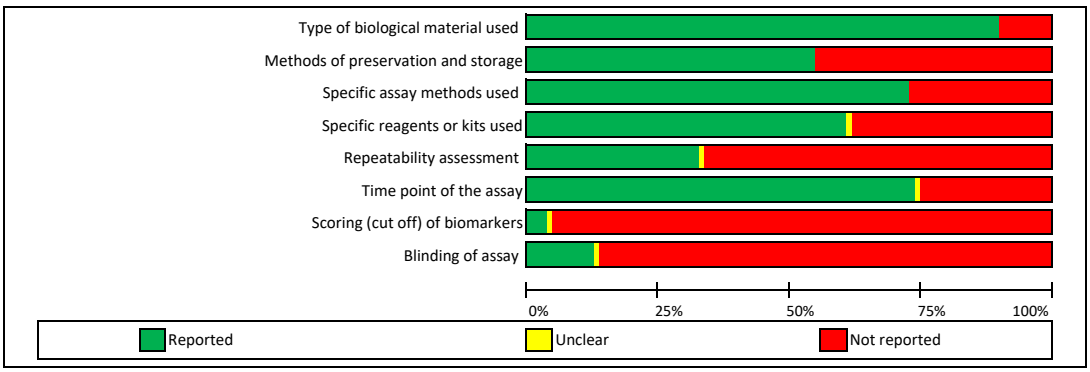

Figure 3.3 Quality assessment graph of the assay procedures: author's judgements about each assay domain of the REMARK checklist, presented as percentages across studies

A more detailed exploration into the quality of the delirium studies only was then undertaken. Of the delirium studies, all but one study stated the participant population in detail. No delirium study reported all elements of the assay procedures outlined in the REMARK checklist. Most studies stated the type of biological material used (n=86, 94%), the methods of preservation and storage (n=48, 66%) the specific assay method used (n=59, 81%) and the specific reagents or kits used (n=55, 76%). A lower frequency of reporting for other critical descriptors was identified. Only 20 studies (27%) reported a repeatability assessment, 46 (64%) specified the timing of the biomarker collection in relation to delirium, 4 (6%) described a scoring or reporting protocol, and 18 (25%) reported whether the biomarker was blinded to the clinical endpoint. The methodological quality of the delirium studies is depicted in Figure 3.4.

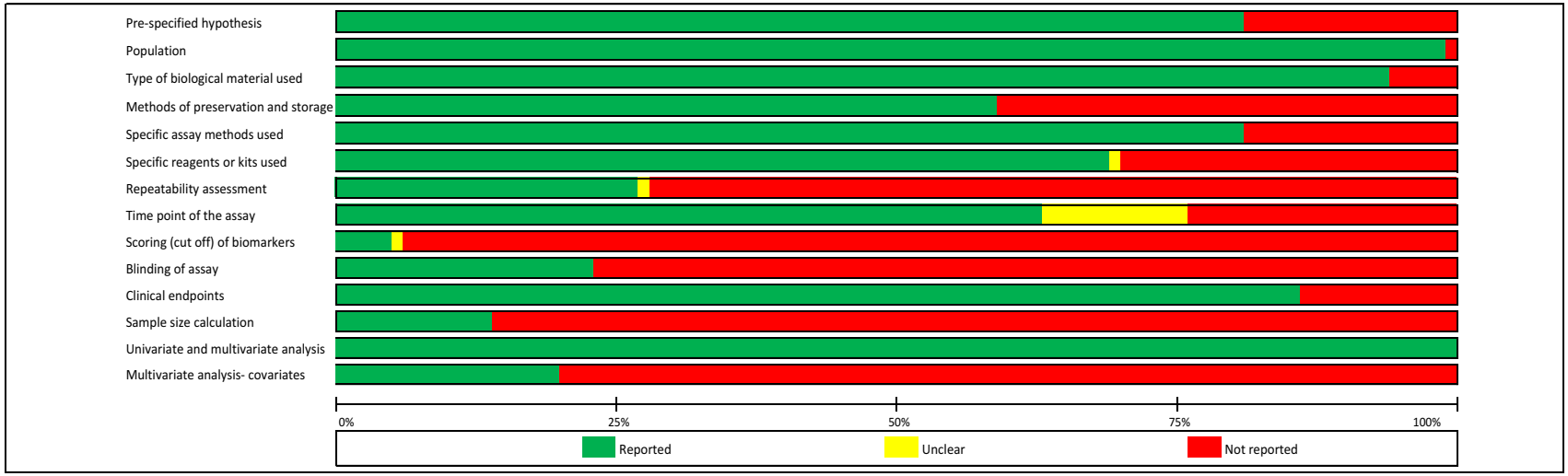

Figure 3.4 Quality assessment graph of the delirium studies, presented as percentages across studies

The full quality assessment for both the delirium and cancer studies can be found in Appendix 3.1 and 3.2.

3.5 Discussion

To date, there has been limited empirical consideration of the distinction between delirium pathophysiology and that of the underlying disease, for example, cancer, where the mechanisms are also common in advanced cancer syndromes. This review used cancer as an exemplar of a condition with its own biological drivers in which delirium is common and for which the pathophysiology may be inter-related or overlapping.

This is the first systematic review to our knowledge, to demonstrate the high degree of overlap in biomarkers in delirium, cancer prognosis and advanced cancer syndromes. This systematic review of 151 studies found that 41 biomarkers were independently investigated in studies of both delirium and prognosis/advanced cancer syndromes; with over half having a positive association in at least one study.

Biomarkers fall into three categories (though not mutually exclusive); those which present before disease onset that can help identify individuals who are most at risk of a particular disease (for example, genetic markers), those which are disease markers and as such, increase during disease progression and decrease after resolution, and thirdly, biomarker as an end-product of a disease for which levels are proportionate to 'damage' due to the disease.[159] The findings of this systematic review suggest that categorization along these lines is less understood in delirium. For example, there is evidence to show that conditions such as sepsis and hip fracture cause changes in inflammatory markers,[160,161] however, there is little evidence about whether delirium self-propagates. Some animal model data in delirium suggests that there might be a

direct impact of inflammatory markers on brain dysfunction.[162] To our knowledge there was no published relationship between tumor markers and neurological brain dysfunction. Although clinical evidence suggests long term impacts on brain function, the exact pathophysiological mechanism is poorly understood, and biomarkers to measure this are also unclear.

The issue of biomarker overlap between associated conditions has been researched in women with pre-eclampsia and polycystic ovary syndrome,[163] however the overlap with respect to delirium and its associated conditions has not been well addressed. Of the 71 delirium studies, only five studies sought to determine the association with the participants' common primary condition in their analysis. Tomasi et al. (2017)[10] found that biomarkers differed between patients in the three groups in those with sepsis alone and those who developed sepsis-associated encephalopathy, or delirium, suggesting different mechanisms of sepsis-associated encephalopathy, delirium in people with sepsis, and sepsis itself. Likewise, Pfister et al. (2008)[64] found differences in CRP, s100 calcium binding protein B (s100B) and cortisol in patients with sepsis-associated delirium, compared to non-sepsis associated delirium. In two studies, delirium in stroke was examined[9,76] but these studies did not identify differences in cortisol[76] or TNF- α, IL- 1β, IL-18, Brain-derived neurotrophic factor (BDNF) and Neuron specific enolase (NSE)[9] between patients who developed delirium after stroke compared to those who did not develop delirium. Moreover, Sun et al. (2016)[18] attempted to explore the overlap of biomarkers in delirium and dementia in patients with cancer, however, no multivariate analysis was undertaken, therefore results of this study are inconclusive.

Although the aim of this systematic review was to explore the overlap of biomarkers in delirium and advanced cancer syndromes, the findings highlighted a bigger problem

in the methodology of delirium biomarker research. The quality assessment in this systematic review found that many of the included studies were of poor methodological quality, inadequately reported, or were influenced by potential confounding factors. A potential barrier to the complete understanding of delirium pathophysiology is the lack of guidelines for conducting and reporting delirium biomarker studies. Results from this review indicate that the absence of such guidelines has likely impeded the quality of individual studies and the overall quality of this critical field of delirium research. Reporting guidelines for delirium biomarker research are an essential step to improving methodological and reporting rigor, and will increase the potential for synthesis of future studies through meta-analyses.

Several studies have previously been performed to determine biomarkers associated with delirium, however potential confounding factors could be the underlying precipitants of delirium; i.e risk factors (sepsis), or underlying conditions present (for example cancer or dementia). The top five most commonly studies biomarkers in this review were inflammatory biomarkers, namely, CRP, IL-6, TNF- α, IL-10 and IL-8. The challenge with inflammatory markers is that they are non-specific and the inflammatory pathways are similar to those implicated in other conditions such as sepsis and depression.[164,165] Likewise, of the six delirium studies where there was concomitant cancer, it is very difficult to determine whether those biomarkers found were related to the cancer or the delirium itself, considering alterations in inflammatory pathways are implicated in both. Therefore, future delirium biomarker studies need to be prospectively evaluated and take into account and assess robustly other active co-morbidities such as cancer that could plausibly impact on the pathophysiological and/or biological findings. Similarly, future cancer biomarker studies must also take into account how delirium may clinically or biologically

confound biomarker studies in cancer, considering the high prevalence of delirium in this population. Of the six delirium studies with cancer, three did not report the type of cancer, and of the remaining three studies, none were primary brain tumours or brain metastases. Understanding the spread of brain cancer is important in delirium studies, and is an important consideration for future delirium biomarker studies.

Majority of the studies in this review (n=98; 65%) undertook a multivariate analysis, taking into account confounding variables. Where studies only undertook univariate analysis, it is uncertain whether any observed changes in biomarkers were related to the delirium itself, or whether these changes may have been lost when adjusted for confounding factors (such as prior cognitive impairment) in a multivariate analysis. Furthermore, there is likely to be a higher proportion of participants with both delirium and cancer in both groups of studies for which this clinical information was not assessed or that were not reported. Key methodological issues which need to be addressed in future delirium studies include adjusting for confounders such as age, gender, concurrent medication, comorbidities, prior cognitive impairment, frailty and other neurological conditions. These clinical covariates must also be clearly defined and justified. Assay procedures ought to be reported in detail, including a detailed protocol of the reagents/kits used, repeatability assessments, methods of preservation and storage, assay validity, sensitivity limits of the assay and a scoring and reporting protocol. The timing of the assay is crucial in delirium studies, and the fluctuating pathophysiological processes occurring during delirium, after delirium resolution, and in those who have not yet developed delirium, must be taken into consideration, and be separated in future studies. More standardised and detailed methods of delirium biomarker studies is a crucial step in carrying out future subgroup analyses within this cohort and improving the overall understanding of delirium pathophysiology.

3.5.1 Strengths and limitations

Strengths of this review were that we undertook a systematic approach adhering to the PRISMA[5] and an extensive quality assessment of the included studies was undertaken. Limitations of this study are that only English language and published studies were included. It is possible that articles were missed; however, two reviewers independently screened all citations derived from a search of six relevant and diverse databases, and all reference lists of included articles were also searched. Another limitation of our study is the lack of a risk of bias tool for biomarker studies, therefore we used an adaptation of tumor marker reporting guidelines, the REMARK checklist.[7] Lastly, the heterogeneity of the data precluded the conduct of a meta-analysis, and precluded any firm conclusions about the biomarkers in delirium and cancer, thus, limiting the rigor of this review.

3.6 Conclusion

This systematic review used cancer as an exemplar to consider the impacts of the underlying biology of the index condition, on the research approach to exploring the pathophysiology of delirium in this condition. The review found that there is large overlap in the biomarkers in delirium and in advanced cancer-related syndromes, although because of the heterogeneity of the studies firm conclusions about the true overlap of delirium and advanced cancer syndrome biomarkers was not possible. Therefore more robust conduct and reporting of delirium biomarker studies are needed to better understand the pathophysiology of delirium in the context of co-existing pathophysiology. An improved understanding of the clinical and biological associations of delirium and advanced cancer syndromes in future prospective studies will provide and inform the directions of research into delirium in people with advanced cancer.

3.7 References

1. Maldonado JR. Delirium pathophysiology: An updated hypothesis of the etiology of acute brain failure. *International Journal of Geriatric Psychiatry.* 2017;33(11):1428-1457.

2. Berr C. Cognitive impairment and oxidative stress in the elderly: results of epidemiological studies. *Biofactors.* 2000;13(1- 4):205-209.

3. Haggstrom L, Nelson J, Wegner E, Caplan G. 2-18F-fluoro-2-deoxyglucose positron emission tomography in delirium. *Journal of Cerebral Blood Flow & Metabolism.* 2017;37(11):3556-3567.

4. Caplan GA, Kvelde T, Lai C, Yap SL, Lin C, Hill MA. Cerebrospinal fluid in long-lasting delirium compared with Alzheimer's dementia. *Journals of Gerontology Series A-Medical Sciences.* 2010;65(10):1130-1136.

5. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS medicine.* 2009;6(7):e1000100.

6. Covidence. Better systematic review management n.d.; https://www.covidence.org/. Accessed 28 March, 2017.

7. Altman DG, McShane LM, Sauerbrei W, Taube SE. Reporting recommendations for tumor marker prognostic studies (REMARK): explanation and elaboration. *BMC Medicine.* 2012;10(1):51.

8. Egberts A, Mattace-Raso F. Increased neutrophil–lymphocyte ratio in delirium: a pilot study. *Clinical Interventions in Aging.* 2017;12:1115.

9. Kozak HH, Uguz F, Kilinc I, et al. Delirium in patients with acute ischemic stroke admitted to the non-intensive stroke unit: Incidence and association between clinical features and inflammatory markers. *Neurologia Neurochirurgia Polska.* 2017;51(1):38-44.

10. Tomasi CD, Vuolo F, Generoso J, et al. Biomarkers of Delirium in a Low-Risk Community-Acquired Pneumonia-Induced Sepsis. *Molecular Neurobiology.* 2017;54(1):722-726.

11. Vasunilashorn SM, Dillon ST, Inouye SK, et al. High C-Reactive Protein Predicts Delirium Incidence, Duration, and Feature Severity After Major Noncardiac Surgery. *Journal of the American Geriatrics Society.* 2017.

12. Chu CS, Liang CK, Chou MY, et al. Lack of association between Pre-operative insulin-like growth factor-1 and the risk of post-operative delirium in elderly Chinese patients. *Psychiatry Investigation.* 2016;13(3):327-332.

13. Dillon ST, Vasunilashorn SM, Ngo L, et al. Higher C-Reactive Protein Levels Predict Postoperative Delirium in Older Patients Undergoing Major Elective

Surgery: A Longitudinal Nested Case-Control Study. *Biological Psychiatry.* 2017;81(2):145-153.

14. Guo Y, Jia P, Zhang J, Wang X, Jiang H, Jiang W. Prevalence and risk factors of postoperative delirium in elderly hip fracture patients. *Journal of International Medical Research.* 2016;44(2):317-327.

15. Karlicic IS, Stasevic M, Jankovic S, Dejanovic SD, Milovanovic S. Markers of inflammation as risk predictors of lethal outcome in patients diagnosed with delirium. *Vojnosanitetski Pregled.* 2016;73(9):838-843.

16. Neerland BE, Hall RJ, Seljeflot I, et al. Associations Between Delirium and Preoperative Cerebrospinal Fluid C-Reactive Protein, Interleukin-6, and Interleukin-6 Receptor in Individuals with Acute Hip Fracture. *Journal of the American Geriatrics Society.* 2016;64(7):1456-1463.

17. Shen H, Shao Y, Chen J, Guo J. Insulin-like growth factor-1, a potential predicative biomarker for postoperative delirium among elderly patients with open abdominal surgery. *Current Pharmaceutical Design.* 2016;22(38):5879-5883.

18. Sun L, Jia P, Zhang J, et al. Production of inflammatory cytokines, cortisol, and Abeta1-40 in elderly oral cancer patients with postoperative delirium. *Neuropsychiatric Disease and Treatment.* 2016;12:2789-2795.

19. Yen TE, Allen JC, Rivelli SK, et al. Association between Serum IGF-I levels and Postoperative Delirium in Elderly Subjects Undergoing Elective Knee Arthroplasty. *Scientific Reports.* 2016;6:20736.

20. Avila-Funes JA, Ledesma-Heyer JP, Navarrete-Reyes AP, Chavira-Ramirez R, Boeck-Quirasco L, Aguilar-Navarro S. Association between high serum estradiol levels and delirium among hospitalized elderly women *Revisa de Investiaciong Clinica.* 2015;67(1):20-24.

21. Brum C, Stertz L, Borba E, Rumi D, Kapczinski F, Camozzato A. Association of serum brain-derived neurotrophic factor (BDNF) and tumor necrosis factor-alpha (TNF-alpha) with diagnosis of delirium in oncology inpatients. *Revista Brasileira de Psiquiatria.* 2015;37(3):197-202.

22. Egberts A, Wijnbeld EH, Fekkes D, et al. Neopterin: a potential biomarker for delirium in elderly patients. *Dementia & Geriatric Cognitive Disorders.* 2015;39(1-2):116-124.

23. Foroughan M, Delbari A, Said SE, AkbariKamrani AA, Rashedi V, Zandi T. Risk factors and clinical aspects of delirium in elderly hospitalized patients in Iran. *Aging Clinical and Experimental Research.* 2016;28(2):313-319.

24. Skrede K, Wyller TB, Watne LO, Seljeflot I, Juliebo V. Is there a role for monocyte chemoattractant protein-1 in delirium? Novel observations in elderly hip fracture patients. *BMC Research Notes.* 2015;8:186.

25. Vasunilashorn SM, Ngo L, Inouye SK, et al. Cytokines and Postoperative Delirium in Older Patients Undergoing Major Elective Surgery. *Journals of Gerontology Series A-Medical Sciences.* 2015;70(10):1289-1295.

26. Alexander SA, Ren D, Gunn SR, et al. Interleukin 6 and Apolipoprotein E as predictors of acute brain dysfunction and survival in critical care patients *American Journal of Critical Care.* 2014;23(1):49-57.

27. Baranyi A, Rothenhausler HB. The impact of soluble interleukin-2 receptor as a biomarker of delirium.[Erratum appears in Psychosomatics. 2014 Jul-Aug;55(44):418-9]. *Psychosomatics.* 2014;55(1):51-60.

28. Cape E, Hall RJ, van Munster BC, et al. Cerebrospinal fluid markers of neuroinflammation in delirium: a role for interleukin-1beta in delirium after hip fracture. *Journal of Psychosomatic Research.* 2014;77(3):219-225.

29. Capri M, Yani SL, Chattat R, et al. Preoperative, high IL-6 blood level is a risk factor of postoperative delirium onset in old patients. *Frontiers in Endocrinology.* 2014;5 (SEP) (no pagination)(173).

30. Chen XW, Shi JW, Yang PS, Wu ZQ. Preoperative plasma leptin levels predict delirium in elderly patients after hip fracture surgery. *Peptides.* 2014;57:31-35.

31. Hatta K, Kishi Y, Takeuchi T, et al. The predictive value of a change in natural killer cell activity for delirium. *Progress in Neuro-Psychopharmacology and Biological Psychiatry.* 2014;48:26-31.

32. Kazmierski J, Banys A, Latek J, et al. Mild cognitive impairment with associated inflammatory and cortisol alterations as independent risk factor for postoperative delirium. *Dementia & Geriatric Cognitive Disorders.* 2014;38(1-2):65-78.

33. Kazmierski J, Banys A, Latek J, Bourke J, Jaszewski R. Raised IL-2 and TNF-alpha concentrations are associated with postoperative delirium in patients undergoing coronary-artery bypass graft surgery. *International Psychogeriatrics.* 2014;26(5):845-855.

34. Ritchie CW, Newman TH, Leurent B, Sampson EL. The association between C-reactive protein and delirium in 710 acute elderly hospital admissions. *International Psychogeriatrics.* 2014;26(5):717-724.

35. Ritter C, Tomasi CD, Dal-Pizzol F, et al. Inflammation biomarkers and delirium in critically ill patients. *Critical Care.* 2014;18(3):R106.

36. Zhang Z, Pan L, Deng H, Ni H, Xu X. Prediction of delirium in critically ill patients with elevated C-reactive protein. *Journal of Critical Care.* 2014;29(1):88-92.

37. Cerejeira J, Batista P, Nogueira V, Vaz-Serra A, Mukaetova-Ladinska EB. The stress response to surgery and postoperative delirium: evidence of hypothalamic-pituitary-adrenal axis hyperresponsiveness and decreased

suppression of the GH/IGF-1 Axis. *Journal of Geriatric Psychiatry and Neurology.* 2013;26(3):185-194.

38. Colkesen Y, Giray S, Ozenli Y, Sezgin N, Coskun I. Relation of serum cortisol to delirium occurring after acute coronary syndromes. *American Journal of Emergency Medicine.* 2013;31(1):161-165.

39. Kazmierski J, Banys A, Latek J, Bourke J, Jaszewski R. Cortisol levels and neuropsychiatric diagnosis as markers of postoperative delirium: a prospective cohort study. *Critical Care* 2013;17(2):R38.

40. Liu P, Li YW, Wang XS, et al. High serum interleukin-6 level is associated with increased risk of delirium in elderly patients after noncardiac surgery: a prospective cohort study. *Chinese Medical Journal.* 2013;126(19):3621-3627.

41. Plaschke K, Hauth S, Jansen C, et al. The influence of preoperative serum anticholinergic activity and other risk factors for the development of postoperative cognitive dysfunction after cardiac surgery. *Journal of Thoracic Cardiovascular Surgery.* 2013;145(3):805-811.

42. Skrobik Y, Leger C, Cossette M, Michaud V, Turgeon J. Factors predisposing to coma and delirium: fentanyl and midazolam exposure; CYP3A5, ABCB1, and ABCG2 genetic polymorphisms; and inflammatory factors. *Critical Care Medicine.* 2013;41(4):999-1008.

43. Westhoff D, Witlox J, Koenderman L, et al. Preoperative cerebrospinal fluid cytokine levels and the risk of postoperative delirium in elderly hip fracture patients. *Journal of Neuroinflammation.* 2013;10:122.

44. Bakker RC, Osse RJ, Tulen JH, Kappetein AP, Bogers AJ. Preoperative and operative predictors of delirium after cardiac surgery in elderly patients. *Europenan Journal of Cardiothoracic Surgery.* 2012;41(3):544-549.

45. Baranyi A, Rothenhausler HB. The impact of intra- and postoperative albumin levels as a biomarker of delirium after cardiopulmonary bypass: Results of an exploratory study. *Psychiatry Research.* 2012;200(2-3):957-963.

46. Cerejeira J, Nogueira V, Luis P, Vaz-Serra A, Mukaetova-Ladinska EB. The cholinergic system and inflammation: common pathways in delirium pathophysiology. *Journal of the American Geriatrics Society.* 2012;60(4):669-675.

47. Girard TD, Ware LB, Bernard GR, et al. Associations of markers of inflammation and coagulation with delirium during critical illness. *Intensive Care Medicine.* 2012;38(12):1965-1973.

48. Osse RJ, Fekkes D, Tulen JH, et al. High preoperative plasma neopterin predicts delirium after cardiac surgery in older adults. *Journal of the American Geriatrics Society.* 2012;60(4):661-668.

49. Bisschop PH, de Rooij SE, Zwinderman AH, van Oosten HE, van Munster BC. Cortisol, insulin, and glucose and the risk of delirium in older adults with hip fracture. *Journal of the American Geriatrics Society.* 2011;59(9):1692-1696.

50. Holmes C, Cunningham C, Zotova E, Culliford D, Perry VH. Proinflammatory cytokines, sickness behavior, and Alzheimer disease. *Neurology.* 2011;77(3):212-218.

51. Lee HJ, Hwang DS, Wang SK, Chee IS, Baeg S, Kim JL. Early assessment of delirium in elderly patients after hip surgery. *Psychiatry Investigation.* 2011;8(4):340-347.

52. McGrane S, Girard TD, Thompson JL, et al. Procalcitonin and C-reactive protein levels at admission as predictors of duration of acute brain dysfunction in critically ill patients. *Critical Care.* 2011;15(2):R78.

53. Morandi A, Gunther ML, Pandharipande PP, et al. Insulin-like growth factor-1 and delirium in critically ill mechanically ventilated patients: a preliminary investigation. *International Psychogeriatrics.* 2011;23(7):1175-1181.

54. van den Boogaard M, Kox M, Quinn K, et al. Biomarkers associated with delirium in critically ill patients and their relation with long-term subjective cognitive dysfunction; indications for different pathways governing delirium in inflamed and non-inflamed patients. *Critical Care.* 2011:R297.

55. van den Boogaard M, van Swelm RPL, Russel FGM, et al. Urinary protein profiling in hyperactive delirium and non-delirium cardiac surgery ICU patients. *Proteome Science.* 2011;9 (no pagination)(13).

56. Burkhart C, Dell-Kuster S, Gamberini M, et al. Modifiable and nonmodifiable risk factors for postoperative delirium after cardiac surgery with cardiopulmonary bypass. *Journal of Cardiothoracic and Vascular Anesthesia.* 2010;24(4):555-559. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/538/CN-00781538/frame.html.

57. Mu DL, Wang DX, Li LH, et al. High serum cortisol level is associated with increased risk of delirium after coronary artery bypass graft surgery: A prospective cohort study. *Critical Care.* 2010;14 (6).

58. Pearson A, de Vries A, Middleton S, et al. Cerebrospinal fluid cortisol levels are higher in patients with delirium versus controls. *BMC Research Notes.* 2010;3(1):33.

59. Plaschke K, Fichtenkamm P, Schramm C, et al. Early postoperative delirium after open-heart cardiac surgery is associated with decreased bispectral EEG and increased cortisol and interleukin-6. *Intensive Care Medicine.* 2010;36(12):2081-2089.

60. Tsuruta R, Nakahara T, Miyauchi T, et al. Prevalence and associated factors for delirium in critically ill patients at a Japanese intensive care unit. *General Hospital Psychiatry.* 2010;32(6):607-611.

61. van Munster BC, Bisschop PH, Zwinderman AH, et al. Cortisol, interleukins and S100B in delirium in the elderly. *Brain & Cognition.* 2010;74(1):18-23.

62. Adamis D, Lunn M, Martin FC, et al. Cytokines and IGF-I in delirious and non-delirious acutely ill older medical inpatients. *Age and Ageing.* 2009;38(3):326-251.

63. van Munster BC, Korse CM, de Rooij SE, Bonfrer JM, Zwinderman AH, Korevaar JC. Markers of cerebral damage during delirium in elderly patients with hip fracture. *BMC Neurology.* 2009;9:21.

64. Pfister D, Siegemund M, Dell-Kuster S, et al. Cerebral perfusion in sepsis-associated delirium. *Critical Care.* 2008;12(3):R63.

65. Rudolph JL, Ramlawi B, Kuchel GA, et al. Chemokines are associated with delirium after cardiac surgery. *Journals of Gerontology Series A-Medical Sciences.* 2008;63(2):184-189.

66. Van Munster BC, Korevaar JC, Zwinderman AH, Levi M, Wiersinga WJ, De Rooij SE. Time-course of cytokines during delirium in elderly patients with hip fractures. *Journal of the American Geriatrics Society.* 2008;56(9):1704-1709.

67. Adamis D, Treloar A, Martin FC, Gregson N, Hamilton G, Macdonald AJD. APOE and cytokines as biological markers for recovery of prevalent delirium in elderly medical inpatients. *International Journal of Geriatric Psychiatry.* 2007;22(7):688-694.

68. de Rooij SE, van Munster BC, Korevaar JC, Levi M. Cytokines and acute phase response in delirium. *Journal of Psychosomatic Research.* 2007;62(5):521-525.

69. Plaschke K, Hill H, Engelhardt R, et al. EEG changes and serum anticholinergic activity measured in patients with delirium in the intensive care unit. *Anaesthesia.* 2007;62(12):1217-1223.

70. White S, Calver BL, Newsway V, et al. Enzymes of drug metabolism during delirium. *Age and Ageing.* 2005;34(6):603-608.

71. Wilson K, Broadhurst C, Diver M, Jackson M, Mottram P. Plasma insulin growth factor-1 and incident delirium in older people. *International Journal of Geriatric Psychiatry.* 2005;20(2):154-159.

72. Beloosesky Y, Grinblat J, Pirotsky A, Weiss A, Hendel D. Different C-reactive protein kinetics in post-operative hip-fractured geriatric patients with and without complications. *Gerontology.* 2004;50(4):216-222.

73. Robertsson B, Blennow K, Brane G, et al. Hyperactivity in the hypothalamic-pituitary-adrenal axis in demented patients with delirium. *International Clinical Psychopharmacology.* 2001;16(1):39-47.

74. van der Mast RC, van den Broek WW, Fekkes D, Pepplinkhuizen L, Habbema JD. Is delirium after cardiac surgery related to plasma amino acids and physical condition? *Journal of Neuropsychiatry and Clinical Neuroscience.* 2000;12(1):57-63.

75. van der Mast RC, van den Broek WW, Fekkes D, Pepplinkhuizen L, Habbema JDF. Incidence of and preoperative predictors for delirium after cardiac surgery. *Journal of Psychosomatic Research.* 1999;46(5):479-483.

76. Gustafson Y, Olsson T, Asplund K, Hägg E. Acute confusional state (delirium) soon after stroke is associated with hypercortisolism. *Cerebrovascular Diseases.* 1993;3(1):33-38.

77. McIntosh TK, Bush HL, Yeston NS. Beta-endorphin, cortisol and postoperative delirium: A preliminary report. *Psychoneuroendocrinology.* 1985;10(3):303-313.

78. Amano K, Maeda I, Morita T, et al. C- reactive protein, symptoms and activity of daily living in patients with advanced cancer receiving palliative care. *Journal of Cachexia, Sarcopenia and Muscle.* 2017.

79. Demiray G, DeGirmencioGlu S, Ugurlu E, Yaren A. Effects of serum leptin and resistin levels on cancer cachexia in patients with advanced-stage non-small cell lung cancer. *Clinical Medicine Insights: Oncology.* 2017;11 (no pagination)(1179554917690144).

80. Fogelman DR, Morris J, Xiao L, et al. A predictive model of inflammatory markers and patient-reported symptoms for cachexia in newly diagnosed pancreatic cancer patients. *Supportive Care in Cancer.* 2017;25(6):1809-1817.

81. Luo Y, Kim HS, Kim M, Lee M, Song YS. Elevated plasma fibrinogen levels and prognosis of epithelial ovarian cancer: a cohort study and meta-analysis. *Journal of Gynecologic Oncology.* 2017;28(3).

82. Paulsen O, Laird B, Aass N, et al. The relationship between pro-inflammatory cytokines and pain, appetite and fatigue in patients with advanced cancer. *PLoS ONE.* 2017;12 (5) (no pagination)(e0177620).

83. Amano K, Maeda I, Morita T, et al. Clinical implications of C-reactive protein as a prognostic marker in advanced cancer patients in palliative settings. *European Journal of Cancer.* 2016;51:S207.

84. Bye A, Wesseltoft-Rao N, Iversen PO, et al. Alterations in inflammatory biomarkers and energy intake in cancer cachexia: a prospective study in patients with inoperable pancreatic cancer. *Medical Oncology.* 2016;33(6):54.

85. Mitsunaga S, Ikeda M, Shimizu S, et al. C-Reactive Protein Level Is an Indicator of the Aggressiveness of Advanced Pancreatic Cancer. *Pancreas.* 2016;45(1):110-116.

86. Morgado PC, Giorlando A, Castro M, Navigante A. Relationship between weight loss and parameters of skeletal muscle function in patients with

advanced cancer and fatigue. *Supportive Care in Cancer.* 2016;24(9):3961-3966.

87. Rodrigues AR, Trufelli DC, Fonseca F, de Paula LC, Giglio Ad. Fatigue in patients with advanced terminal cancer correlates with inflammation, poor quality of life and sleep, and anxiety/depression. *American Journal of Hospice and Palliative Medicine.* 2016;33(10):942-947.

88. Srdic D, Plestina S, Sverko-Peternac A, Nikolac N, Simundic AM, Samarzija M. Cancer cachexia, sarcopenia and biochemical markers in patients with advanced non-small cell lung cancer-chemotherapy toxicity and prognostic value. *Supportive Care in Cancer.* 2016;24(11):4495-4502.

89. Wu Y, Li C, Zhao J, et al. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios predict chemotherapy outcomes and prognosis in patients with colorectal cancer and synchronous liver metastasis. *World Journal of Surgical Oncology.* 2016;14(1):289.

90. Bilir C, Engin H, Can M, Temi YB, Demirtas D. The prognostic role of inflammation and hormones in patients with metastatic cancer with cachexia. *Medical Oncology.* 2015;32(3):56.

91. Miura T, Mitsunaga S, Ikeda M, et al. Characterization of patients with advanced pancreatic cancer and high serum interleukin-6 levels. *Pancreas.* 2015;44(5):756-763.

92. Miura T, Matsumoto Y, Hama T, et al. Glasgow prognostic score predicts prognosis for cancer patients in palliative settings: a subanalysis of the Japan–prognostic assessment tools validation (J-ProVal) study. *Supportive Care in Cancer.* 2015;23(11):3149-3156.

93. Barrera L, Montes-Servín E, Barrera A, et al. Cytokine profile determined by data-mining analysis set into clusters of non-small-cell lung cancer patients according to prognosis. *Annals of Oncology.* 2014;26(2):428-435.

94. Blakely AM, Heffernan DS, McPhillips J, Cioffi WG, Miner TJ. Elevated C-reactive protein as a predictor of patient outcomes following palliative surgery. *Journal of Surgical Oncology.* 2014;110(6):651-655.

95. Fujiwara Y, Kobayashi T, Chayahara N, et al. Metabolomics evaluation of serum markers for cachexia and their intra-day variation in patients with advanced pancreatic cancer. *PLoS ONE* 2014;9(11):e113259.

96. Lindenmann J, Neubock N, Smolle J, Maier A, Smolle-Juttner FM. The influence of elevated levels of C-reactive protein and hypoalbuminaemia on survival in patients with advanced inoperable oesophageal cancer undergoing palliative treatment. *European Surgery - Acta Chirurgica Austriaca.* 2014;46:S57.

97. Mondello P, Lacquaniti A, Mondello S, et al. Emerging markers of cachexia predict survival in cancer patients. *BMC Cancer.* 2014;14(1):828.

98. Moriwaki T, Ishige K, Araki M, et al. Glasgow Prognostic Score predicts poor prognosis among advanced biliary tract cancer patients with good performance status. *Medical Oncology.* 2014;31(11):287.

99. Szkandera J, Stotz M, Absenger G, et al. Validation of C-reactive protein levels as a prognostic indicator for survival in a large cohort of pancreatic cancer patients. *British Journal of Cancer.* 2014;110(1):183.

100. Zhang SY, Zeng D, Peng YH, et al. Cancer-related fatigue and chemotherapy-associated adverse effects: correlation with TNF-alpha, IL-1 and 17-hydroxycorticosteroids. *Future Oncology.* 2014;10(9):1619-1626.

101. Jafri SH, Shi R, Mills G. Advance lung cancer inflammation index (ALI) at diagnosis is a prognostic marker in patients with metastatic non-small cell lung cancer (NSCLC): a retrospective review. *BMC Cancer.* 2013;13(1):158.

102. Laird BJ, McMillan DC, Fayers P, et al. The systemic inflammatory response and its relationship to pain and other symptoms in advanced cancer. *Oncologist.* 2013;18(9):1050-1055.

103. Laird BJ, Kaasa S, McMillan DC, et al. Prognostic factors in patients with advanced cancer: a comparison of clinicopathological factors and the development of an inflammation-based prognostic system. *Clinical Cancer Research.* 2013;19(19):5456-5464.

104. Paiva CE, Paiva BSR. Prevalence, predictors, and prognostic impact of fatigue among Brazilian outpatients with advanced cancers. *Supportive Care in Cancer.* 2013;21(4):1053-1060.

105. Suh SY, Choi YS, Yeom CH, et al. Interleukin-6 but not tumour necrosis factor-alpha predicts survival in patients with advanced cancer. *Supportive Care in Cancer.* 2013;21(11):3071-3077.

106. de Raaf P, Sleijfer S, Lamers C, Jager A, Gratama J, van der Rijt C. The Association between Inflammation and Fatigue Dimensions in Advanced Cancer Patients and Cancer Survivors. *Palliative Medicine.* 2012;26(4):449-450.

107. Gioulbasanis I, Patrikidou A, Kitikidou K, et al. Baseline Plasma Levels of Interleukin-8 in Stage IV Non-Small-Cell Lung Cancer Patients: Relationship With Nutritional Status and Prognosis. *Nutrition and Cancer.* 2012;64(1):41-47.

108. Gulen ST, Karadag F, Karul AB, et al. Adipokines and systemic inflammation in weight-losing lung cancer patients. *Lung.* 2012;190(3):327-332.

109. Heitzer E, Sandner-Kiesling A, Schippinger W, et al. IL-7, IL-18, MCP-1, MIP1-beta, and OPG as biomarkers for pain treatment response in patients with cancer. *Pain Physician.* 2012;15(6):499-510.

110. Minton O, Strasser F, Radbruch L, Stone P. Identification of factors associated with fatigue in advanced cancer: a subset analysis of the European palliative

care research collaborative computerized symptom assessment data set. *Journal of Pain and Symptom Management.* 2012;43(2):226-235.

111. Partridge M, Fallon M, Bray C, McMillan D, Brown D, Laird B. Prognostication in advanced cancer: a study examining an inflammation-based score. *Journal of Pain and Symptom Management.* 2012;44(2):161-167.

112. Pond GR, Armstrong AJ, Wood BA, Leopold L, Galsky MD, Sonpavde G. Ability of C- reactive protein to complement multiple prognostic classifiers in men with metastatic castration resistant prostate cancer receiving docetaxel-based chemotherapy. *BJU International.* 2012;110(11b).

113. Wang D-s, Luo H-y, Qiu M-z, et al. Comparison of the prognostic values of various inflammation based factors in patients with pancreatic cancer. *Medical Oncology.* 2012;29(5):3092-3100.

114. Aydin Y, Kaplan I, Gundogdu B, Albayrak B, Turkyilmaz A, Eroglu A. Prognostic importance of serum CRP, prealbumin, and transferrin levels in patients with advanced stage esophageal cancer. *Turk Gogus Kalp Damar Cerrahisi Derg.* 2011;19(3):384-390.

115. Dev R, Hui D, Dalal S, et al. Association between serum cortisol and testosterone levels, opioid therapy, and symptom distress in patients with advanced cancer. *Journal of Pain and Symptom Management.* 2011;41(4):788-795.

116. Gioulbasanis I, Georgoulias P, Vlachostergios PJ, et al. Mini Nutritional Assessment (MNA) and biochemical markers of cachexia in metastatic lung cancer patients: interrelations and associations with prognosis. *Lung Cancer.* 2011;74(3):516-520.

117. Hwang J-E, Kim H-N, Kim D-E, et al. Prognostic significance of a systemic inflammatory response in patients receiving first-line palliative chemotherapy for recurred or metastatic gastric cancer. *BMC Cancer.* 2011;11(1):489.

118. Kwak SM, Choi YS, Yoon HM, et al. The relationship between interleukin-6, tumor necrosis factor-α, and fatigue in terminally ill cancer patients. *Palliative Medicine.* 2012;26(3):275-282.

119. Lee JS, Kwon OY, Choi HS, Hong HP, Ko YG. Serum C-reactive protein level is a predictive factor for 14-day mortality of patients with advanced cancer who present to the emergency department with acute symptoms. *Academic Emergency Medicine.* 2011;18(4):440-442.

120. Scheede-Bergdahl C, Watt HL, Trutschnigg B, et al. Is IL-6 the best pro-inflammatory biomarker of clinical outcomes of cancer cachexia? *Clinical Nutrition.* 2012;31(1):85-88.

121. Vlachostergios P, Gioulbasanis I, Kamposioras K, et al. Baseline insulin-like growth factor-I plasma levels, systemic inflammation, weight loss and clinical outcome in metastatic non-small cell lung cancer patients. *Oncology.* 2011;81(2):113-118.

122. Diakowska D, Krzystek-Korpacka M, Markocka-Maczka K, Diakowski W, Matusiewicz M, Grabowski K. Circulating leptin and inflammatory response in esophageal cancer, esophageal cancer-related cachexia–anorexia syndrome (CAS) and non-malignant CAS of the alimentary tract. *Cytokine.* 2010;51(2):132-137.

123. Meek CL, Wallace AM, Forrest LM, McMillan DC. The relationship between the insulin-like growth factor-1 axis, weight loss, an inflammation-based score and survival in patients with inoperable non-small cell lung cancer. *Clinical Nutrition.* 2010;29(2):206-209.

124. Ishizuka M, Nagata H, Takagi K, Kubota K. Influence of inflammation-based prognostic score on mortality of patients undergoing chemotherapy for far advanced or recurrent unresectable colorectal cancer. *Annals of Surgery.* 2009;250(2):268-272.

125. Karapanagiotou EM, Polyzos A, Dilana KD, et al. Increased serum levels of ghrelin at diagnosis mediate body weight loss in non-small cell lung cancer (NSCLC) patients. *Lung Cancer.* 2009;66(3):393-398.

126. Paddison JS, Temel JS, Fricchione GL, Pirl WF. Using the differential from complete blood counts as a biomarker of fatigue in advanced non-small-cell lung cancer: An exploratory analysis. *Palliative and Supportive Care.* 2009;7(2):213-217.

127. Takahashi M, Terashima M, Takagane A, Oyama K, Fujiwara H, Wakabayashi G. Ghrelin and leptin levels in cachectic patients with cancer of the digestive organs. *International Journal of Clinical Oncology.* 2009;14(4):315-320.

128. Inagaki M, Isono M, Okuyama T, et al. Plasma interleukin-6 and fatigue in terminally ill cancer patients. *Journal of Pain and Symptom Management.* 2008;35(2):153-161.

129. Karapanagiotou EM, Tsochatzis EA, Dilana KD, Tourkantonis I, Gratsias I, Syrigos KN. The significance of leptin, adiponectin, and resistin serum levels in non-small cell lung cancer (NSCLC). *Lung Cancer.* 2008;61(3):391-397.

130. Sharma R, Zucknick M, London R, Kacevska M, Liddle C, Clarke SJ. Systemic inflammatory response predicts prognosis in patients with advanced-stage colorectal cancer. *Clinical Colorectal Cancer.* 2008;7(5):331-337.

131. Weryńska B, Kosacka M, Gołecki M, Jankowska R. Leptin serum levels in cachectic and non-cachectic lung cancer patients. *Advances in Respiratory Medicine.* 2009;77(6):500-506.

132. Ravasco P, Monteiro-Grillo I, Camilo M. How relevant are cytokines in colorectal cancer wasting? *The Cancer Journal.* 2007;13(6):392-398.

133. Richey LM, George JR, Couch ME, et al. Defining cancer cachexia in head and neck squamous cell carcinoma. *Clinical Cancer Research.* 2007;13(22):6561-6567.

134. Suh S-Y, Ahn H-Y. A prospective study on C-reactive protein as a prognostic factor for survival time of terminally ill cancer patients. *Supportive Care in Cancer.* 2007;15(6):613.

135. Al Murri A, Bartlett J, Canney P, Doughty J, Wilson C, McMillan D. Evaluation of an inflammation-based prognostic score (GPS) in patients with metastatic breast cancer. *British Journal of Cancer.* 2006;94(2):227.

136. Kayacan O, Karnak D, Beder S, et al. Impact of TNF-[alpha] and IL-6 Levels on Development of Cachexia in Newly Diagnosed NSCLC Patients. *American Journal of Clinical Oncology.* 2006;29(4):328-335.

137. Ramsey S, Lamb GW, Aitchison M, Graham J, McMillan DC. Evaluation of an inflammation- based prognostic score in patients with metastatic renal cancer. *Cancer.* 2006;109(2):205-212.

138. Di Nisio M, Niers T, Reitsma P, Buller H. Plasma cytokine and P- selectin levels in advanced malignancy. *Cancer.* 2005;104(10):2275-2281.

139. Rich T, Innominato PF, Boerner J, et al. Elevated serum cytokines correlated with altered behavior, serum cortisol rhythm, and dampened 24-hour rest-activity patterns in patients with metastatic colorectal cancer. *Clinical Cancer Research.* 2005;11(5):1757-1764.

140. Bolukbas FF, Kilic H, Bolukbas C, et al. Serum leptin concentration and advanced gastrointestinal cancers: a case controlled study. *BMC Cancer.* 2004;4(1):29.

141. Dülger H, Alici S, ŞekeroĞlu M, et al. Serum levels of leptin and proinflammatory cytokines in patients with gastrointestinal cancer. *International Journal of Clinical Practice.* 2004;58(6):545-549.

142. Elahi MM, McMillan DC, McArdle CS, Angerson WJ, Sattar N. Score based on hypoalbuminemia and elevated C-reactive protein predicts survival in patients with advanced gastrointestinal cancer. *Nutrition and Cancer.* 2004;48(2):171-173.

143. Jamieson N, Brown D, Wallace A, McMillan D. Adiponectin and the systemic inflammatory response in weight-losing patients with non-small cell lung cancer. *Cytokine.* 2004;27(2-3):90-92.

144. Songur N, Kuru B, Kalkan F, Ozdilekcan C, Cakmak H, Hizel N. Serum interleukin-6 levels correlate with malnutrition and survival in patients with advanced non-small cell lung cancer. *Tumori.* 2004;90(2):196-200.

145. Scott HR, McMillan DC, Brown DJ, Forrest LM, McArdle CS, Milroy R. A prospective study of the impact of weight loss and the systemic inflammatory response on quality of life in patients with inoperable non-small cell lung cancer. *Lung Cancer.* 2003;40(3):295-299.

146. Alemán MR, Santolaria F, Batista N, et al. Leptin role in advanced lung cancer. A mediator of the acute phase response or a marker of the status of nutrition? *Cytokine.* 2002;19(1):21-26.

147. Orditura M, De Vita F, Catalano G, et al. Elevated serum levels of interleukin-8 in advanced non-small cell lung cancer patients: relationship with prognosis. *Journal of Interferon and Cytokine Research.* 2002;22(11):1129-1135.

148. Scott H, McMillan D, Forrest L, Brown D, McArdle C, Milroy R. The systemic inflammatory response, weight loss, performance status and survival in patients with inoperable non-small cell lung cancer. *British Journal of Cancer.* 2002;87(3):264.

149. De Vita F, Romano C, Orditura M, et al. Interleukin-6 serum level correlates with survival in advanced gastrointestinal cancer patients but is not an independent prognostic indicator. *Journal of Interferon and Cytokine Research.* 2001;21(1):45-52.

150. Jatoi A, Loprinzi CL, Sloan JA, Klee GG, Windschitl HE. Neuropeptide Y, leptin, and cholecystokinin 8 in patients with advanced cancer and anorexia - A North Central Cancer Treatment Group exploratory investigation. *Cancer.* 2001;92(3):629-633.

151. Mantovani G, Maccio A, Madeddu C, et al. Serum values of proinflammatory cytokines are inversely correlated with serum leptin levels in patients with advanced stage cancer at different sites. *Journal of Molecular Medicine.* 2001;79(7):406-414.

152. Mantovani G, Maccio A, Mura L, et al. Serum levels of leptin and proinflammatory cytokines in patients with advanced-stage cancer at different sites. *Journal of Molecular Medicine.* 2000;78(10):554-561.

153. Nenova K, Kovatchev D. TNF-A levels in cachectic cancer patients. *Archives of Hellenic Medicine* 2000;17(6):619-622.

154. O'Gorman P, McMillan DC, McArdle CS. Longitudinal study of weight, appetite, performance status, and inflammation in advanced gastrointestinal cancer. *Nutrition and Cancer.* 1999;35(2):127-129.

155. Okada S, Okusaka T, Ishii H, et al. Elevated serum interleukin-6 levels in patients with pancreatic cancer. *Japanese Journal of Clinical Oncology.* 1998;28(1):12-15.

156. Wallace A, Sattar N, McMillan D. Effect of weight loss and the inflammatory response on leptin concentrations in gastrointestinal cancer patients. *Clinical Cancer Research.* 1998;4(12):2977-2979.

157. Maltoni M, Marco P, Oriana N, et al. Biological Indices Predictive of Survival in 519 Italian Terminally Ill Cancer Patients *Journal of Pain and Symptom Management.* 1997;13(1).

158. Simons J, Schols A, Campfield L, Wouters E, Saris W. Plasma concentration of total leptin and human lung-cancer-associated cachexia. *Clinical Science.* 1997;93(3):273-277.

159. Marcantonio ER, Rudolph JL, Culley D, Crosby G, Alsop D, Inouye SK. Serum biomarkers for delirium. *Journals of Gerontology Series A-Medical Sciences.* 2006;61(12):1281-1286.

160. Kellum JA, Kong L, Fink MP, et al. Understanding the inflammatory cytokine response in pneumonia and sepsis: results of the Genetic and Inflammatory Markers of Sepsis (GenIMS) Study. *Archives of Internal Medicine.* 2007;167(15):1655-1663.

161. Saribal D, Hocaoglu-Emre F, Erdogan S, Bahtiyar N, Okur SC, Mert M. Inflammatory cytokines IL-6 and TNF-α in patients with hip fracture. *Osteoporosis International.* 2019;30(5):1025-1031.

162. Hennessy E, Gormley S, Lopez-Rodriguez AB, Murray C, Murray C, Cunningham C. Systemic TNF-α produces acute cognitive dysfunction and exaggerated sickness behavior when superimposed upon progressive neurodegeneration. *Brain, behavior, and Immunity.* 2017;59:233-244.

163. Khan GH, Galazis N, Docheva N, Layfield R, Atiomo W. Overlap of proteomics biomarkers between women with pre-eclampsia and PCOS: a systematic review and biomarker database integration. *Human Reproduction.* 2014;30(1):133-148.

164. Strawbridge R, Young AH, Cleare AJ. Biomarkers for depression: recent insights, current challenges and future prospects. *Neuropsychiatric Disease and Treatment.* 2017;13:1245.

165. Cho S-Y, Choi J-H. Biomarkers of sepsis. *Infection and Chemotherapy.* 2014;46(1):1-12.

Chapter 4: Development of Reporting Essentials for DElirium bioMarker Studies (REDEEMS): A Delphi study and consensus meeting

4.1 Chapter preface

Chapter three identified considerable overlap in the biomarkers in delirium and the biomarkers of the advanced cancer-related syndromes of interest. In addition to addressing its primary aim, the systematic review highlighted a broader systemic problem of poor quality of reporting of delirium biomarker studies. Unfortunately, many of the included delirium studies were not rigorously reported, with many lacking sufficient information for adequate assessment of their quality and synthesis of results. Because systemic reporting deficits so clearly hampers progress in the understanding of delirium pathophysiology, exploration of how delirium biomarker study reporting could be improved was indicated.

This chapter reports on Stage 1 and Stage 2 of the REDEEMS guideline development, outlining the methods and the results of both the Delphi and the consensus meeting. The next, Chapter five, reports on the final stage of the development of the REDEEMS guideline (figure 4.1).

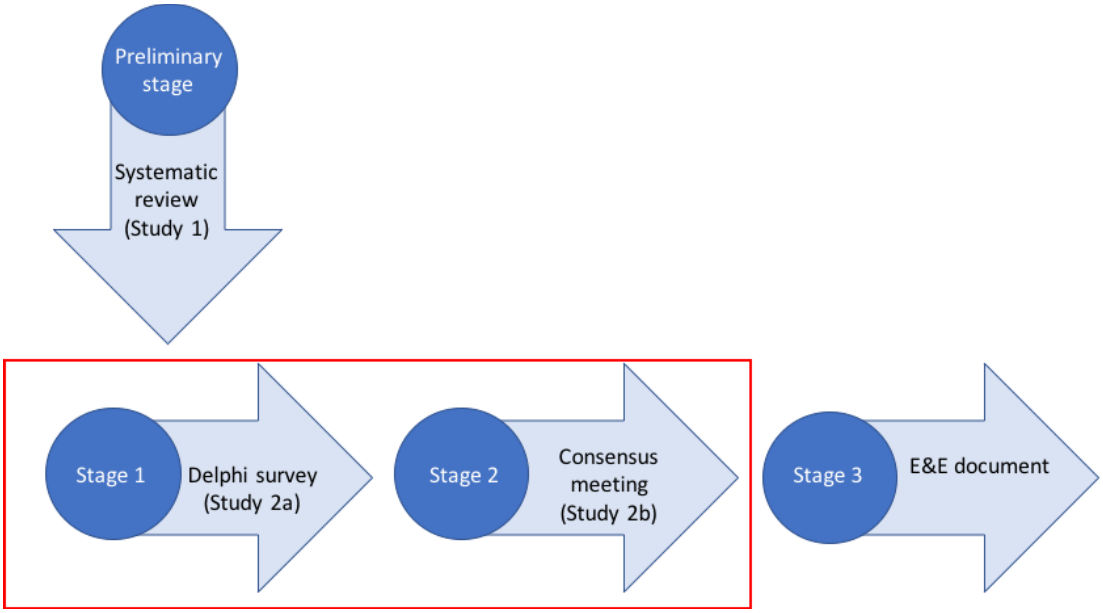

Figure 4.1 The REDEEMS guideline development process employed in Study 2, highlighting the stages reported in this chapter

Stage 1 of this study was published in 2020 in the *Journal of International Geriatric Psychiatry* (Impact factor*:* 3.180). This Chapter contains an edited version of the publication, which is provided in its published form in Appendix 1.2.

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4.2 Introduction

Attempts to synthesise the results of delirium biomarker studies in the systematic review in Chapter two highlighted the issue of incomplete and inconsistent study reporting. Many included studies did not provide sufficient detail to enable replication or accurate interpretation of the study findings. Without diligent, standardised reporting of biomarker research, synthesis of studies will remain untenable and thereby hinder development of understanding of delirium pathophysiology.

4.2.1 Background to reporting guidelines

Systematic reviews and meta-analyses synthesise results from multiple primary studies and are considered the highest level of evidence; however, the process is impeded by inconsistent and incomplete reporting of primary research.[1] Inadequate reporting of study methodology and/or results prevents critical appraisal and limits effective dissemination.[2] Reporting guidelines emerged in the mid-1990s in response to widespread deficiencies in research publications. For example, initiatives to improve the quality of reports of randomized controlled trials (RCTs) led to the development of the CONSORT (CONsolidated Standards Of Reporting Trials) Statement, first published in 1996, that is now one of the most well-established reporting guidelines in health research.[3] The CONSORT Statement led the way for the development of a multitude of reporting guidelines.[4] Reporting guidelines help researchers to meet certain reporting standards by providing a checklist of items to adhere to for best practice methods, in their study manuscripts.[5]

In 2008, the EQUATOR (Enhancing the QUAlity and Transparency Of Reporting) network[6] was established as a free online library for reporting guideline developers, to enhance the reliability of health research studies and promote transparent and accurate reporting practices. Currently, the EQUATOR Network lists 431 reporting guidelines.

Studies have found that reporting guidelines such as the CONSORT (Consolidated Standards of Reporting Trials) Statement[7] has led to improvements in the reporting rigor, particularly in the method of sequence generation and the allocation concealment, compared to studies that did not explicitly adhere to the CONSORT Statement.[8]

4.2.2 Need for reporting guidelines for delirium biomarker studies

Reporting guidelines relevant to biomarker studies currently exist (see Table 4.1), however, no reporting guidelines currently exist for delirium biomarker studies, and, prior to this research, it was not established how these existing guidelines may be modified to inform optimal delirium biomarker research. In the absence of such a guideline, the REMARK checklist for reporting tumour marker prognostic studies[9] was used to assess the quality of studies in the systematic review in Chapter two[10] and to develop the REDEEMS guideline, as it was the most detailed of all the above named guidelines, particularly with respect to assay procedures.

Table 4.1 Other reporting guidelines relevant to biomarker studies

Reporting guideline	Applicability	Development process
CONSORT[11]	Randomised controlled trials	Face-to-face meetings
STROBE[12]	Observational studies in epidemiology	Face-to-face meetings
STARD[13]	Studies of diagnostic accuracy	Two online surveys, face-to-face meeting and pilot testing
Guidelines for uniform reporting of body fluid biomarker studies in neurologic disorders[14]	Body fluid biomarker research studies in neurological disorders	Email discussions
REMARK[9]	Tumor marker prognostic studies	Face-to-face conference, online meeting and email discussions
BRISQ[15]	Human biospecimen studies	A face-to-face workshop

4.2.3 Background to the Delphi method

The Delphi technique (subsequently referred to as the 'Delphi') is a well-established, iterative process for collating and distilling knowledge from a group of experts using a series of questionnaires interspersed with controlled feedback.[19-22] The Delphi has been described as 'the achievement of concurrence in a given area where none previously existed.'[21] The questionnaires are designed to focus on problems, opportunities, solutions or forecasts.[23] Each subsequent questionnaire (round) is developed based on the results from the previous round. The round final outcome of a Delphi study represents a consensus among the participants (referred to as 'experts').[20]

4.2.4 The Classical Delphi

Since its introduction, the Delphi has been modified for use across several disciplines, with multiple approaches. These approaches are conceptualized as three main types of Delphi: Classical Delphi, Decision Delphi and Policy Delphi.

More recently, there have been several widely accepted modifications made to the Classical Delphi (termed a 'Modified Delphi'), which was the method employed in this study. The most common application focuses on the online implementation rather

than postal, albeit with the same fundamental principles as in the Classic Delphi.[24] The Classical Delphi method is described below.

The original Delphi method arose historically, from a methodology developed by Norman Dalkey of the RAND corporation in the 1950's[25] and was designed to elicit expert opinion in a systematic manner for technological forecasting.[26] The RAND corporation was a research institution that was focused on national security issues that later became focused on science and education. RAND researchers developed a structured survey ("project DELPHI") as a means of gaining the most reliable consensus of opinions to estimate their bombing requirements. For security reasons, the content of the experiment wasn't published until 10 years later by Dalkey and Helmer.[25]

The classical Delphi method normally consists of two or more rounds of questionnaires administrated via post to a panel of informed participants in a specific field of application ('experts'). The first round of the Classic Delphi is usually qualitative in nature, comprising open-ended questions.[17,21] This allows the experts free scope to elaborate on their views in a particular area of interest.[27] These responses are then analysed by the researchers and presented back to participants in the form of targeted closed statements.[17] The expert panel rank the statements according to their opinion on the subject. In the subsequent round(s) following this, individual responses are passed back to the participants along with all the other anonymous responses.[28] This process continues until a consensus is reached.[20]

The Classical Delphi differs from the Decision Delphi as the expert panel are not anonymous, although their responses are.[29] Similarly, the Policy Delphi (also known

as ‘Dissensus Delphi’) is not aimed at gaining consensus as in the Classical Delphi, but rather aims to define and differentiate diverse views.[30]

4.2.5 Reliability, validity and trustworthiness

There are several criticisms regarding rigor of the Delphi method.[31] These encompass issues around the lack of guidelines on conducing a Delphi study, the sample size required for a Delphi, the implications of anonymity, determining what constitutes consensus, and the definition of what constitutes an ‘expert’.[32] Keeney et al. (2011)[20] examined the limitations in the use of reliability, validity and trustworthiness measures in Delphi studies,[20] of which, the key challenges are summarised below.

The expert panel

Traditionally, the term ‘expert’ has been used to describe Delphi participants; however, a common criticism is that there is no universally agreed definition of what an expert is[18,31] or how they are selected.[17] An ‘expert’ has been defined in the Delphi literature as someone with knowledge in a particular topic area[18], a ‘specialist’ in their respective fields,[33] or an informed individual or advocate.[21,33] Sackman (1974) asserts that there is no way to verify that the opinions made by the experts are any more valid than ‘non-experts’.[26] Since the definition of ‘expert’ in the Delphi method is ‘somewhat arbitrary’[33] (Goodman, 1987, p. 732), the expertise of the participants alone does not guarantee the validity of the results.

Furthermore, the number of experts on a panel required to constitute a representative sample in a Delphi study is ambiguous and, as such, Delphi sample sizes vary significantly from less than 15 participants to several hundred.[20] Some argue that the number of experts required is dependent upon funding and practical logistics criteria,[17] while others argue that since the focus of the Delphi is to reach consensus among a

panel of experts, the sample size does not depend on a statistical power calculation, and instead, relies on group dynamics to reach a consensus. Based on this latter reason, the literature suggests that 10-18 Delphi experts is sufficient.[34]

Anonymity

One of the key features of the Delphi is that it ensures participant anonymity, allowing participants to openly express their views without conforming to group pressure.[18,35] All responses have equal weight and are given equal importance in the analysis.[33] Although this is one of the main advantages of the Classical Delphi, it can lead to a lack of accountability for the opinions expressed.[33,36] Issues concerned with the complete anonymity of the Delphi have been challenged. Firstly, individual responses in the e-Delphi are analysed by the researcher, and sent back to the participants via email; therefore, some argue that the research can link the responses to the participant. Secondly, depending on the size of the Delphi and the subject field, some argue that if participants know one another, then individual responses might be able to be attributed to a given person. This concept, referred to as a 'quasi-anonymous' was first adopted by Rauch, 1979.[37] Despite this limitation, the Delphi is an appropriate method to use when distance, time or cost precludes face-to-face meetings required by other group consensus methods such as the Nominal Group Technique.[38]

4.2.6 Aim

To obtain international consensus from leaders in delirium research on the core elements for delirium biomarker studies that are required to improve understanding of delirium pathophysiology.

4.2.7 Objectives

1. To survey international experts in delirium research, using a modified Delphi

method, about the critical items to include in a reporting guideline for delirium biomarker studies.

2. To reach a consensus among international experts in delirium research about which borderline items (i.e. consensus of 70%-80% in the Delphi process) to include in the reporting guideline.

4.3 Methods

4.3.1 Framework used for the REDEEMS guidelines

There is no set process for how reporting guidelines should be developed. Yet, if reporting guidelines aren't developed robustly, they may be of little use to users.[16] Therefore, the framework used reflected Steps 1-4 of guideline development proposed by Moher et al. (2010)[4] (Table 4.2). This process is supported by Delphi researchers and guideline developers [4,17] and is endorsed by the Equator Network.[6] Following the initial systematic review (Study 1) and the Delphi (Study 2a), which formed the preliminary framework for the REDEEMS items, the next stage in the development was to validate the items that reached a 70%-80% consensus from the Delphi process to enhance the credibility of the guidelines (Study 2b). Although Moher et al. (2010) proposes a face-face consensus meeting, we undertook the meeting via teleconference due international travel restrictions as a result of the COVID-19 pandemic.

Table 4.2 Stages of development for the REDEEMS checklist adapted from Moher et al (2010)

Development stages for the REDEEMS	Steps recommended by Moher et. al (2010) implemented in development of the REDEEMS	
STUDY 1: Systematic review	**Step 1: Initial steps**	Review the literature Identify the need for a reporting guideline
STUDY 2a: Delphi study	**Step 2: Pre-meeting activities**	Identify participants Conduct a Delphi survey Generate a list of items for consideration at the consensus meeting Prepare for the consensus meeting (decide size and duration of the meeting, develop meeting logistics and agenda, and prepare materials to be sent to participants prior to the meeting)
STUDY 2b: Consensus meeting	**Step 3: The consensus meeting**	Present and discuss results of pre-meeting activities and relevant evidence Discuss the rationale for including items in the checklist Discuss authorship
Explanation and Elaboration (E&E) document development	**Step 4: Post-meeting activities**	Develop the guidance statement Develop an explanatory document (E&E) Develop publication strategy (consider multiple and simultaneous publications)
Activities not included in this thesis (i.e. Post-thesis activities)	Step 5: Post-publication activities	Seek and deal with feedback and criticism Evaluate the impact of the guideline Develop website Translate/update guideline

4.3.2 Study design

A multi-method design was employed, comprising a three-round modified Delphi survey[18] (Study 2a), and an online consensus meeting with an expert panel (Study 2b).

Study 2a: International Modified Delphi Study

4.3.3 Rationale for selecting the Delphi method

Findings of inconsistent reporting in delirium biomarker studies in Chapter two confirmed the need for reporting recommendations to guide future researchers in the field. Given the nature and international scope of the problem, a consensus approach was considered the most appropriate. Delphi consensus methods are used to gain an informed opinion in the absence of a gold standard such as practice guidelines.[39] Deciding on best practice methods for delirium biomarker studies required exploration of a variety of viewpoints to generate a consensus. There are a number of group consensus methods that can be used,[40] such as face-to-face meetings or the Nominal Group technique,[38] however, these require participants to be in the same place at the same time. An online Delphi technique was therefore deemed the most appropriate and feasible consensus method to combine the opinions of delirium experts, who are a limited group of geographically dispersed people from a diverse range of clinical and academic disciplines;[41] for example, psychiatry, geriatrics, ICU, neurology, and basic science.

The Delphi is also flexible in regards to sample size, which ranges largely depending on the research questions and availability of eligible participants.[19] This was another important consideration for this study because of the limited number of delirium experts worldwide. Furthermore, the Delphi applies both qualitative and quantitative methods in the form of open-ended questions followed by closed statements, thereby allowing an initial exploratory approach that enables the collection of richer data.[42]

4.3.4 Survey preparation

Piloting of the survey

Before sending the survey to participants, each round one was piloted by the study supervisors and three researchers with sufficient clinical understanding of delirium and basic knowledge of biomarker research. These latter researchers were not involved in the development of the surveys and were not eligible to be study participants (n=3). Pilot testing determined the accessibility of the electronic survey, completion of the survey in the time set out in the participant information sheet, and clarity of the survey questions. Minor issues were identified by the pilot and amendments were made.

Strategies to increase the response rate

Although there is no universally accepted definition for an adequate response rate for online surveys[43]; the survey questions were kept short and concise, with logical flow throughout each round to help boost response rates. All three rounds also included a progress bar at the end of each survey page so participants could monitor their progress. Email reminders to non-responders were sent around 14 days after dissemination of each survey round, with a second reminder sent around 28 days, if required.

4.3.5 Participant selection and recruitment

Participants

International experts in the field of delirium research were identified and invited to take part in the three-stage Delphi study. Those eligible were researchers who had investigated delirium in humans, including but not restricted to biomarkers. Basic science and animal researchers focused on delirium were also eligible. All were required to have delirium research experience in the last ten years (with no minimum number of years pre-specified), plus computer and internet access and an email

address. Those eligibility criteria were designed to recruit participants with adequate knowledge, expertise, and opportunity to make a meaningful contribution.

Recruitment

A combination of purposive sampling[19] and snowballing[44] was used to recruit. *Purposive sampling* was used to enable participants from a broad range of geographic locations and clinical settings. Approaches included: 1) email invitation via membership lists of Delirium Societies (Australasian Delirium Association, American Delirium Society, and the European Delirium Association); 2) email invitations sent through colleagues' and professional networks; and 3) researchers identified from recent and relevant journal articles in delirium biomarker studies. An indirect approach included a Twitter advertisement on the 2019 'World Delirium Awareness Day.'[45] *Snowball sampling* was achieved by asking eligible participants and presidents of delirium societies to invite any other eligible researchers who might be interested in participating.

4.3.6 Data collection

The doctoral researcher (IAD) sent each potential participant an email invitation with a link to the online REDCap survey[46] in three parts: A participant information sheet outlining the study procedures and their involvement in the study (Appendix 5.1), a demographics section, and the survey questions (Appendix 6). Consent was implied if the survey was completed. Participants were reminded that completing all three rounds would minimize attrition bias; however, non-completion of a round did not prohibit participants from participating in subsequent rounds. Demographic details were collected at the beginning of each round, but only once per participant.

Round 1

The first round of the Delphi is particularly important, with the selection of an expert panel and development of the initial open-ended questions that inform the subsequent rounds and the end result.[47] In this study, development of round one was informed by results from the quality assessment of a prior systematic review and predominantly used an open-ended qualitative method, in accordance with the Classic Delphi approach.[20] In round 1, participants were provided with both open- and closed-ended questions about biomarker research in delirium, based on each key domain of the REMARK checklist.[9] Participants were also invited to provide comments after each question. Round 1 answers informed development of a list of statements for round 2 of the Delphi.

Round 2

In round 2, 56 statements were reduced by a rating process whereby participants rated each statement on a 5-point Likert scale (1= not important at all; 2=slightly important; 3) not important or unimportant; 4) moderately important; and 5=very important). This scale provided a standardized and strongly favoured method to measure consensus.[18]

Participants were also invited to provide comments and suggest alternate wording for each statement. Reasons for excluding comments or items suggested by participants were recorded. An email invitation with a URL to the Redcap round 2 survey was sent to eligible participants, in the same way as round 1.

Round 3

This final round aimed to refine the list of statements pertaining to recommendations for reporting of delirium biomarker studies. In round 3, participants were sent the survey along with: 1) a summary of round 2 statements that reached consensus; 2) a

summary of statements that did not reach consensus (which were repeated in this round); and 3) newly suggested statements from participants' comments in round 2. Participants were asked to provide a new rating on the 5-point Likert scale. Only statements that did not achieve consensus from round 2 were carried into round 3 (n=5). Round 2 statements that already achieved a consensus were excluded from round 3, although still presented in summary for participants.

4.3.7 Data analysis

Round 1

Qualitative and quantitative data were analysed separately. Demographic data from each round was collated and inputted into the IBM Statistical Package for Social Science (SPSS), Version 25, 2017. This information was presented as frequency distributions and percentages for each participant.

Each participant was allocated a random identification number for reporting and collation of results. Thematic analysis[48] was applied to open-ended responses using manual methods by the doctoral researcher (IAD). These were downloaded verbatim to a spreadsheet (Microsoft Excel, Version 15, 2017). Two other researchers (MA and AM) provided additional guidance and oversight of the coding and development of themes. This process involved reading each of the responses, eliminating duplicates, creating sub-groups of similar statements and grouping these into themes, and developing representative closed statements for round two. Reviewers discussed any uncertainties about the coding or themes until an agreement was met. Reasons recorded for excluding or amending comments or items prior to round 2 were that the item/comment(s) were:

1. too vague

2. a misunderstanding of the question
3. not relevant to the topic or study
4. repetitious in meaning or intent
5. already encompassed within another item and/or or better combined with another item

Rounds 2 and 3

The purpose of the consensus process used in round 2 and 3 was to explore items that achieve a high level of agreement among experts, based on the sequential rating. However, key concerns relate to the definition of 'consensus' as there is no universally agreed consensus for the process of item refinement in a Delphi. Over the years, 'consensus' has been defined in several ways and there is still much debate on the level of consensus, which depends largely on sample size, aim of the research and resources.[32] Some follow the rule that 51% agreement on an item is acceptable,[21,49] while others maintain anywhere from 75%[17] to 100% agreement amongst respondents.[50] Despite which level of consensus is chosen, the level of agreement should be clearly defined and set a *priori* as it decides which items are retained from the previous rounds.[51] For this study, a statistician was consulted to provide expert advice, and a *priori* 70% agreement was chosen. Consensus was therefore achieved when at least 70% of participants' responses fell within two categories on the 5-point Likert scale. It should be noted that although the Delphi concludes when a consensus has been achieved, the end results aren't necessarily the most reliable or accurate answer to the question,[20] rather, they represent a majority opinion.[37]

Rounds 2 and 3 aimed to fulfil the consensus process. In each round, participants were provided with a summary of the results from the previous rounds, as well as instructions for completing the survey. Round 2 items with the greatest participant

agreement in the very low and low importance categories (Likert score 1 and 2) were deemed unlikely to be included in the list of recommendations. Items with the participant agreement in the moderate importance category (Likert score 3) were considered for inclusion in the recommendations and items with the greatest participant agreement in the high to very high importance category (Likert scores ≥4), were included in the recommendations. REDCap data were exported to SPSS for statistical analysis. Descriptive data for each item were obtained, including the mean Likert scores, standard deviation (SD) and the median. Percentages were calculated to determine the level of agreement on a statement. Data analysts were blinded to participants' identities.

Study 2b: Consensus meeting

4.3.8 Recruitment of the second expert panel

To find suitable participants for the expert panel, delirium researchers and reporting guideline developers were identified from the Delphi participant list and authorship of recent and relevant publications. The doctoral researcher (IAD) sent invitations to 35 potential participants. If they were not able to or did not wish to participate, they were invited to suggest a suitable alternative person.

4.3.9 Consensus meeting preparation

A Poll Everywhere™[52] presentation was prepared to host the online consensus meeting. Poll Everywhere is an interactive voting application that provides live participant responses and feedback.

Participants who agreed to take part in the consensus meeting were sent an invitation to attend a Zoom meeting one week prior to the meeting. Participants were also sent the meeting agenda, instructions on how to access the live poll, the published

manuscript of the Delphi study, and a copy of the REMARK checklist. Participants were also asked to sign a written consent form, and answer some basic demographic questions (Table 3.7) to be sent back to the doctoral researcher before the meeting.

Items that reached a 70-80% agreement (i.e. borderline consensus) in the Delphi study were the key items for discussion in the consensus meeting (Table 4.6). For each item, participants were asked to indicate whether or not the item should be included in the REDEEMS checklist (Yes / No). Consensus agreement was determined *a priori as* a majority (i.e. ≥50% agreement). Items that did not achieve consensus agreement were discussed until a consensus opinion was reached. In the cases where a consensus opinion could not be reached, the items were re-presented to the panel in an email, until a consensus was achieved. Participants were also asked whether each item was clearly worded and if not, were asked to provide suggestions to improve the wording and clarity of the item through open-ended text in Poll Everywhere. All voting was facilitated by the meeting chair (IAD).

4.4 Ethical considerations

4.4.1 Ethical approval

Ethical approval was obtained from the University of Technology Sydney Human Research Ethics Committee on 25/01/2019 (approval no. ETH18-2673) (Appendix 4).

4.4.2 Considerations for participants

This was a low risk study with the study participants, and the content of the surveys and consensus meeting discussion were not anticipated to cause any physical psychological or emotional harm. However, some participants may have authored studies included in the preceding systematic review; therefore, sensitivity was required when raising issues about study quality and reporting.

4.4.3 Confidentiality

The confidentiality of all participants was guaranteed as this is a key advantage of the Delphi.[32] Participants were informed that they would remain anonymous, and that they were free to withdraw from the project at any time without any consequences, and without needing to provide a reason for their withdrawal. As the survey was anonymous, identifying information or participants' responses in the Delphi was not shared with the participant group. Participants' names and email addresses were separated from the participant ID numbers so that no responses could be linked to any identifying information.

4.4.4 Data management and storage

A dedicated password protected REDCap[46] account was established for this study. This is a "Gold" account which features enhanced security (SSL) and can only be accessed by members of the research team. Survey data downloaded from the account was stored on a password protected computer. Once data had been downloaded and the analysis was complete through SPSS, the corresponding survey data was deleted from the REDCAP account to further protect participants' privacy. Data will be securely stored for five years after the completion of the study, after which it will be destroyed.

4.5 Results

Study 2a: Delphi

4.5.1 Participants

Surveys were delivered over three rounds from February to August 2019 via email. Twenty-nine participants completed round 1; however, one participant's data was removed as it was clear that they had not understood the questions, and therefore the responses were not codeable. Nineteen participants completed round 2, and 20

completed round 3, with a total of 32 completing at least one round and 10 completing all three rounds. Participants were from 12 countries (Argentina, Australia, Belgium, Germany, Italy, Norway, Portugal, Sweden, Switzerland, The Netherlands, United Kingdom (UK) and United States (US)). Overall, participants were predominantly clinician researchers (n=21; 64%), with 47% of participants having over 10 years' experience in delirium research and 47% having conducted more than 10 delirium studies. Twenty-five (78%) participants had conducted between 0 - 5 biomarker studies, 13% between 5 - 10, and three participants (9%) had conducted more than 10. Twenty-two (69%) had conducted a delirium biomarker study, and nine (28%) had a higher research degree in delirium and two (6%) in biomarkers (Table 4.3).

Table 4.3 Demographic characteristics of Delphi participants (n=32)

	N=32	(%)
Country of residence		
US	14	(44)
Europe	11	(34)
United Kingdom	4	(13)
Australia	2	(6)
Latin America	1	(3)
Years in delirium research		
>10 years	15	(47)
5-10 years	10	(31)
<5 years	7	(22)
Current role		
Clinician/researcher	21	(64)
Researcher	6	(19)
Clinician	5	(15)
Place of work*		
Hospital	26	
University	22	
Research centre	8	
Other	1	
Main delirium research area*		
Clinical trials	22	
Epidemiology	14	
Health services	9	
Implementation/knowledge translation/education	9	
Qualitative research	6	
Other	2	
Number of delirium studies conducted		
>10	15	(47)
5-10	9	(28)
<5	8	(25)
Number of biomarker studies conducted		
>10	3	(9)
5-10	4	(13)
<5	25	(78)
Conducted a delirium biomarker study		
Yes	22	(69)
No	10	(31)
Research higher degree (Masters or doctorate)		
In delirium	9	(28)
In biomarkers	2	(6)
Both	6	(19)
No	15	(47)

**Participants could choose more than one option*

4.5.2 Consensus

The 18 open-ended questions and 5 closed questions of round 1 were grouped and reduced to 56 statements for round 2, with statements adjusted or removed if unclear, repetitive or already encompassed in another statement, not relevant to topic, or better combined with another item. An outline of the process of including items in the final delirium biomarker recommendations is shown in Figure 4.2. Following round 2, 51 statements reached consensus for inclusion, and 5 statements did not. Twelve newly-suggested statements arising from round 2 were carried into round 3, along with the 5 statements that did not reach a consensus (n=17 items in total). Following round 3, 60 statements reached a consensus, and 8 did not.

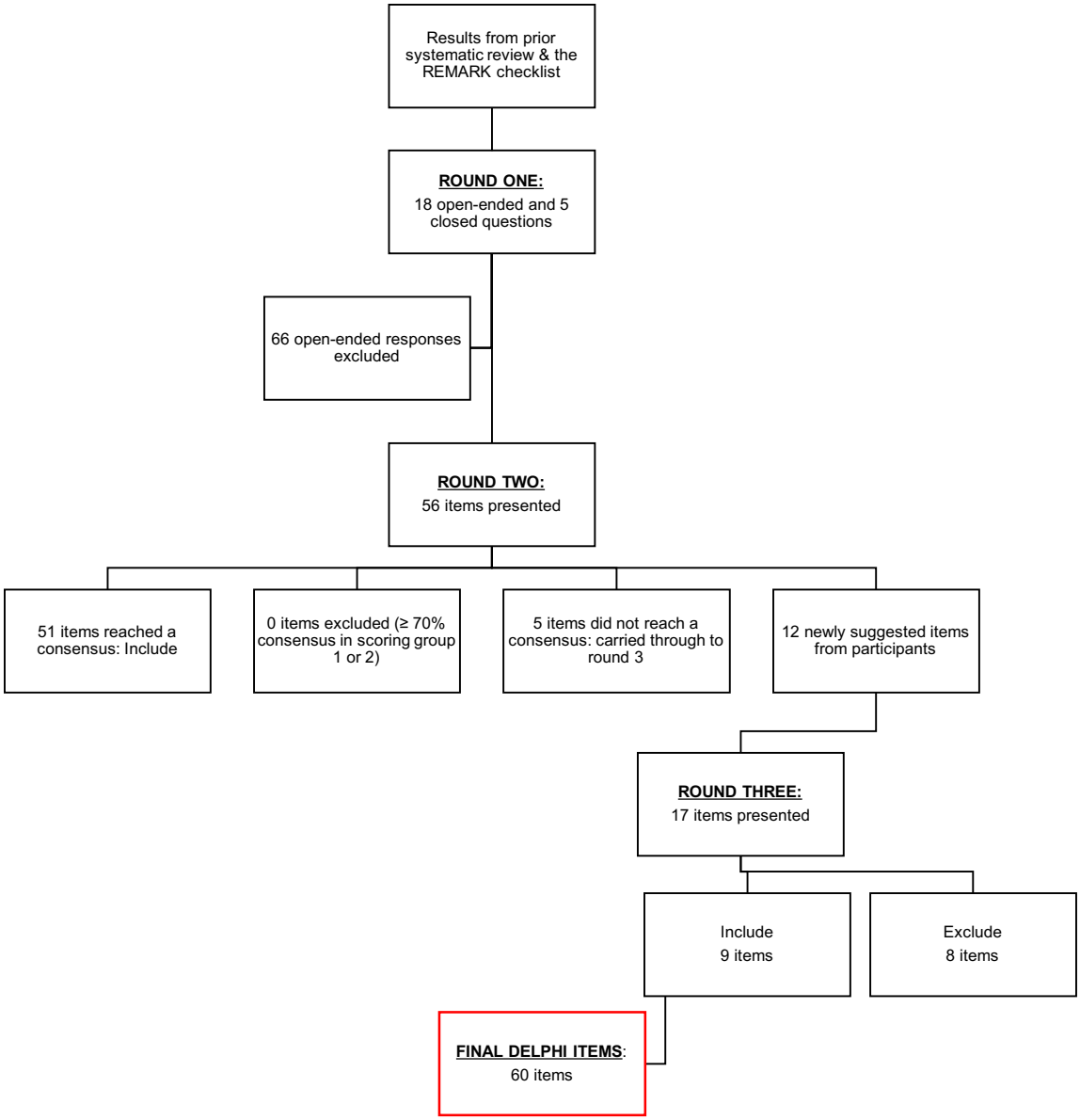

Figure 4.2 Flow chart illustrating the three-stage Delphi process, informed by a prior systematic review

The 60 statements that achieved *a priori* level of consensus for inclusion in the delirium biomarker study reporting guidelines (i.e ≥ 70% agreement with scores 4 or 5) is shown in Table 4.4. Table 4.5 lists the 8 items that did not achieve consensus after 3 rounds of the Delphi. No item received a score of ≤2 and hence were not excluded based on this criterion.

Table 4.4 Summary of ratings for items that reached a ≥70% consensus after three Delphi rounds*

Statement	Very important (5)	Moderately important (4)	Not important or unimportant (3)	Slightly important (2)	Not important at all (1)	Mean rating/Median rating	SD	Total % consensus achieved (category)
In delirium biomarker studies, the study objective statement should at a minimum, include the following key elements:								
The biomarker under study (including source)	14 (87.5)	2 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	4.8/5	.34	87.5% (5)
The time of collection in relation to delirium onset	11 (68.8)	3 (18.8)	2 (12.5)	0 (0.0)	0 (0.0)	4.5/5	.72	87.6% (5,4)
The clinical endpoint(s) including their definition	13 (81.3)	2 (12.5)	1 (6.3)	0 (0.0)	0 (0.0)	4.6/5	.79	81.3% (5)
The clinical covariates	9 (45.0)	8 (40.0)	3 (15.0)	0 (0.0)	0 (0.0)	4.3/4	.73	85% (5,4)
The methods of biomarker collection	9 (45.0)	6 (30.0)	3 (15.0)	1 (5.0)	0 (0.0)	4.2/4	.91	75% (5,4)
Clarify which delirium pathophysiological theory the study will address	6 (30.0)	10 (50.0)	2 (10.0)	1 (5.0)	1 (5.0)	3.9/4	1.05	80% (5,4)
The biomarker in a delirium study should be:								
Chosen a priori	9 (56.3)	7 (43.8)	0 (0.0)	0 (0.0)	0 (0.0)	4.5/5	.51	100% (5,4)
Supported by a biologically plausible rationale	12 (75.0)	3 (18.8)	1 (6.3)	0 (0.0)	0 (0.0)	4.6/5	.60	75% (5)
Supported by a clear hypothesis	10 (62.5)	3 (18.8)	3 (18.8)	0 (0.0)	0 (0.0)	4.4/5	.81	81.3% (5,4)
Putting practical considerations aside, the type of biological specimen chosen should:								
Be based on the capacity to measure the proposed biological process being evaluated	7 (43.8)	9 (56.3)	0 (0.0)	0 (0.0)	0 (0.0)	4.4/4	.51	100% (5,4)
Have high specificity and sensitivity	8 (50.0)	7 (43.8)	1 (6.3)	0 (0.0)	0 (0.0)	4.4/4.5	.62	83.8% (5,4)
In biomarker studies:								
Delirium cases should be diagnosed by a trained assessor or specialist doctor	6 (37.5)	9 (56.3)	1 (6.3)	0 (0.0)	0 (0.0)	4.2/4	.77	93.8% (5,4)
Delirium should be assessed using a validated delirium diagnosis tool	13 (81.3)	2 (12.5)	1 (6.3)	0 (0.0)	0 (0.0)	4.6/5	1.02	81.3% (5)
Delirium should be prospectively evaluated	8 (50.0)	6 (37.5)	2 (12.5)	0 (0.0)	0 (0.0)	4.4/4.5	.71	87.5% (5,4)

Adult and paediatric populations should be considered separately	8 (50.0)	5 (31.3)	2 (12.5)	1 (6.3)	0 (0.0)	4.2/4.5	.93	81.3% (5,4)
In biomarker studies, confounding variables need to:								
Be decided a priori	5 (31.3)	8 (50.0)	3 (18.8)	0 (0.0)	0 (0.0)	4.1/4	.71	81.3% (5,4)
Take into account the population being studied/the clinical condition	12 (75.0)	4 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	4.7/5	.44	75% (5)
Be clearly defined and justified	13 (81.3)	3 (18.8)	0 (0.0)	0 (0.0)	0 (0.0)	4.8/5	.40	81.3% (5)
Be accounted for in the analysis	15 (93.8)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	4.9/5	.50	93.8% (5)
The minimum clinical covariates that should be taken into account in delirium biomarker studies are:								
Age, gender, concurrent medication, comorbidities, prior cognitive impairment, prior neurological conditions, frailty, delirium risk and delirium precipitants	12 (75.0)	3 (18.8)	1 (6.3)	0 (0.0)	0 (0.0)	4.7/5	.60	75% (5)
Illness severity	14 (70.0)	4 (25.0)	1 (5.0)	0 (0.0)	0 (0.0)	4.6/5	.58	70% (5))
Sepsis	6 (30.0)	9 (45.0)	3 (15.0)	2 (10.0)	0 (0.0)	3.9/4	.94	75% (5,4)
Inflammation	7 (35.0)	10 (50.0)	1 (5.0)	2 (10.0)	0 (0.0)	4.1/4	.91	85% (5,4)
The following control groups are appropriate in a delirium biomarker study:								
Participants without delirium	10 (62.5)	5 (31.3)	1 (6.3)	0 (0.0)	0 (0.0)	4.5/5	.81	93.8% (5,4)
As delirium is a complex clinical condition with many influencing clinical variables several control groups will strengthen the ability to interpret the findings	7 (35.0)	7 (35.0)	3 (15.0)	3 (15.0)	0 (0.0)	3.9/4	1.07	70% (5,4)
Same illness severity with and without delirium	9 (45.0)	8 (40.0)	2 (10.0)	1 (5.0)	0 (0.0)	4.2/4	1.0	85% (5,4)
Delirium superimposed on dementia	6 (30.0)	8 (40.0)	3 (15.0)	1 (5.0)	1 (5.0)	3.7/4	1.2	70% (5,4)
In studies which follow participants longitudinally, appropriate additional comparator groups are:								
Participants with delirium of a shorter duration	4 (25.0)	8 (50.0)	3 (18.8)	1 (6.3)	0 (0.0)	3.9/4	.85	75% (5,4)
Participants who do not develop delirium	10 (62.5)	4 (25.0)	1 (6.3)	1 (6.3)	0 (0.0)	4.4/5	.89	87.5% (5,4)
Delirium biomarker studies should support the person with delirium and their proxy decision maker by:								
Clear participant information that explains the study to the person with delirium and/or their proxy decision maker	11 (68.8)	4 (25.0)	1 (6.3)	0 (0.0)	0 (0.0)	4.6/5	.81	93.8% (5,4)

Clear procedures to assist staff in interacting and supporting the patient during biomarker collection and other data collection	12 (75.0)	2 (12.5)	2 (12.5)	0 (0.0)	0 (0.0)	4.6/5	.71	75% (5)
The value of the research in lay terms and how it can contribute to the understanding of delirium	12 (75.0)	3 (18.8)	1 (6.3)	0 (0.0)	0 (0.0)	4.6/5	.80	75% (5)
Having clear processes for informed consent	12 (75.0)	3 (18.8)	1 (6.3)	0 (0.0)	0 (0.0)	4.6/5	.80	75% (5)
Description of the assay procedure should include the following as a minimum:								
A detailed assay protocol that includes the reagents/kits used	11 (68.8)	2 (12.5)	2 (12.5)	1 (6.3)	0 (0.0)	4.4/5	.96	81.3% (5,4)
An assay validation for assay repeatability and robustness	6 (37.5)	6 (37.5)	3 (18.8)	1 (6.3)	0 (0.0)	4.0/4	.92	75% (5,4)
The inter- and intra- assay coefficients of variation	7 (43.8)	5 (31.3)	2 (12.5)	2 (12.5)	0 (0.0)	4.0/4	1.06	75.6% (5,4)
Methods of preservation, storage and processing of the biological sample	11 (68.8)	3 (18.8)	1 (6.3)	1 (6.3)	0 (0.0)	4.5/5	.89	87.6% (5,4)
The assay validity	8 (50.0)	7 (43.8)	1 (6.3)	0 (0.0)	0 (0.0)	4.4/4.5	.62	93.8% (5,4)
The sensitivity limits of the assay	9 (56.3)	6 (37.5)	1 (6.3)	0 (0.0)	0 (0.0)	4.4/5	.81	93.8% (5,4)
A scoring and reporting protocol	8 (50.0)	6 (37.5)	2 (12.5)	0 (0.0)	0 (0.0)	4.4/4.5	.71	87.5% (5,4)
In biomarker studies:								
Blinding of the assay is essential if the clinical outcome is subjective	12 (75.0)	2 (12.5)	1 (6.3)	1 (6.3)	0 (0.0)	4.6/5	.89	75% (5)
Method of blinding should be explicit	9 (56.3)	4 (25.0)	2 (12.5)	1 (6.3)	0 (0.0)	4.3/5	.94	81.3% (5,4)
Please indicate your level of agreement with the following statements								
Timing of the sample collection should be determined based on the clinical scenario	6 (37.5)	8 (50.0)	2 (12.5)	0 (0.0)	0 (0.0)	4.2/4	.68	87.5% (5,4)
Timing of the sample collection should be determined based on the hypothesis being tested	12 (75.0)	3 (18.8)	1 (6.3)	0 (0.0)	0 (0.0)	4.7/5	.60	75% (5)
In longitudinal sampling of populations AT RISK OF DELIRIUM, it is recommended that samples are collected prior to delirium onset, during delirium episode, and after delirium resolution	9 (56.3)	7 (43.8)	0 (0.0)	0 (0.0)	0 (0.0)	4.6/5	.51	100% (5,4)

In longitudinal sampling of populations WITH DELIRIUM, it is recommended that samples are collected at delirium onset and again after delirium resolution	6 (37.5)	8 (50.0)	1 (6.3)	1 (6.3)	0 (0.0)	4.2/4	.83	87.5% (5,4)
Please indicate your level of agreement with the following statements on sample size in a delirium biomarker study.								
Sample size should be decided a priori based on previous studies/pilot data	6 (37.5)	7 (43.8)	2 (12.5)	1 (6.3)	0 (0.0)	4.1/4	.88	81.3% (5,4)
Sample size should be determined based on the estimated effect size of the biomarker in predicting the outcome	8 (50.0)	6 (37.5)	2 (12.5)	0 (0.0)	0 (0.0)	4.4/4.5	.71	87.5% (5,4)
The analysis plan should plan for clinical and biomarker missing data due to:								
Clinical issues such as overall deterioration, worsening cognition, and death	11 (68.8)	5 (31.3)	0 (0.0)	0 (0.0)	0 (0.0)	4.7/5	.47	100% (5,4)
Practical challenges of biomarker collection in people with delirium	12 (75.0)	4 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	4.8/5	.44	75% (5)
Univariate analyses of biomarker and clinical endpoints of interest should report the following:								
Estimated effect size	6 (37.5)	7 (43.8)	1 (6.3)	0 (0.0)	2 (12.5)	3.9/4	1.2	81.3% (5,4)
Whether biomarker result was dichotomised using a cut-point and/or threshold	11 (68.8)	3 (18.8)	1 (6.3)	0 (0.0)	1 (6.3)	4.4/5	1.09	87.6% (5,4)
How missing data were handled	12 (75.0)	2 (12.5)	1 (6.3)	0 (0.0)	1 (6.3)	4.5/5	1.09	75% (5))
Number of included participants	14 (87.5)	1 (6.3)	0 (0.0)	0 (0.0)	1 (6.3)	4.7/5	1.01	87.5% (5)
Multivariate analyses of biomarker and clinical endpoints of interest should report the following:								
Estimated effect size	8 (50.0)	8 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	4.5/4.5	.51	100% (5,4)
Whether biomarker result was dichotomised using a cut-point and/or threshold	11 (68.8)	5 (31.3)	0 (0.0)	0 (0.0)	0 (0.0)	4.7/5	.47	100% (5,4)
How model assumptions were verified	10 (62.5)	5 (31.3)	1 (6.3)	0 (0.0)	0 (0.0)	5.6/5	.62	93.8% (5,4)
How missing data were handled	12 (75.0)	3 (18.8)	1 (6.3)	0 (0.0)	0 (0.0)	4.7/5	.60	75% (5)
Number of included participants	15 (93.8)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	4.9/5	.25	93.8% (5)
Covariates (including how they were defined)	14 (87.5)	2 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	4.9/5	.34	87.5% (5)

**Red font:* *participant suggestions/comments*
[1] *One participant did not respond to this item*

Table 4.5 Summary of ratings for items that did NOT reach a consensus after three rounds of Delphi*

Statement	Very important	Moderately important	Not important or unimportant	Slightly important	Not important at all	Mean rating/Median rating	SD
The following control groups are appropriate in a delirium biomarker study:							
Healthy participants matched by baseline characteristics such as age and gender	3 (15.0)	8 (40.0)	3 (15.0)	5 (25.0)	1 (5.0)	3.3/4.0	1.18
Participants with dementia, without delirium	4 (20.0)	9 (45.0)	5 (25.0)	1 (5.0)	1 (5.0)	3.7/4.0	1.03
In studies which follow participants longitudinally, an appropriate additional comparator group is:							
Participants with less severe delirium	3 (15.0)	6 (30.0)	8 (40.0)	3 (15.0)	0 (0.0)	3.4/3.0	.94
Description of the assay procedure should include:							
Information about where the kit was purchased and whether it was commercially available	4 (20.0)	9 (45.0)	4 (20.0)	3 (15.0)	0 (0.0)	3.7/4.0	.97
The minimum clinical covariates that should be taken into account in delirium biomarker studies are:							
Ethnicity/race	3 (15.0)	6 (30.0)	6 (30.0)	3 (15.0)	2 (10.0)	3.2/3.0	1.20
Education[1]	4 (20.0)	9 (45.0)	3 (15.0)	1 (10.0)	1 (5.0)	3.6/4.0	1.10
Psychiatric history	4 (20.0)	8 (40.0)	4 (20.0)	2 (10.0)	2 (10.0)	3.5/4.0	1.23
Injuries	3 (15.0)	10 (50.0)	6 (30.0)	1 (5.0)	0 (0.0)	3.7/4.0	.78

**Red font*: participant suggestions/comments*
[1] *One participant did not respond to this item*

The preliminary list of recommendations is presented in Table 4.6.

Table 4.6 The preliminary list of recommendations for reporting delirium biomarker studies, following the Delphi*

Item number	Item	Consensus
1	**The study objective should include the following:**	
1(a)	The biomarker under study (including source)	87.5%
1(b)	The time of collection in relation to delirium onset	87.6%
1(c)	The clinical endpoint(s) including their definition	81.3%
1(d)	The clinical covariates	85%
1(e)	The methods of biomarker collection	75%
1(f)	A description of which delirium pathophysiological theory the study will address	80%
2	**In defining the population:**	
2(a)	Delirium cases should be diagnosed by a trained assessor or specialist doctor	93.8%
2(b)	Delirium should be assessed using a validated delirium diagnosis tool	81.3%
2(c)	Delirium should be prospectively evaluated	87.5%
2(d)	Adult and paediatric populations should be considered separately	81.3%
3	**Delirium biomarker studies should support the person with delirium and their proxy decision maker by:**	
3(a)	Providing a clear participant information that explains the study to the person with delirium and/or their proxy decision maker	93.8%
3(b)	Providing clear procedures to assist staff in interacting and supporting the patient during biomarker collection and other data collection	75%
3(c)	Explaining the value of the research in lay terms and how it can contribute to the understanding of delirium	75%
3(d)	Clear processes for informed consent	75%
4	**When selecting control(s) group:**	
	As delirium is a complex clinical condition with many influencing clinical variables several control groups will strengthen the ability to interpret the findings	70%
4(a)	**The following control groups would be appropriate to consider:**	
	Participants without delirium	93.8%
	Participants with the same illness severity, with and without delirium	85%
	Participants with delirium superimposed onto dementia	70%
4(b)	**In studies which follow participants longitudinally, the following are appropriate additional comparator groups:**	
	Participants with delirium of a shorter duration	75%
	Participants who do not develop delirium	87.5%
5	**The biomarker in a delirium study should be:**	
5(a)	Chosen *a priori*	100%
5(b)	Supported by a biologically plausible rationale	75%
5(c)	Supported by a clear hypothesis	81.3%
6	**The type of biological specimen chosen should:**	
6(a)	Be based on the capacity to measure the proposed biological process being evaluated	100%
6(b)	Have high specificity and sensitivity	83.8%
7	**Description of the assay procedure should include the following as a minimum:**	
7(a)	A detailed assay protocol that includes the reagents/kits used	81.3%
7(b)	An assay validation for assay repeatability and robustness	75%
7(c)	The inter- and intra- assay coefficients of variation	75.6%
7(d)	Methods of preservation, storage and processing of the biological sample	87.6%
7(e)	The assay validity	93.8%
7(f)	The sensitivity limits of the assay	93.8%
7(g)	A scoring and reporting protocol	87.5%
7(h)	Method of blinding should be explicit	81.3%
8	**In biomarker studies, confounding variables need to:**	
8(a)	Be decided *a priori*	81.3%
8(b)	Take into account the population being studied/the clinical condition	75%

8(c)	Be clearly defined and justified	81.3%
8(d)	Be accounted for in the analysis	93.8%
9	**The minimum clinical covariates that should be taken into account are:**	
	Age, gender, concurrent medication, comorbidities, prior cognitive impairment, illness severity, sepsis, prior neurological conditions, frailty, inflammation, delirium risk and delirium precipitants	75%
10	**Timing of collection**	
10(a)	Timing of the sample collection should be determined based on the clinical scenario and/or the hypothesis being tested	87.5%
10(b)	In longitudinal sampling of populations AT RISK OF DELIRIUM, it is recommended that samples are collected prior to delirium onset, during delirium episode, and after delirium resolution	100%
10(c)	In longitudinal sampling of populations WITH DELIRIUM, it is recommended that samples are collected at delirium onset and again after delirium resolution	87.5%
11	**Sample size**	
11(a)	Sample size should be decided *a priori* based on previous studies/pilot data	81.3%
11(b)	Sample size should be determined based on the estimated effect size of the biomarker in predicting the outcome	87.5%
12	**The analysis plan should plan for clinical and biomarker missing data due to:**	
12(a)	Clinical issues such as overall deterioration, worsening cognition, and death	100%
12(b)	Practical challenges of biomarker collection in people with delirium	75%
13	**Univariate analyses of biomarker and clinical endpoints of interest should report the following:**	
13(a)	Estimated effect size	81.3%
13(b)	Whether biomarker result was dichotomised using a cut-point and/or threshold	87.6%
13(c)	How missing data were handled	75%
13(d)	Number of included participants	87.5%
14	**Multivariate analyses of biomarker and clinical endpoints of interest should report the following:**	
14(a)	Estimated effect size	100%
14(b)	Whether biomarker result was dichotomised using a cut-point and/or threshold	100%
14(c)	How model assumptions were verified	93.8%
14(d)	How missing data were handled	75%
14(e)	Number of included participants	93.8%
14(f)	Covariates	87.5%

**Items highlighted in red achieved a 70-80% consensus and were brought to the consensus meeting (Study 2b)*

Study 2b: Consensus meeting

4.5.3 Participants

Twelve participants and three chairs (IAD, MA, AH) took part in the online consensus meeting on June 30, 2020, which was approximately 90 minutes in duration. The consensus meeting was recorded through Zoom, and minutes were taken by the meeting chairs (IAD, MA, AH). Although expert guideline developer members of the EQUATOR Network were also invited to take part, only delirium researchers participated.

Eight (67%) of participants had previously contributed to the Delphi survey. Participants were from six countries (Australia, Ireland, Norway, Sweden, Switzerland and US); and were predominantly clinician researchers (n=9; 75%), with over 10 years' experience in delirium research (75%) and had conducted more than 10 delirium studies (58%). Five (42%) had conducted 10 or more biomarker studies, 25% between 5 and 10, three (25%) had conducted less than 5, and one participant had conducted none (Table 4.7).

Table 4.7 Consensus meeting participant characteristics (N=12)

	N=12	(%)
Country of residence		
US	5	(42)
Australia	2	(17)
Ireland	2	(17)
Sweden	1	(8)
Norway	1	(8)
Switzerland	1	(8)
Years in delirium research		
>10 years	9	(75)
5-10 years	3	(25)
Current role		
Clinician/researcher	9	(75)
Researcher	3	(25)
Number of delirium studies conducted		
>10	7	(58)
5-10	4	(33)
<5	1	(8)
Number of biomarker studies conducted		
>10	5	(42)
5-10	3	(25)
<5	3	(25)
0	1	(8)
Conducted a delirium biomarker study		
Yes	10	(83)
No	2	(17)
Delphi participant		
Yes	8	(67)
No	4	(33)

4.5.4 Delphi items discussed in the consensus meeting

Items with 70-80% agreement in the Delphi study (n=16) were the key items for discussion in the consensus meeting (Table 4.6). Of the 16 items presented to the panel, 7 (44%) items were excluded, 6 (38%) items remained included, and 3 (19%) items were merged with another item. Participants then rated whether the item was clearly worded and easily understood (yes/no). The majority of participants (≥50%) believed

that three items were clearly worded, and that four items needed re wording (Table 4.8).

Table 4.8 Participants' votes for inclusion/exclusion of items

Item number	Checklist item	Include N (%)	Exclude N (%)	Item clearly worded (Yes) N (%)	Item clearly worded (No) N (%)
1(e)	The study objective should include: the method of biomarker collection	11 (91)	1 (9)	4 (36)[a]	7 (65)[a]
1(f)	The study objective should include: A description of which delirium pathophysiological theory the study will address	10 (86)	2 (14)	1 (9)	11 (91)
3(a)	Delirium biomarker studies should support the person with delirium and their proxy decision maker by: Providing clear procedures to assist staff in interacting and supporting the patient during biomarker collection and other data collection	3 (20)	9 (80)	N/A	N/A
3(b)	Delirium biomarker studies should support the person with delirium and their proxy decision maker by: Explaining the value of the research in lay terms and how it can contribute to the understanding of delirium	0 (0)	12 (100)	N/A	N/A
3(c)	Delirium biomarker studies should support the person with delirium and their proxy decision maker by: Clear processes for informed consent	0 (0)	12 (100)	N/A	N/A
4(a)	When selecting control(s) group: As delirium is a complex clinical condition with many influencing clinical variables, several control groups will strengthen the ability to interpret the findings	5 (40)	7 (60)	N/A	N/A
4(b)	The following control groups would be important to consider: Participants with delirium superimposed onto dementia	4 (30)	8 (70)	3 (25)[a]	8 (75)[a]
4(c)	In studies which follow participants longitudinally, the following are appropriate additional comparator groups: Participants with delirium of a shorter duration	0 (0)	12 (100)	N/A	N/A
5(b)	The biomarker in a delirium study should be: Supported by a biologically plausible rationale	0 (0)	12 (100)[b]	N/A	N/A
7(b)	Description of the assay procedure should include the following as a minimum: An assay validation for assay repeatability and robustness	12 (100)	0 (0)	12 (100)	0 (0)
7(c)	Description of the assay procedure should include the following as a minimum: The inter- and intra- assay coefficients of variation	12 (100)	0 (0)	12 (100)	0 (0)
8(b)	In biomarker studies, confounding variables need to take into account the population being studied/the clinical condition	12 (100)	0 (0)	9 (82)[a]	2 (18)[a]
9	The minimum clinical covariates that should be taken into account are: Age, gender, concurrent medication, comorbidities, prior cognitive impairment,	4 (30)	8 (70)	N/A	N/A

	illness severity, sepsis, prior neurological conditions, frailty, inflammation, delirium risk and delirium precipitants				
12(b)	The analysis plan should plan for clinical and biomarker missing data due to: Practical challenges of biomarker collection in people with delirium	8 (70)	4 (30)	4 (38)	7 (63)
13(c)	Univariate analyses of biomarker and clinical endpoints of interest should report the following: How missing data were handled	0 (0)	12 (100)[c]	N/A	N/A
14(d)	Multivariate analyses of biomarker and clinical endpoints of interest should report the following: How missing data were handled	0 (0)	12 (100)[c]	N/A	N/A

[a] *Only 11 out of 12 participants voted for this item*
[b] *To be merged with item 1*
[c] *To be merged with item 12*
N/A Not applicable

Participants were then asked to provide alternative wording suggestions in open-text form in PollEverywhere. Minor wording suggestions were added for five items. Although two (18%) participants voted for item eight not being clearly worded (Table 4.8), no wording suggestions were added for this item, and it was later agreed that the item should remain as is. Of the 7 included items, two items (7c and 8b) were included without any wording changes, four (1e, 1f, 7b and 12b) underwent minor wording changes and three (5b, 13c and 14d) were merged with another item. (Table 4.9).

Table 4.9 Participant wording suggestions in open-text form

Item number	Checklist item	Wording suggestions	Updated wording for the REDEEMS
1(e)	The study objective should include: the method of biomarker collection	1. "Describe the collection of biological sample, time, storage and method of measurement of all analytes" 2. "Include time of collection in relationship to the study timeline and include biomarker specimen processing method" 3. Remove 'study objective'	The study should include: a description of the method of biomarker collection
1(f)	The study objective should include: A description of which delirium pathophysiological theory the study will address	1. Remove 'study objective' 2. Write 'biological hypothesis' instead of 'pathophysiological theory' 3. Add a plural term on theory 4. "The study needs to contextualize the experiment in a biologically plausible way" 5. "Hypothesis" 6. "Should refer to the hypothesis that it addresses but should not insist on limiting to a specific pathophysiological theory. If not testing a specific hypothesis you should state unbiased or exploratory"	The study should include: A description of the biological hypotheses(/is) it is addressing. If the study is not testing a specific hypothesis, it should state that it is undertaking an un-biased or exploratory approach
3(a)	Delirium biomarker studies should support the person with delirium and their proxy decision maker by: Providing clear procedures to assist staff in interacting and supporting the patient during biomarker collection and other data collection	N/A	Exclude
3(b)	Delirium biomarker studies should support the person with delirium and their proxy decision maker by: Explaining the value of the research in lay terms and how it can contribute to the understanding of delirium	N/A	Exclude
3(c)	Delirium biomarker studies should support the person with delirium and their proxy	N/A	Exclude

	decision maker by: Clear processes for informed consent		
4(a)	When selecting control(s) group: As delirium is a complex clinical condition with many influencing clinical variables, several control groups will strengthen the ability to interpret the findings	A. "Consider more than one control group" B. Remove the word 'groups' and just have the word 'controls' C. "Consider more than one control to support your study aim"	Exclude
4(b)	The following control groups would be important to consider: Participants with delirium superimposed onto dementia	N/A	Exclude
4(c)	In studies which follow participants longitudinally, the following are appropriate additional comparator groups: Participants with delirium of a shorter duration	N/A	Exclude
5(b)	The biomarker in a delirium study should be: Supported by a biologically plausible rationale	N/A	Merge with item 1
7(b)	Description of the assay procedure should include the following as a minimum: An assay validation for assay repeatability and robustness	i) "An assay validation for repeatability and robustness"	Description of the assay procedure should include the following as a minimum: An assay validation for repeatability and robustness
7(c)	Description of the assay procedure should include the following as a minimum: The inter- and intra- assay coefficients of variation	N/A	Remain the same
8(b)	In biomarker studies, confounding variables need to take into account the population being studied/the clinical condition	None	Remain the same
9	The minimum clinical covariates that should be taken into account are: Age, gender, concurrent medication, comorbidities, prior cognitive impairment, illness severity, sepsis, prior neurological conditions, frailty, inflammation, delirium risk and delirium precipitants	N/A	Exclude
12(b)	The analysis plan should plan for clinical and biomarker missing data due to: Practical challenges of biomarker collection in people with delirium	A> "Remove the word 'practical'" B> "The analysis plan should plan for clinical and biomarker missing data"	The analysis plan should account for clinical and biomarker missing data
13(c)	Univariate analyses of biomarker and clinical endpoints of interest should report the following: How missing data were handled	N/A	Merge with item 12
14(d)	Multivariate analyses of biomarker and clinical endpoints of interest should report	N/A	Merge with item 12

	the following: How missing data were handled		

4.5.5 The final REDEEMS checklist

The items were further revised and reworded through email collaboration, where participants provided feedback on the wording of all items, resulting in the final REDEEMS checklist (Table 4.10). The overlap of items with the REDEEMS and the reporting guidelines relevant to biomarker studies is shown in Table 4.11.

Table 4.10 Final REDEEMS checklist items

Item number	REDEEMS items
1	**Study rationale**
a	State the biomarker under study (including nature of the specimen)
b	Describe the biological hypothesis(/es) tested*
2	**Ascertainment of delirium**
a	Describe the training and/or credentials of personnel who ascertained delirium cases
b	Specify the delirium tool and/or diagnostic process that was used to ascertain cases
c	Describe frequency, timing and duration of delirium assessment
3	**Outcome measures**
a	Define and justify all clinical endpoint(s) and their measures (including relationship to delirium where relevant)
4	**Assay procedure**
a	Specify the assay method used with a detailed protocol that includes reagents/kits
b	Describe the methods of preservation, storage and processing of the biological sample
c	Describe the assay validation method for repeatability and robustness including the sensitivity limits of the assay
d	Specify the inter- and intra- assay coefficients of variation
e	Specify the method of blinding biomarker results
5	**Timing of collection of the biological sample**
a	Precisely describe the time of collection of the biological sample in relation to delirium (onset, presence, resolution)
b	Provide a rationale for the timing of the sample collection based on the clinical scenario, the hypothesis being tested, and/or the study design
6	**Confounding variables**
a	State the confounding variables assessed and whether or not they were specified *a priori*
b	Clearly define and provide justification for the confounding variables (including the relationship to delirium where relevant)
7	**Sample size**
a	Describe how sample size was determined and provide a rationale
8	**Statistical analysis**
a	Account for clinical and biomarker missing data in the analysis plan based on the design of the study
b	State how confounding variables were accounted for in the analysis
9	**Univariate and multivariable analysis**
a	Report the estimated effect size or the p values with their Confidence Intervals (CI)
b	Specify whether the biomarker was dichotomised using a cut-point and/or threshold
c	Specify the number of included participants and reasons for attrition or missing data
d	Describe how model assumptions were verified (multivariable)

Table 4.11 Comparison of the REDEEMS checklist against current reporting guidelines relevant to biomarker studies

REDEEMS checklist item	REMARK	STARD	STROBE	Neurological Disorders[1]	CONSORT	BRISQ
Study rationale						
State the biomarker under study (including nature of the specimen)	✓			✓		✓
Describe the biological hypothesis(/es) tested*	✓	✓	✓	✓	✓	
Ascertainment of delirium						
Describe the training and/or credentials of personnel who ascertained delirium cases						
Specify the delirium tool and/or diagnostic process that was used to ascertain cases						
Describe frequency, timing and duration of delirium assessment						
Outcome measures						
Define and justify all clinical endpoint(s) and their measures (including relationship to delirium where relevant)	✓		✓	✓	✓	
The assay procedure						
Specify the assay method used with a detailed protocol that includes reagents/kits	✓			✓		✓
Describe the methods of preservation, storage and processing of the biological sample	✓			✓		✓
Describe the assay validation method for repeatability and robustness including the sensitivity limits of the assay	✓			✓		✓
Specify the inter- and intra- assay coefficients of variation	✓			✓		
Specify the method of blinding biomarker results	✓			✓		
Timing of collection of the biological sample						
Precisely describe the time of collection of the biological sample in relation to delirium (onset, presence, resolution)						✓*

Provide a rationale for the timing of the sample collection based on the clinical scenario, the hypothesis being tested, and/or the study design						
Confounding variables						
State the confounding variables assessed and whether or not they were specified *a priori*						
Clearly define and provide justification for the confounding variables (including the relationship to delirium where relevant)			✓			
Sample size						
Describe how sample size was determined and provide a rationale	✓	✓	✓	✓	✓	
Statistical analysis						
Account for clinical and biomarker missing data in the analysis plan based on the design of the study	✓	✓	✓	✓	✓	
State how confounding variables were accounted for in the analysis			✓			
Univariate and multivariable analysis						
Report the estimated effect size or the p values with their Confidence Intervals (CI)	✓	✓	✓	✓	✓	
Specify whether the biomarker was dichotomised using a cut-point and/or threshold	✓			✓		
Specify the number of included participants and reasons for attrition or missing data		✓	✓		✓	
Describe how model assumptions were verified (multivariable)	✓			✓		

[1] *Guidelines for uniform reporting of body fluid biomarker studies in neurologic disorders*

✓Item included in the guideline

**Time between diagnosis and sampling*

4.6 Discussion

This study presents the first reporting guideline to aid in the conduct and reporting of delirium biomarker research. Consensus in the Delphi was achieved for 60 items, with a total of 8 items that did not reach a consensus. Following the consensus meeting with experts in delirium research, nine items with 22 sub-items were included in the final version.

Inadequate reporting of studies is well documented. For example, a review of RCTs by Chan et. al (2005)[53] found that of 519 trials, only 109 (21%) of authors reported on the method of sequence generation, and only 94 (18%) reported the method of allocation concealment, both which are considered gold standard in the conduct of RCTs. Furthermore, only 232 (45%) of trials defined a primary endpoint, and only 142 (27%) reported a sample size calculation.[53] That review was updated in 2006, by comparing two cross-sectional investigations of RCTs indexed in 2000 and 2006 found only slight improvements in the reporting of RCTs from 2000 to 2006. Of the 616 trials, only 209 (34%) reported a method of random sequence generation (compared to 21% in 2000) and 156 trials (25%) reported a method of allocation concealment, a slight improvement from 18% in 2000.[54] Only 324 trials (53%) defined their primary endpoint, and only 279 (45%) reported a sample size calculation. Although elsewhere improvements in reporting rigor when using reporting guidelines have been demonstrated,[8,55] a systematic review of journals' use of reporting guidelines found that only 19 (46%) of online instructions to authors mentioned them.[56] The use, and not just the development, of reporting guidelines is therefore necessary to promote standardised and transparent study reporting that facilitates reliable interpretation, application, and synthesis of results.

4.6.1 Limitations and strengths

There are a number of noteworthy limitations to this study. As stated earlier, there is no universally agreed definition of 'consensus' for a Delphi, and participant agreement ranges anywhere from 50-100%.[17,49,50] Also, the end results aren't necessarily the most reliable, but rather, a majority opinion.[32,37]

Since delirium is a condition which often occurs in the context of other conditions with overlapping pathophysiological processes, such as cancer, some complex areas of study design where multiple competing issues need to be considered in the methodological choices are not well suited to be reduced down to simple statements within a Delphi method. Such considerations require a more in-depth qualitative approach to identify the nuanced methodological considerations needed, exploring the pros and cons for several different methodological approaches and also identifying where the 'jury is still out' with no clear solution yet identified. Hence, the guideline items identified by this study may not be universally applicable or comprehensive and researchers will still need to consider whether there are additional special considerations to be considered when applying them to specific scenarios and settings.

The REDEEMS guideline was not intended to replicate 'gold standard' items that are included in other existing reporting guidelines. In several other cases, where a need for additional information for reporting studies was identified, authors instead have developed an extension to the existing guidelines, with the addition of the specific information requirements. Rather than create an extension to an existing guideline like the REMARK, the REDEEMS was instead created as a stand-alone guideline to be used in conjunction with another reporting guideline appropriate for study design. Therefore, an extra layer of effort is required for authors and reviewers, who must

firstly apply a reporting guideline specific to the study design and then use the REDEEMS for reporting the delirium biomarker-specific component.

Many of the existing reporting guidelines have been tried and tested in practice. For example, the CONSORT guidelines has empirical evidence which identifies the impacts of poor design which inform the reporting requirements for items such as randomisation, blinding and allocation concealment.[7] Poor allocation concealement for example has been shown to overestimate the benefits of the experimental intervention.[57] This is not the case for delirium biomarker studies, where empirical evidence is lacking. Therefore the final REDEEMS items are based on expert consensus opinion, rather than evidence-base.

Strengths included: the systematic approach to develop the REDEEMS guideline using existing recommendations for developing reporting guidelines in health research.[4] At each stage in the process, care was taken to ensure this framework was closely followed to minimize the potential for investigator bias. Another strength was the breadth of expertise within the international expert panel, although we acknowledge that we may have not encompassed all possible perspectives. Lastly, although there is no universal agreement of the ideal sample size for Delphi studies, most Delphi's have included between 15 and 20 participants, and the expertise of the panel is considered more important that the size of the sample itself.[18,34,58] Considering the small cohort of expert delirium researchers worldwide, we believe the 32 informed participants comprised a sufficient Delphi sample.[20]

4.6.2 Implications for future research and practice

This study proposes the first reporting guideline specific to delirium biomarker studies, that can be refined after experience of their utility in practice. The systematic review

undertaken in Chapter three demonstrated a number of poor quality studies that were likely affected by a lack of guidelines for delirium biomarker research. Developing reporting guidelines was therefore an essential step to improving methodological and reporting rigor, which will increase the potential for future studies to be synthesised through meta-analyses.

To supplement the proposed guideline, follow-up interviews with experts in the field were conducted (Chapter five) which discussed key complex methodological issues for which the Delphi approach could not address. Namely: how to account for other co-existing conditions (e.g. cancer or sepsis) that plausibly impact on the pathophysiological and/or biological findings; and the practicalities of obtaining biomarkers from people with delirium for research. The final stage (Stage 3, Explanation and Elaboration) of the REDEEMS guideline development is reported in Chapter six.

4.7 Summary

This study developed a reporting guideline for delirium biomarker studies through a rigorously conducted Delphi and follow-up consensus meeting with international experts in delirium research. Results will support the development of greater methodological rigor in future delirium biomarker research, which will ultimately contribute to better understanding of delirium pathophysiology.

4.8 References

1. Chalmers I, Bracken MB, Djulbegovic B, et al. How to increase value and reduce waste when research priorities are set. *The Lancet.* 2014;383(9912):156-165.
2. Simera I, Altman DG, Moher D, Schulz KF, Hoey J. Guidelines for reporting health research: the EQUATOR network's survey of guideline authors. *PLoS Medicine.* 2008;5(6):e139.
3. Begg C, Cho M, Eastwood S, et al. Improving the quality of reporting of randomized controlled trials: the CONSORT statement. *Jama.* 1996;276(8):637-639.
4. Moher D, Schulz KF, Simera I, Altman DG. Guidance for developers of health research reporting guidelines. *PLoS Medicine.* 2010;7(2).
5. Simera I, Moher D, Hoey J, Schulz KF, Altman DG. A catalogue of reporting guidelines for health research. *European Journal of Clinical Investigation.* 2010;40(1):35-53.
6. Equator Network. Developing your reporting guideline 2018; https://www.equator-network.org/toolkits/developing-a-reporting-guideline/developing-your-reporting-guideline/. Accessed June 25, 2020.
7. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMC Medicine.* 2010;8(1):18.
8. Plint AC, Moher D, Morrison A, et al. Does the CONSORT checklist improve the quality of reports of randomised controlled trials? A systematic review. *Medical Journal of Australia.* 2006;185(5):263-267.
9. Altman DG, McShane LM, Sauerbrei W, Taube SE. Reporting recommendations for tumor marker prognostic studies (REMARK): explanation and elaboration. *BMC Medicine.* 2012;10(1):51.
10. Amgarth-Duff I, Hosie A, Caplan G, Agar M. A systematic review of the overlap of fluid biomarkers in delirium and advanced cancer-related syndromes. *BMC psychiatry.* 2020;20(1):1-32.
11. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *International Journal of Surgery.* 2012;10(1):28-55.
12. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *International Journal of Surgery.* 2014;12(12):1495-1499.
13. Bossuyt PM, Reitsma JB, Bruns DE, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *Radiology.* 2015;277(3):826-832.
14. Gnanapavan S, Hegen H, Khalil M, et al. Guidelines for uniform reporting of body fluid biomarker studies in neurologic disorders. *Neurology.* 2014;83(13):1210-1216.

15. Moore HM, Kelly AB, Jewell SD, et al. Biospecimen reporting for improved study quality (BRISQ). *Cancer Cytopathology.* 2011;119(2):92-102.

16. Moher D, Weeks L, Ocampo M, et al. Describing reporting guidelines for health research: a systematic review. *Journal of Clinical Epidemiology.* 2011;64(7):718-742.

17. Keeney S, Hasson F, McKenna H. Consulting the oracle: ten lessons from using the Delphi technique in nursing research. *Journal of Advanced Nursing.* 2006;53(2):205-212.

18. Hsu C-C, Sandford BA. The Delphi technique: making sense of consensus. *Practical Assessment, Research & Evaluation.* 2007;12(10):1-8.

19. Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. *Journal of Advanced Nursing.* 2000;32(4):1008-1015.

20. Keeney S, McKenna H, Hasson F. *The Delphi technique in nursing and health research.* John Wiley & Sons; 2011.

21. McKenna HP. The Delphi technique: a worthwhile research approach for nursing? *Journal of Advanced Nursing.* 1994;19(6):1221-1225.

22. McMillan SS, King M, Tully MP. How to use the nominal group and Delphi techniques. *International Journal of Clinical Pharmacy.* 2016;38(3):655-662.

23. Skulmoski GJ, Hartman FT, Krahn J. The Delphi method for graduate research. *Journal of Information Technology Education: Research.* 2007;6(1):1-21.

24. Heiko A. Consensus measurement in Delphi studies: review and implications for future quality assurance. *Technological Forecasting and Social Change.* 2012;79(8):1525-1536.

25. Dalkey N, Helmer O. An experimental application of the Delphi method to the use of experts. *Management Science.* 1963;9(3):458-467.

26. Sackman H. *Delphi assessment: Expert opinion, forecasting, and group process.* Rand Corp Santa Monica CA;1974.

27. Rowe G, Wright G, Bolger F. Delphi: a reevaluation of research and theory. *Technological Forecasting and Social Change.* 1991;39(3):235-251.

28. Cohen L, Manion L, Morrison K. *Research methods in education.* Routledge; 2002.

29. Crisp J, Pelletier D, Duffield C, Adams A, Nagy S. The Delphi method? *Nursing Research.* 1997;46(2):116-118.

30. Steinert M. A dissensus based online Delphi approach: An explorative research tool. *Technological Forecasting and Social Change.* 2009;76(3):291-300.

31. Sackman H. *Delphi critique.* . Massachusetts: D. C: Lexington; 1975.

32. Keeney S, Hasson F, McKenna HP. A critical review of the Delphi technique as a research methodology for nursing. *International Journal of Nursing Studies.* 2001;38(2):195-200.

33. Goodman C. The Delphi technique: a critique. *Journal of Advanced Nursing.* 1987;12(6):729-734.

34. Okoli C, Pawlowski SD. The Delphi method as a research tool: an example, design considerations and applications. *Information and Management.* 2004;42(1):15-29.

35. Dalkey N. An experimental study of group opinion: the Delphi method. *Futures.* 1969;1(5):408-426.

36. Mullen PM. *Delphi-type studies in the health services: the impact of the scoring system.* University of Birmingham. Health Services Management Centre; 1983.

37. Rauch W. The decision delphi. *Technological Forecasting and Social Change.* 1979;15(3):159-169.

38. Delbecq AL, Van de Ven AH. A group process model for problem identification and program planning. *The Journal of Applied Behavioral Science.* 1971;7(4):466-492.

39. McGinnis PQ, Wainwright SF, Hack LM, Nixon-Cave K, Michlovitz S. Use of a Delphi panel to establish consensus for recommended uses of selected balance assessment approaches. *Physiotherapy Theory and Practice.* 2010;26(6):358-373.

40. Jones J, Hunter DJBBMJ. Consensus methods for medical and health services research. *British Medical Journal* 1995;311(7001):376.

41. Donohoe HM, Needham RD. Moving best practice forward: Delphi characteristics, advantages, potential problems, and solutions. *International Journal of Tourism Research.* 2009;11(5):415-437.

42. Powell C. The Delphi technique: myths and realities. *Journal of Advanced Nurings.* 2003;41(4):376-382.

43. Nulty DD. The adequacy of response rates to online and paper surveys: what can be done? *Assessment & Evaluation in Higher Education.* 2008;33(3):301-314.

44. Marshall MN. Sampling for qualitative research. *Family Practice.* 1996;13(6):522-526.

45. iDelirium. The International Federation of Delirium Societies. 2019; http://www.idelirium.org/. Accessed October 2nd, 2019.

46. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics.* 2009;42(2):377-381.

47. Delbecq AL, Van de Ven AH, Gustafson DH. *Group techniques for program planning: A guide to nominal group and Delphi processes.* Scott Foresman; 1975.

48. Joffe H, Yardley L, Marks D. *Content and thematic analysis.* Great Britain Sage Publications Ltd; 2004.

49. Loughlin KG, Moore LF. Using Delphi to achieve congruent objectives and activities in a pediatrics department. *Journal of Medical Education.* 1979;54(2):101-106.

50. Williams PL, Webb C. The Delphi technique: a methodological discussion. *Journal of Advanced Nursing.* 1994;19(1):180-186.

51. Jünger S, Payne S, Brine J, Radbruch L, Brearley S. Guidance on Conducting and REporting DElphi Studies (CREDES) in palliative care: Recommendations based on a methodological systematic review. *Palliative Medicine.* 2017;31(8):684-706.

52. PollEverywhere. PollEverywhere. 2020; https://www.polleverywhere.com/. Accessed May 27 2020.

53. Chan A-W, Altman DG. Epidemiology and reporting of randomised trials published in PubMed journals. *The Lancet.* 2005;365(9465):1159-1162.

54. Hopewell S, Dutton S, Yu L-M, Chan A-W, Altman DG. The quality of reports of randomised trials in 2000 and 2006: comparative study of articles indexed in PubMed. *British Medical Journal.* 2010;340:c723.

55. Smidt N, Rutjes A, Van der Windt D, et al. The quality of diagnostic accuracy studies since the STARD statement: has it improved? *Neurology.* 2006;67(5):792-797.

56. Hirst A, Altman DG. Are peer reviewers encouraged to use reporting guidelines? A survey of 116 health research journals. *PloS one.* 2012;7(4):e35621.

57. Pildal J, Hrobjartsson A, Jørgensen K, Hilden J, Altman D, Gøtzsche P. Impact of allocation concealment on conclusions drawn from meta-analyses of randomized trials. *International Journal of Epidemiology.* 2007;36(4):847-857.

58. Murphy M, Black N, Lamping D, et al. Consensus development methods, and their use in clinical guideline development. *Health Technology Assessment.* 1998;2(3):i-88.

Chapter 5: Delirium Researchers' Perspectives of the Challenges in Delirium Biomarker Research: A Qualitative study

5.1 Chapter preface

Chapter four reported findings from a modified Delphi study that identified, through consensus from a range of delirium experts, nine recommendations for reporting delirium biomarker studies. Chapter five builds on the previous chapter by reporting a qualitative study that sought more in-depth understanding of delirium researchers' perspectives of the key challenges in conducting delirium biomarker research, and the Delphi study recommendations.

The study reported in this chapter was published in *PLoS ONE* in 2021. Chapter five contains an edited version of the publication, which is provided in its published form in Appendix 1.3.

Publication reference

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5.2 Introduction

To date, there has been remarkably high variability of findings in delirium biomarker studies aiming to unpack the pathophysiology of delirium. Additionally, the unsolved question of whether delirium is a single, unified physiological condition or whether there are physiologically discrete subtypes;[1] adds to the challenge of furthering the scientific understanding of delirium. Lack of clarity in terminology (e.g. delirium vs acute encephalophathy) has contributed to specialist-specific silos.[2] These high-level barriers to the conceptualisation of delirium mean that high quality methodological approaches to biomarker research are critical to accelerate understanding of delirium pathophysiology in order to lead to potential therapies. The poor quality of reporting, as identified in Chapter three, has likely contributed to heterogeneity of findings and the ongoing biological and conceptual uncertainty.[3]

In response to the need to improve understanding of delirium pathophysiology through a stronger evidence-base, the Delphi study presented in Chapter four gathered opinions of international experts on delirium research methodology that resulted in a list of reporting guidelines for future delirium biomarker studies. To supplement these recommendations, interviews with Delphi participants and other delirium researchers were then undertaken for an in-depth exploration into the more complex aspects of biomarker study methods. The consensus and primarily quantitative approach of the Delphi method was not suited to fully explore these aspects. Furthermore our present goal was not to obtain recommendations but rather to understand the key considerations and the reasons underpinning them. *A priori* identified key methodological challenges of delirium biomarker studies were: the practicalities of biomarker research in delirium; and how to account for other co-existing conditions

(e.g. cancer or sepsis) that plausibly may also impact on pathophysiological and/or biological findings.

5.3 Aim

To explore the perspectives of delirium researchers about key methodological issues in delirium biomarker research.

5.4 Objectives

To identify delirium researchers' perspectives of how to:

1. Address practical challenges of obtaining biomarkers from people with delirium for research purposes;
2. Account for underlying conditions in delirium biomarker studies;
3. Address key gaps in delirium biomarker research and improve current methodological shortcomings.

5.5 Methods

5.5.1 Study design

A qualitative study reported in accordance with the Consolidated Criteria for Reporting Qualitative Research (COREQ).[4]

5.5.2 Participants

Initially, we determined eligible participants to be delirium researchers as well as clinicians and basic scientists with and without experience in delirium research. These criteria were modified after recruitment and data collection commenced for the initial modified Delphi component of the study, when it became evident that participants who had not conducted delirium research lacked sufficient in-depth knowledge of the topic to provide informed responses to questions about complexities of delirium biomarker

research. Following this refinement, those eligible were researchers, clinicians and basic scientists with experience in delirium research in either humans or animals, including but not restricted to biomarker research. There was no pre-specified minimum number of years of clinical or research experience; however, experience in delirium research was required to have been in the last ten years to ensure recent knowledge of the study topic.

5.5.3 Recruitment

Purposive sampling was employed whereby potential participants were actively chosen and selected to take part.[5] Delirium researchers were identified by authorship of relevant papers in the field of delirium, as well as through the lead researchers' supervisory networks. Purposive sampling is widely used in qualitative research to identify participants with in-depth knowledge and/or experience of the phenomenon of interest.[5] Unlike random sampling which aims to be representative of a large population, the aim of purposive sampling in qualitative research facilitates exploration of highly-informed persons' perceptions, understandings and experiences.[6] Snowball sampling[7] was also employed by asking invitees whether they knew any other relevant persons who may be interested in participating.

International delirium researchers who completed the final round of the Delphi (Chapter four) and other delirium researchers who were not involved in the Delphi process, were invited by email to take part in a semi-structured interview (n=27). Participants were sent a participant information sheet and a consent form (Appendix 5.3) by the doctoral researcher (IAD), which was required to be signed and sent back prior to the interviews taking place. The participant information sheet explained the aim of the study, general content to be discussed, anticipated length of the interview, measures for privacy and confidentiality, and use of data for academic and research

purposes. Due to the international sample and participants' busy schedules, they were given the options of a telephone interview or a face-to-face interview if Sydney based.

5.5.4 Data collection

Semi-structured interviews

During all telephone interviews, the doctoral researcher (IAD) was located in a private office. The semi-structured interview method enabled reciprocity between the interviewer and participant and the interviewer to improvise follow-up questions and prompts based on participants' responses.[8,9] Questions were open-ended and designed to gain an in-depth understanding of the challenges and nuances of delirium biomarker methodology. Participants were reassured that the interview was voluntary and that the aim was not to 'test' their knowledge or performance in the way they conducted delirium biomarker studies, but purely to explore their perspectives.

The interview guide was aligned with the key findings from the earlier Delphi study,[10] while also allowing other topics to arise (Textbox 5.1). The three key areas explored were: 1) the practical challenges of conducting delirium biomarker research and how they can be overcome; 2) how to account for underlying conditions that are present in many patients with delirium, and 3) the key gaps and methodological shortcomings in current delirium biomarker studies.

The initial interview guide was piloted with two clinicians who did not formally take part in an interview. The first had extensive experience in delirium research, and the other had clinical experience of caring for patients with delirium. Piloting the interview guide to determine clarity of the questions identified minor issues and amendments were made. The final interview guide is presented in Textbox 5.1.

Textbox 5.1. Interview guide

A.	Delirium is a condition that often occurs in the context of other conditions with similar pathophysiological processes. What are your thoughts on accounting for co-existing conditions such as cancer in delirium biomarker studies?
B.	Delirium biomarker research poses many practical challenges. In your experience, what some of the key challenges and some ways to overcome these challenges?
C.	Where do you think current biomarker studies are falling short?
D.	Do you have any comments on the Delphi statements? (for Delphi participants only)
E.	Is there anything else you would like to add before we finish up?

All interviews were conducted by the doctoral researcher (IAD), a female research assistant and PhD candidate who holds undergraduate and honours qualifications in biomedical science. IAD has prior interviewing and qualitative analysis experience and an in-depth knowledge of existing deficiencies in the quality of reporting of delirium biomarker research,[11] but no prior experience of conducting biomarker research. There were no pre-existing relationships between IAD and participants, although her doctoral supervisors knew some of the participants through delirium research collaborations, conferences and advocacy networks. IAD had minimal contact with participants from the time of the Delphi through to the interviews, except when scheduling interviews over email.

At the beginning of each interview, IAD introduced herself to participants and provided an overview of the project. Participants were reassured that they did not have to answer questions if they did not want to, and that any content they provided would remain confidential. Participants were also asked to maintain confidentiality, including that when they used real-life examples that they did so in a de-identified manner. Throughout the interviews, key points and the researcher's interpretations of their responses were fed back to participants to ensure these accurately reflected their statements. All interviews were audio recorded and saved as a digital recording in a

de-identified format. Data collection continued until no new information emerged (i.e. data saturation).

5.5.5 Data analysis

IAD transcribed all interviews verbatim. Each transcript was assigned a code number to protect participant privacy. NVIVO QSR International Pty Ltd. Version 12 software package was used to help manage data. A combination of inductive and deductive thematic data analysis[12] was used, as follows:

Firstly, and as stated above, key areas identified in Round 1 qualitative analysis of the modified Delphi study[10] that were too complex to be resolved through a consensus process (and therefore required a more in-depth analysis) formed the framework for the interview guide. The doctoral researcher (IAD) familiarised herself with the data through the transcription process and rereading of the final transcripts. Initial data coding was guided by the semi-structured interview questions, with codes and collated data examined for potential sub-themes. Line-by-line coding of the transcripts was conducted, and a coding tree was developed to form categories. Codes were considered important if they were mentioned more than once. Categories were then collapsed into themes. IAD identified preliminary sub-themes, that were then refined through an iterative process until the final sub-themes were confirmed by a second researcher (AH). This process occurred in six phases, as proposed by Braun & Clarke (2006):[12]

1. Data familiarisation through transcription of interviews and multiple readings of transcripts.
2. Development of provisional codes, through coding key features in the data in a systematic manner and labelling the data associated with them.
3. Collating and refining the provisional codes into potential sub-themes.

4. Reviewing the sub-themes and checking to see if the themes worked in relation to the provisional codes (level 1) and the entire data set (level 2);
5. Ongoing analysis to define and name each sub-theme;
6. Producing a scholarly report of the analysis, relating back to the research questions and literature.

5.5.6 Trustworthiness of the data (credibility, transferability, dependability, and confirmability)

To ensure trustworthiness of the data, methods to generate findings were guided by four criteria for qualitative research: credibility, transferability, dependability and confirmability.[13]

Credibility was achieved by using purposive sampling targeting delirium researchers. Participants were assured that their identities would be protected on all transcripts, reports and publications that resulted from the interviews. Member checking was carried out in the form of sending a summary of the main themes and sub-themes to participants for their comments on interpretation of the data. Study planning, validation and analysis discussions among an interdisciplinary research team with expertise relevant to the topic also enhanced trustworthiness of the data analysis.[14]

To enhance *transferability* of findings, the impetus for the study and participants were described in detail, and an international approach was taken.[13,15]

Data collection and analysis was congruent with accepted standards of a qualitative design and was clearly documented and reported to ensure *transparency* and *dependability* of the project findings.[13]

Lastly, each stage of the research process was clearly described to lend *confirmability* to the findings. According to Guba and Lincoln (1989), confirmability is established when credibility, transferability, and dependability are all achieved.[16]

5.6 Ethical considerations

5.6.1 Ethical approval

Ethical approval for the interviews was obtained from the University of Technology Human Research Ethics Committee on 25/01/2019 (Approval no. ETH18-2673) (Appendix 4).

5.6.2 Confidentiality and informed consent

Prior to commencing the interviews, participants were given a participant information sheet (PIS) and a consent form (Appendix 5.3). The PIS stated the aim of the study; general content to be discussed; anticipated length of the interview; measures for privacy and confidentiality; and use of data for academic and research purposes. Participants were asked to sign the consent form prior to the interview. Audio-recording of interviews was explained on the information sheet and the interviewer also obtained participants' verbal consent for this process prior to commencing interviews.

5.6.3 Data management and storage

Participant invitee and participant lists were stored on a password protected computer. Participant names were removed from all data transcripts. Participant confidentiality, privacy and anonymity were ensured through the allocation of participant ID codes in the transcripts and manuscript.

Data were only accessible to the doctoral researcher (IAD) and shared only with her three supervisors (MA, AH and GC) for their input into analysis and interpretation.

All data arising from the interviews, including audiotapes, electronic transcripts, signed participant consent forms, were stored on a secured, password protected computer, in accordance with the University of Technology Sydney Human Research Ethic Committee guidelines and Australian National Ethics guidelines.[17] The publication and presentations arising from this study report only de-identified data. All study data will be retained for a period of five years from the date of the last associated publication.

5.7 Findings

Fifteen delirium researchers participated in semi-structured interviews between August and November 2019. Most participants were male (n=12; 75%), clinician/researchers (n=13; 86%), had conducted five or more delirium studies (n=12; 80%) and had more than 10 years' experience in delirium research (n=9; 60%). Participants were from Europe (n=7), USA (n=3), Australia (n=2), the United Kingdom (UK) (n=2) and South America (n=1). Demographic characteristics of participants are outlined in Table 5.1.

All participants opted for a telephone interview. Interview duration ranged from 18 to 80 minutes (mean 37 (±16)).

Table 5.1Participant demographics (n=15)

	N=15	(%)
Gender		
Male	12	(80)
Female	3	(20)
Continent		
Europe	6	(40)
USA	4	(27)
Australia	2	(13)
UK	2	(13)
South America	1	(7)
Years in delirium research		
10+	9	(60)
5-10	3	(20)
1-5	3	(20)
Current role		
Clinician/researcher	13	(87)
Researcher	2	(13)
Number of delirium studies conducted		
10+	7	(47)
5-10	5	(33)
1-5	3	(20)
Number of biomarker studies conducted		
10+	3	(20)
5-10	2	(13)
1-5	5	(33)
0	5	(33)

Thematic analysis resulted in two major themes and ten sub-themes.

1. **Practical and scientific challenges of delirium biomarker research: stagnation versus driving improved methods and reporting**
    i. Accuracy of diagnostic assessment of delirium
    ii. Delirium superimposed on dementia (DSD)
    iii. Hypothesis driven
    iv. Limited infrastructure and resource investment
    v. Fluctuating nature of delirium means time point of biomarker collection is a crucial consideration
    vi. Collecting CSF and imaging in people with delirium
    vii. Accounting for the complexity/biology of the whole person
    viii. Standardise delirium biomarker research
2. **Valuing delirium research through investment and collaboration:**

1. Ethical committee barriers
2. Transdisciplinary collaboration

5.7.1 Practical and scientific challenges of delirium biomarker research: stagnation versus ways driving improved methods and reporting

Participants generally asserted that delirium biomarker research is an extremely difficult and complex field:

> *"Yes well the hard thing with this is it is such a complex area and no one actually knows. People know what you have to do but they don't know how to get there. It's very difficult. It's a very grey area." (P09)*

Some expressed a sense of frustration, stagnation and pessimism in the field, due to the complexities, challenges and overall uncertainty:

> *"It's a difficult field. There is quite a lot of frustration. There are no quick wins. There is no money coming into the research. I'm not frustrated but I am seeing more difficulties and I am not sure how to get around them in the long*

run because ethics committees get more difficult, money gets scarce, the pressure of clinical work … probably there would be very few units that could do a lot of delirium studies. If I look at ours it is already too small. I'm such a pessimist! But that's the way I see the course of delirium research going in our institution." (P03)

"We are kind of getting a bit stagnant. We need to continue to pursue the truth. I don't know what that necessarily is." (P07)

Another participant on the other hand, expressed an enjoyment of the challenges:

"It's a huge issue. It's very difficult and it's here to stay and the patients pay a really high price. I mean if you look at the cognitive long-term outcomes of ICU survivors. It's just too complex. Which makes it fun!" (P03)

One participant suggested comparing delirium biomarkers to conditions with similar pathophysiological pathways:

"I think the next step is still doing that splitting piece but lumping delirium into you know… delirium in cancer, delirium in Alzheimer's, and trying to find similarities and differences. It's a very difficult problem to research. In clinical studies, we need to translate some of the evidence we have in practice, so when practice improves we can use that data to do bigger research." (P07)

While another, focused on the search for delirium biomarkers for predictive purposes rather than identification of new treatments, expressed a sense of futility:

"Because the sad reality is that there is no treatment for delirium so whether you can predict it or not [through finding a biomarker that predicts delirium],

it's not going to change what you can do. Those which has been proven to be useful is [sic] non-pharmacological interventions for delirium." (P04)

The need to branch out from siloed investigations and from biomarkers already shown to be associated with delirium was noted:

"In the 1940's they found similar things to us now. And it's like… ok let's move forward! […] I think there is some element of reconfirming. But I also think there are some elements of splitting it into medical delirium, or ICU delirium- its important but we have kind of just got so into that, that we have delirium in the cardiac population, delirium in the vascular population, and delirium in… you know. We have so many of these little pocket categories. We are reconfirming results because we are interested to see if it's the same in those populations which is good but I also think it's kind of not leading to a huge mass of knowledge […] I think we need to be more innovative. We have somehow established that CRP, IL-6, IL-8, IL-10 – these biomarkers have been shown in multiple studies, even if they're small, they have been shown to be elevated in delirium. So I think it's time we either need to branch out, or use a different method." (P07)

Delirium biomarker research was perceived to have been a "*hype*" that has since been dulled as there have been no *"quick wins" (P03),* which ironically had become a short-term enterprise:

"Delirium is something like a hype. Everyone was very excited when the first paper came out – the ones from the States, but it's gone a bit quiet since then because I think we all realise it's not going to be a quick win. So we try to focus on something that is easy to sell." (P03)

Accuracy of diagnostic assessment of delirium

Participants perceived clinical recognition of delirium to be generally poor, adding to the difficulties of timely diagnosis:

> *"The downside is that I'm seeing a very small percentage of people that need to be seen. Because the outcomes [for delirium] are so bad I know there are people coming in and out of hospital that end up with delirium that probably aren't seen. Because they're not recognized. People think 'oh they're old' or 'they have dementia' without even knowing if they have dementia. Or 'oh they have been in intensive care, of course they are going to be confused.' So outside of the geriatric medicine it's quite challenging." (P13)*

It appeared that there were conflicting processes for delirium assessment and that most identification of delirium for research purposes relied on clinicians' identification of delirium, rather than researcher assessment. This was seen as problematic because participants felt they could not rely on the accuracy of clinicians' recognition and assessment of delirium:

> *"The first is how to classify patients having delirium or not. Because we have to define whether the patient has delirium and sometimes when we are assessing the patient, he has no delirium, but we have previous reports from the nursing staff or from clinical records that the day before he was on delirium. So it's difficult to classify this type of patient." (P10)*

One participant described a prevalent attitude of clinical futility and lack of interest, especially towards people with co-existing dementia:

"So one of the problems is that a lot of our patients [with delirium] have also got dementia and people know that with dementia there is nothing you can do for them and so they just go 'well it's not worth anybody's time so no.'" (P01)

Participants readily acknowledged the difficulty of precisely defining delirium, noting that it is a syndrome that varies from person to person:

"Because delirium is a set of signs and symptoms and it's not necessarily a diagnosis that you make with histopathology or with very specific lab tests. So you may not detect delirium until a certain time point but that doesn't mean the brain wasn't injured prior to that time point, so there is a lot of uncertainty about when delirium started and when it's resolved – these make it very challenging." (P12)

Others highlighted uncertainties with the classification of sub-syndromal delirium, noting that these individuals are often placed in the 'control group' (i.e. no delirium) in delirium biomarker studies:

"I think when you use the binary of delirium – the yes/no it is because there can be symptoms present- like sub-syndromal delirium – and they're not going to sell it by the full-blown delirium. […] I think understanding the symptom burden at the time of the biomarker being drawn is really important because someone could have…you know, maybe they are fluctuating and have some disorganised thinking but they don't have inattention - so technically they can't qualify as having delirium but some can certainly argue that there definitely is some brain dysfunction going on. Therefore, if they do not have a proper diagnosis of delirium at the time of blood draw then they would be categorised as non-delirious. So it's introducing a lot of noise into the data." (P07)

There was concern with the lack of standardisation in the classification of people with sub-syndromal delirium:

> *"Yes it's a huge problem. I have done both. I have analysed [patients with sub-syndromal delirium] as controls, but in another paper I treated them as cases- as delirium positive." (P11)*

Delirium superimposed on dementia (DSD)

DSD was a significant challenge mentioned by several participants, and the importance of adjusting for dementia in all delirium biomarker studies was highlighted:

> *"If you are doing biomarker studies in delirium you really need to have a picture of the dementia status of the patient both because dementia is the strongest risk factor for delirium and because dementia also impacts on the biomarkers that you want to measure and sometimes the relation is in the opposite direction. For example, we measured amino acids in the CSF and amino acids if you have dementia - several of the amino acids are lower - the concentration goes down in dementia. But they increase in delirium. So if you don't adjust for dementia in your analysis then they will level one another out." (P11)*

The need to have multiple control groups in delirium biomarker studies to understand which biomarkers are affected by dementia was identified:

> *"Well that's why we are doing this study…to distinguish. We are classifying patients into four groups. So we have patients who are totally normal, with no delirium and no dementia. And then we have patients with dementia and*

delirium, then dementia without delirium and also patients with no dementia and [with] delirium. So we can compare the effects of delirium superimposed on dementia […] That's why we have to get these groups to understand these differences (P10)

Hypothesis driven

The importance of taking into consideration the underlying biology of delirium by testing for a plausible hypothesis was discussed. It was noted that *"there isn't any thought going into it" (P15)* including about which biomarkers were being studied and why:

"People are doing these studies with no eye on the biology. I mean I find it really frustrating […] Everyone is going –'Ok we will just get this kit, put the 27 chemokines or cytokines on there, bang them on' – but there isn't any thought going into it. For me, it's a huge problem because no one is actually testing a hypothesis. I think that not enough biomarker studies have a real clear guiding principle, and that is a hypothesis that they are testing. Because if you are testing a hypothesis then you have to think about what it would take to provide support to the hypothesis, or to refute the hypothesis. So the way that you set up your study would relate to the hypothesis that you have. I just feel that no one states a clear hypothesis, no one is studying a hypothesis so we just have very weak associations […] And at the end of the day people read papers and they say 'oh I read this paper and it looks like CRP is a good delirium biomarker' but it won't, it never will be. People just have to get real about this kind of stuff. If you are acutely ill, you are going to have a high CRP and that doesn't mean that you are going to get delirium." (P15)

One participant noted that authors often concluded that there was a 'dysregulation' in inflammatory markers, without taking into account any *priori* hypothesis. The need to clearly state and define a hypothesis was perceived as one reason for weak associations and lack of progress in delirium biomarker studies:

> *"And it means that if they do a panel of 27 markers and only 2 of them change, then they can just say 'this provides evidence for inflammatory dysregulation in delirium' – and that's of no value whatsoever, because if you look at 27 things then statistically at least one of them will change by chance! And therefore you are going to find something and if it goes up or down and you don't really care which, because you can say 'dysregulation' either way and that means you're going into a paper with zero hypothesis, you're just saying throw it at the wall, at least one is going to stick, and we are able to write a paper and get a publication. So I find it very infuriating - those studies are not contributing to the knowledge of delirium." (P15)*

Limited infrastructure and resource investment

The difficulties of conducting biomarker research without appropriate infrastructure was perceived as a barrier to rigorous delirium biomarker research:

> *"I guess it's difficult to do collection of samples for biomarker research or any kind when you don't have the infrastructure. We have only just got a minus 80 freezer so basically if you were in a place that is not an academic centre and they haven't given you a shelf for research samples that can be tricky. We now have minus 80 but we had to ship our samples from our minus 20 to minus 80. Which obviously involves a lot of research governance like shipping and tracking. It's not impossible but it's obviously useful to do research outside of academic." (P6)*

Another participant however, believed that there are fundamental principles of conducting and reporting delirium biomarker studies that should be adhered to if the results are to inform the field, regardless of funding.

> "*I guess it's a resource argument. But I disagree, because if we aren't following some sort of guidelines then we are really doing our patients a disservice because we are not going to make any progress. There has to be a balance between the expectations, and what's required to make it rigorous research and what's actually going to show a relationship and what you can and can't do I guess. Whenever you draw a biomarker you should follow the same steps regardless of whether you have funding or not. You're not saying what assay they should use, you're saying when you write up your findings you need to share which assay and how they did it. I don't see how you need money for that." (P07)*

Fluctuating nature of delirium means time point of biomarker collection is a crucial consideration

Several participants acknowledged the great challenge with ensuring the right timing of biomarker collection due to the fluctuating nature of delirium:

> *"We have also tried looking at interleukins and to stratify but that's really difficult and timing of sampling is crucial so if you sample too late, they're just gone." (P03)*

Some highlighted the need for longitudinal samples to track delirium over time:

> *"And then you need to follow the patient, ideally several times a day to be safe. Because delirium episodes can be for maybe some hours, and it can*

develop during the weekend or during the night and if you don't have a plan for how you are going to assess this information then you will lose it and falsely classify the patient as non-delirious." (P11)

However, two other participants thought that longitudinal sampling was not always feasible:

"You need to make a system where you still are able to pick up the CSF the day it comes and that is very hard unless you want to employ a person to be at the hospital 24/7 - it will be extremely expensive." (P11)

"It adds cost to the collection. It adds cost to the storage. It adds cost to the analysis." (P09)

Collecting CSF and imaging in people with delirium

CSF was considered the 'gold standard' in delirium biomarker research, due to the proximity to the brain, providing an advantage over blood. Despite most participants believing that CSF collection posed too many practical challenges, two others emphasised the need for more of it because it was more likely to directly reflect brain processes during delirium:

"So the first problem is, in my opinion, you really need CSF. You cannot do delirium biomarker studies in blood. Well you can, but there are not so many good candidates for biomarkers in blood that give you good information about the brain." (P11)

"If you want to get to the truth of the disease process it would be better to go as close to the brain as possible." (P09)

Yet most participants also spoke about the difficulties of CSF collection via lumbar puncture, namely its invasiveness and burden on patients:

> *"CSF is not easy to get hold of because you need to do a lumbar puncture which is considered invasive." (P11)*

Problems with coagulation in settings such as the ICU were also described:

> *"It's too difficult I mean, you can't go around collecting CSF on ICU patients. Half the time you can't do CSF because they have a range of clotting of platelets - that's why we rely on serum as CSF is not available." (P06)*

Another participant identified the challenge of collecting CSF for longitudinal sampling:

> *"The CSF you can take only once - when you do the anaesthesia. You can't take every 3 or 5 days. So it's more challenging." (P05)*

Similarly, neuroimaging had been readily used in studying disorders of the central nervous system such as dementia, and offered the potential to develop a better understanding of delirium pathophysiology, although they have only been scantily studied in the field of delirium. Despite the great opportunity that neuroimaging had to offer, several participants focused on the practical challenges of imaging studies and the difficulties associated with undertaking a PET scan when a patient is agitated, noting that *"the practicalities are unresolved." (P03)*

> *"Yes well you can't do a PET during the delirium, you would have to wait for the delirium to be resolved so that you can coach him through a PET session. And a PET session is a long thing, it's not a quick – it takes 20 or 30 minutes*

of lying still in a scanner and you need to be compliant to do that. So it's promising but we are not there yet!" (P03)

In contrast, one participant believed that:

"If you can get a patient into a CT scanner, which they often are put into, then you can get a delirious person into a PET scanner. But this is an extra step with ethics as you can't argue that the PET scanner is essential" (P15)

The perceived need to sedate agitated patients during a PET scan was also described, acknowledging that sedation would adversely affect the patient and the validity of the imaging:

"…Because if you have a patient that has delirium and he's agitated, how are you going to put him in the MRI for one hour? He's not going to stay still then you have to sedate him and then you are worse off than when you started." (P04)

The time constraints associated with PET scans was also described, highlighting that it *"all has to be done in a relatively small window of time" (P01).* This participant also noted that because of the challenges posed by agitation in hyperactive delirium, most of the patients in PET studies had hypoactive delirium:

"Yes that's part of the other problems. We tend to have much more of a bias for the hypoactive delirium [in imaging studies]." (P01)

Accounting for the complexity/biology of the person as a whole

The majority of participants in this study commented on the need to create a homogenous and "*clean*" cohort, acknowledging that people with delirium, particularly in the ICU, often had several underlying conditions affecting the results:

> *"I believe the approach is we must make an attempt to make the most homogenous cohort that we can […] make the best that we can to have reasonable homogenous cohorts and therefore you will end up, if you do that, let's say for hip fracture patients, you will have maybe 60% no delirium, and 40% delirium, they will have all the same aetiology, and all the same insult, so a lot of the peripheral biomarkers for acute trauma should be the same. And then that allows you to see if there are any things that you can pull out that are associated with delirium. So I think that's extremely important. I think lots of people are doing that now, I don't think you can afford not to do it." (P15)*

In contrast, other participants concurred that the next step to broaden delirium biomarker studies is to compare biomarkers across several settings:

> *"But for us to grow… well repeating it in more ICU patients might not be that helpful. For instance, it's a lot easier for me to do it in the ICU because that's where a lot of my research lies. If we really find something that hits then you - start looking at that biomarker in other populations. And if it's hitting across multiple - if it hits in ICU, EDU, after surgery, if you are starting to hit in all three of those places, then that gives you a lot more confidence that it's actually specific to delirium, right? (P02)*

One participant argued that *"existing brain state is going to be the key determinant of whether those acute changes are enough to trigger delirium" (P15),* therefore

emphasising the need to obtain true baseline measurements. Not having a precise baseline was considered a major shortcoming in delirium biomarker studies:

> *"I think a key practical challenge with delirium is that we don't have baselines. So much that you see in delirium is acute hospital admission so you don't get to have a proper baseline. And that's particularly important for somebody with my mindset because I think your brain state before delirium is the major predictor of who will get delirium and how badly they will be affected. So the severity of the acute insult is obviously a major determinant, but who is vulnerable to having delirium in those situations - we learn about that by having a baseline. In those situations we normally don't have baseline information […] So I think that's extremely important, it's a serious shortcoming in delirium studies." (P15)*

The surgical space was considered the best setting for conducting delirium biomarker research with respect to having more reliable baseline measurements:

> *"The other thing… it's a lot easier to do this in the peri-operative space but then I do think this often limits the generalizability. One of the issues for us is when you are running into ICU patients is you don't have a true baseline value for patients before they got sick. So the OR [Operating Room] space at least allows you to get baseline samples to be able to look for change. So if you are just getting started, that's a cleaner model." (P02)*

Some participants asserted that patients in this setting generally had less co-existing conditions that can influence the results and therefore can provide a more accurate depiction of the specific biomarkers for delirium:

"So the hip fracture patient group is a possible patient group because they break their hips and you can distinguish these biomarkers that come from the hip fracture and those that come from the delirium so this is a very interesting population. Normally you don't have sepsis. Normally you don't have cancer or something like that. So this is a very interesting patient group." (P08)

On the other hand, others emphasised that although including elective surgery patients more easily involved pre-operative cognitive testing, the prevalence of delirium in this group was much lower, which subsequently introduced a selection bias:

"If you do cognitive studies in elective surgery patients you will always have a selection bias. So if we look at the patients who participate in our studies they are cognitive [sic] at baseline, pre operatively, they are much better…three points lower …than if you take a random sample of the patients we treat here and that puts you in an awkward position. So there is a methodological flaw right from the start because practically you always have selection bias." (P03)

The heterogeneity of delirium causes was considered a major challenge which varied from person to person. The common approach of relying on clinical identification of delirium left people uncertain:

"Delirium is so multifactorial so if you take an ICU patient, you have so many possible pathophysiological mechanisms that will lead to delirium. An ICU patient will probably choose the pathophysiological path where he's vulnerable. For some, that might be a predisposition because of an already limited cholinergic transmission. In some, it might be a hypoxic problem. That's why it's so heterogeneous and why it will never have a magic bullet or an overall approach to the problem. It's different in every patient. In every patient, it's his

personal mix of mechanisms to go into delirium. That makes therapy so difficult because there are so many underlying causes. If you treat sepsis, that will help but it might not be the only cause if you have hypoxia and sepsis… so there are several mechanisms that lead to delirium that makes standardisation in studies nearly impossible. At least in my opinion. It's a really tough setting." (P03)

When asked about accounting for underlying conditions present in people with delirium, the majority of participants were unable to provide an answer. Participants acknowledged that as a whole, delirium researchers have thus far inadequately tackled this issue:

"Nobody is doing it [accounting for underlying conditions in delirium biomarker studies] and nobody knows what to do about it so it's really good you are writing this. It will give some ideas to people." (P09)

While acknowledging the importance of adjusting for co-existing conditions in delirium biomarker studies, one participant perceived any effort to conduct a delirium biomarker study to be of value. This person stressed that researchers should not be disheartened, because it is *"impossible to do this perfectly" (P11)*.

"Then you just have to accept that this is so hard. Even if it's likely that they are participating because of the delirium, it will impact the biomarkers. You might not be able to adjust for that. You can say that ideally we would like to do it and we think it's important but you shouldn't be too depressed and think that your study is worthless if you're not able to adjust for different precipitating causes of delirium. (P11)

These complexities were further discussed by one participant with respect to differentiating between comorbid conditions that were confounders and those that were mediators:

> *"Then you have the additional challenge of not necessarily knowing which comorbid conditions are confounders versus which ones are mediators. Because you know some of these biomarkers are measuring processes that occur due to an underlying illness like sepsis, if you adjust for sepsis in your model then you may be adjusting for something in the causal pathway. Sepsis could be the cause of your inflammation and so therefore you wouldn't want to adjust for sepsis. So you also have to be very thoughtful with what you include in your regression models and what you don't because adjusting for something that is in the causal pathway is going to eliminate the signal that you otherwise would have seen." (P12)*

Standardisation of delirium biomarker research

All participants had an in-depth awareness that delirium biomarker research was in its infancy and that there was a gap in knowledge, particularly in humans:

> *"I think we have been having some good research in animal models of delirium but I think there is a gap in clinical studies in humans. I don't see many studies trying to study these biomarkers in humans which of course we understand, because it's very difficult. I think that's the biggest problem - to translate these hypotheses to human studies." (P10)*

> *"I think the first thing you have to realise is delirium biomarker research is in its infancy. So you just have to accept that it is[sic] a lot of methodological*

problems and a lot of poorly designed studies. You can't just accept that it will improve dramatically. So that's the first thing you have to understand, we have to be a bit patient." (P11)

Participants reflected on the quality of current delirium biomarker research and highlighted the issue of poorly reported and/or conducted delirium biomarker studies:

"And we don't do a very good job on the side of reporting and reporting that precision so it's rather messy and a lot of the time unable to tell whether the person doing the biomarkers whether they were drawn before or during the delirium. […] I think there is that piece which we are not very good about reporting on those time elements of when the biomarker was drawn and when delirium was assessed." (P07)

Precision and standardisation of delirium diagnosis was considered crucial:

"Besides the biomarkers you should follow a very strict approach to how delirium is diagnosed to make sure that these patients have delirium and not something else." (P08)

As was delirium severity measures:

"But another issue is in the severity of symptoms. It is also difficult to detect or classify patients. We use DRS-98 to measure the intensity of symptoms but it's not consensual – other researchers use other types of measures." (P10)

Participants asserted the need for reporting guidelines, highlighting that often researchers merely replicated procedures of others in the field without considering best practice methods:

"I think our field is missing a metric or a standard to follow. So you just end up doing what your institution or other studies typically do and that's how you report it." (P07)

Using the same protocols for assay procedures was considered important for standardisation, as well as for the potential to combine samples for larger delirium biomarker studies:

"I don't think there are many centres in the world that collect CSF, but those that do should standardise their methods. […] We should try to use similar protocols at different centres so it's possible to combine samples […] You can also standardise the way you handle your samples after you collect them – just basic things like using the same tubes because some biomarkers that you want to analyse they can adhere… if you don't use the correct material to collect the CSF then the proteins can adhere to the surface then you can't trust your results. So AB-42 for example – it's a protein that adheres to plastic - so if you use plastic tubes then your value will be falsely low." (P11)

5.7.2 Valuing delirium research through investment and collaboration

Ethical committee barriers

Many participants shared a frustration towards ethical committees' restrictions in relation to delirium biomarker studies, highlighting it as a notable barrier to progressing the field:

"We are very restrictive for supporting this kind of research. For example, you won't get patients with a very severe dementia and delirium because most of the ethical committees won't let family members give proxy consent and a lot

of the family members say 'oh no this patient already has delirium or dementia.'" (P08)

A reason for the strict restrictions was the perception of ethical committees that patients did not directly profit from being involved in a delirium biomarker study:

"In Switzerland we have a general problem with perception of doing research on patients. They think we use them like guinea pigs. Particularly with delirium research where you don't have a personal profit. It is different if you are in the oncology and you are coming up with a treatment regimen - there you have a potential profit for yourself. In delirium research you don't and they are very reluctant to say yes and go along with that." (P03)

There was a perception that ethical committees considered people with delirium too vulnerable to be included in research; hence, introducing a selection bias whereby cohorts in these studies often consisted of people with lower risk of delirium:

"Essentially our ethics committees are getting more difficult. Many patients who have a high risk of delirium are a cognitively impaired at baseline so they fall into the category of vulnerable group of patients which makes it difficult to approach them. Then we have the problem that the … if you approach, you will get the good ones with too low rates of delirium." (P03)

A pragmatic solution to this barrier was to append the biomarker study onto an already existing trial, alleviating the hurdles of obtaining separate ethical approval for the delirium biomarker component of the study:

"Linking to some sort of ongoing trial that is enrolling people for another reason. Even if it's delirium, it's not necessarily primarily the biomarker. So I

think linking on to randomised controlled trials or big observational cohorts, whatever they're doing, getting funding and adding it on something that is co-existing is a lot easier." (P02)

In contrast, one participant took a long-term approach, and disagreed with tagging the biomarker component onto an existing study. They argued that in order to conduct robust delirium biomarker research, the studies must be "*bespoke*" and original:

"There is an overarching point here and if you want to do a really good biomarker study, or really good pathophysiology work then sometimes you just can't build that on the back of routine clinical care. They have to be bespoke studies where you have to go the extra mile. You need to go to the patients or the carers or whatever, and tell them that you need to take a sample and this time or that time or whatever. Because if it is just opportunistic, which of course the majority of this work is, which can still produce good work, but if its only opportunistic, then you won't be able to do these sorts of studies that you might want to do - the killer biomarker studies. You have to write up a protocol that's more involved, that asks more of the patient and carers, and the nurse, the phlebotomist, the lumbar puncture etc. […] It's one of those things, that if you really want to advance the research, then you need to do a real research study. And by real, I mean bespoke. That's not being critical of the opportunistic studies, but sometimes if you want to answer the hard questions, you have to do the hard studies." (P15)

Transdisciplinary collaboration

Participants described a number of areas where current delirium biomarker studies were falling short. These included that studies were predominantly conducted by clinicians:

> *"I think delirium is a relatively young field and it's been driven primarily by clinicians which is great because they're really invested or embedded in the health system next to the patient so you have that really rich clinical representation. But the down side is that they just aren't necessarily trained very strong methodologically." (P07)*

The importance of collaboration between clinicians and scientists to improve the science of delirium biomarker studies was highlighted by many:

> *"I think for the large part, they are kind of working with clinical research centres who are very good on study design and statistics, but I just find that there is not enough biological thinking. There is no thought going into the papers. There is often not a biologist there and if you combine the lack of clear physiological knowledge with the relative lack of biologists involved in these studies - I think you have got a recipe for disaster!" (P15)*

However, a barrier perceived by participants was the geographical separation of clinicians and scientists, noting that their workplaces were often in different settings to one another:

> *"And then the universities where most of the researchers are at a separate institute [to the clinicians]." (P01)*

Not all participants however, believed that collaboration between clinicians and scientists in delirium biomarker studies was absent:

> *"Mostly it's clinicians asking the question and then they work with PhD or masters or basic scientists to actually run the biomarker. So I feel like there is a fair bit of collaboration there." (P02)*

5.8 Discussion

Delirium researchers identified a range of factors that contribute to the challenges of conducting delirium biomarker research and the risk of the field not accelerating efforts, which have not previously been explicitly acknowledged or reported. This study provides the most in-depth exploration of these challenges to date, and some important insights into how to address the many practical, scientific and quality issues in research into delirium pathophysiology.

Practical and scientific challenges of delirium biomarker research: stagnation versus driving improved methods and reporting

Overall, researchers in this study concurred that delirium biomarker research is in practical terms an extremely difficult and complex field. This led to a sense of frustration and pessimism from some researchers. Such attitudes have also been found in dementia research[18] but efforts are being made to overcome these in a person-centred way, which can similarly be considered in delirium.[19]

A minority took a long-term view, whereas many reported taking short-term approaches, even as they acknowledged that the latter was unlikely to advance scientific knowledge of delirium. Although the practical difficulties and complexities of delirium biomarker research was a common finding, some participants also provided clues and suggestions as to how some issues may be addressed. For example,

the issue of delirium under-recognition and misdiagnosis by clinicians, which has been extensively studied and reported as occurring in 21-79% of cases across settings.[20-22] It appears from the present study that reliance on clinical identification of delirium, as opposed to researcher assessment, has contributed to much uncertainty about whether delirium was indeed present, or not, at the time of biomarker collection. This finding flags the urgent need for more systematic and reliable research processes for delirium identification in research into its biomarkers, which will require greater involvement of researchers and reporting of diagnostic quality.

Furthermore, there are conflicting methods in how the features of delirium are assessed for research purposes. The ability to distinguish between the different etiologic subtypes will be critical to elucidate delirium pathophysiology and to develop effective treatments.

There was congruence in the researchers' views that accounting for co-existing conditions in delirium was important but extremely challenging, and divergent views about how to resolve the question. Most participants were uncertain about how to tackle this topic, and yet addressing this uncertainty in a united way is crucial to advancing the field of research. Delirium superimposed on dementia (DSD) was considered a key challenge by participants, who noted the importance of adjusting for dementia in delirium biomarker studies. Delirium is a risk factor for dementia, and is associated with worsening severity in individuals with existing dementia.[23,24] The prevalence of delirium superimposed on dementia in community and hospitalised settings is well documented and ranges between 22-89% in people aged 65 and older.[25] When dementia and delirium co-exist, it is difficult to ascertain whether the observed changes in a particular biomarker were related to the delirium, or confounded by the underlying dementia.[26] A small number of animal models of delirium during dementia

have been developed, which suggest that prior synaptic loss and microglial priming are predisposing factors for acute cognitive impairment induced by systemic inflammation.[27] Although this model is highly promising, further validation in more studies is required. There is also an urgent need to characterise these two conditions biologically and clinically in human studies. Including multiple control/comparator groups would help to elucidate the distinctions.

A challenge identified in this study was the acuity, fluctuating course and often brief duration of delirium. These factors make precise determination of its onset and resolution extremely difficult; and yet research recruitment and precision in the timing of biomarker collection is crucial in delirium biomarker studies to accurately capture the delirium episode.[28] Furthermore, pathophysiological processes may differ in active delirium vs those individuals who are not yet delirious. A standardised way of determining delirium resolution is also required, as there is currently no consensus on the definition of delirium resolution.[29]

The proximity of CSF to the brain makes it a good target for studying the pathophysiology of central nervous system conditions, providing an advantage over blood.[30] CSF is in direct contact with the extracellular space of the brain, therefore some biochemical changes occurring in the brain are reflected in the CSF.[30] However, obtaining CSF for research purposes has numerous practical challenges. Most delirium researchers discussed the burden of CSF collection by lumbar puncture (LP), and referred to the procedure as "invasive". Although there is no literature on the experience of adults undergoing LP, there has been much research in children and adolescents. One study demonstrated that 75% of parents/caregivers of children who were scheduled to undergo an LP did not consent because of a fear of complications from the procedure.[31] It is important to note that LP is a safe procedure with an overall

low risk of complications; however, post-LP headaches and back pain are known side-effects.[32] One proposed solution to this barrier is to improve the quality and person-centeredness of information given to potential participants, to increase their understanding of the proposed research. A recent scoping review reported that many older people were willing to participate in research even with impaired decision-making capacity, although less so in studies with higher risks or burdens.[19] Reducing study risks and burdens, as well as improved communication processes with potential participants and proxies, are therefore crucial. For example, simplified information and consent forms using lay language that avoids medical jargon as well as extended discussions can lead to improvements in participant understanding and appreciation of study information.[33,34]

Neuroimaging is another method that has sparked interest in attempts to understand the neural correlates of delirium. Neuroimaging is routinely used in clinical practice; however, there are still very few studies on neuroimaging in delirium, which likely reflects the practical and ethical challenges involved in imaging patients with hyperactive delirium. Researchers in this study expressed concerns about the practical challenges of getting a person who is agitated to lie still in a PET scanner. One solution is for a relative or carer to accompany patients to reassure them, as was effectively enacted in another study.[35] Another limitation to neuroimaging studies in delirium are the small sample sizes, which can introduce type II error and preclude adjustment for confounding factors. Although imaging studies are deemed to be extremely difficult, large samples which adjust for confounding factors (e.g. pre-existing cognitive impairment) are needed, as well as long-term vision and planning of research programs to facilitate adequately powered studies.[36]

The need to account for and understand the complexity and biology of the whole person was highlighted as a gap in current delirium biomarker studies. A key limitation of many previous studies in acutely admitted patients was the lack of objective cognitive testing at baseline, therefore making it difficult to know if any observed changes in biomarkers were related to the delirium, or were confounded by underlying conditions. Many researchers suggested that future delirium biomarker studies focus on the surgical setting, where patients have a true pre-operative baseline. Currently, hip fracture patients are the most studied group in the field, and many studies collect CSF opportunistically from patients in surgery who are already undergoing a spinal anaesthesia.[37] The limitation of this approach is that delirium is a multifactorial condition, which almost always occurs in the context of other physiological processes that need to be accounted for in study participants.

This study confirmed that standardised methods in the form of reporting guidelines for delirium biomarker research are urgently required, as was initially identified in the systematic review reported in Chapter three.[11] Inadequate and/or unclear reporting of methodological processes can lead to discrepancies in results, which may be misleading and potentially detrimental to the research.[38] Overall, reporting guidelines are deemed necessary to promote studies that are standardised and reliable. This statement is consistent with other studies that reported improvements in reporting rigor when reporting guidelines such as the CONSORT (Consolidated Standards of Reporting Trials)[39] were adopted. Many journals have taken steps to improve the quality of the research articles that they publish by requiring the use of reporting guidelines, although research shows there is still room for improvement.[40] Having global standardised guidelines to conduct delirium biomarker research with similar

reference standards will help to improve the quality of reporting within studies and thereby increase opportunities for syntheses across studies.

Valuing delirium research through investment and collaboration

There are several ethical challenges to conducting research in patient populations at higher risk of harm, such as delirious patients who are often considered too vulnerable for research participation.[41] The extent and implications of vulnerability of patients with cognitive impairment or impaired capacity to consent to research studies has been highly debated in the literature,[41] and informed consent is complicated when cognitive impairment and impaired decision-making capacity is present. There is an ethical tension in delirium research; namely, balancing the need to protect this more vulnerable population with upholding their rights to be included in research and the need to improve medical care.[28] This study confirmed that ethical committee interpretation of current research regulations when applied to delirium research may sometimes be exceedingly stringent. This is driven by several factors: patients are unlikely to profit directly from participating in a delirium biomarker study; concerns about potential harms to a vulnerable population; and perceived burden of specimen collection and the quality of informed consent. Those with impaired capacity tend to be either excluded from research, or less frequently recruited, to circumvent the challenges of tailoring methods and study measures.[19] However, this evasion compromises the quality of findings and limits external validity due to the recruitment of unrepresentative populations.[28,42]

Common motivations of older people to participate in research in the context of impaired decision-making include altruism, potential personal benefits, and a desire to contribute to scientific knowledge.[19] Greater consumer input into delirium biomarker study development would help to ensure improved value proposition and

communication by researchers to ethical committees and potential participants/proxies so they can better weigh the benefits/risks of delirium studies might help to overcome some of the barriers identified by researchers in this study.

The common approach of relying on the clinical identification of delirium within biomarker research should be replaced with a more rigorous process. Such a process could be elucidated by clinicians, scientists and researchers working in a more united way to improve methods in delirium biomarker research. This issue was identified in this study by the frequent acknowledgment that currently delirium biomarker research is predominantly being conducted by clinicians with minimal background in basic science. To address these gaps, multi-institutional collaborative efforts are needed to generate valid, reproducible and generalisable findings in delirium biomarker research. The Successful Aging after Elective Surgery (SAGES) program[36] is one example of a collaborative project that aims to achieve research rigour and results that would be likely unattainable by investigators working independently.

5.9 Strengths and limitations

A key strength of this study was the inclusion of participants from multiple disciplines and countries who were actively involved in delirium research, allowing data saturation to be reached. Secondly, the qualitative method allowed for an in-depth exploration into the reasons underpinning the participant views, giving clearer guidance of the specific areas for advancement in the field.

Participants were purposefully sampled in order to facilitate in-depth exploration of delirium researchers' perspectives, and so these findings may be specific to the challenges of delirium biomarker research, rather than be transferable to biomarker research more generally. It is not known if the predominance of male and clinician

researcher participants is representative of the field, or had any particular influence on the findings of the study; however, these are worth noting as potential limitations. Lastly, transcripts were not sent back to participants for checking.

5.10 Conclusion

Findings of this qualitative study identified a range of factors that contribute to the challenges of conducting delirium biomarker research, which have not previously been explicitly acknowledged or reported. These factors appear to contribute to the overall quality of research in this field. Findings complemented the preceding systematic review and Delphi survey, and together these studies will inform strategies to improve the methods and reporting of delirium biomarker research. A concerted effort is now required to standardise and strengthen several aspects of the conduct and reporting of delirium biomarker studies, in order to advance this highly promising but yet to deliver scientific field of research.

5.11 References

1. Khachaturian AS, Hayden KM, Devlin JW, et al. International drive to illuminate delirium: A developing public health blueprint for action. *Alzheimer's & Dementia.* 2020;16(5):711-725.
2. Slooter AJ, Otte WM, Devlin JW, et al. Updated nomenclature of delirium and acute encephalopathy: statement of ten Societies. *Intensive Care Medicine.* 2020:1-3.
3. Oh ES, Akeju O, Avidan MS, et al. A roadmap to advance delirium research: Recommendations from the NIDUS Scientific Think Tank. *Alzheimer's & Dementia.* 2020;16(5):726-733.
4. Tong A, Sainsbury P, Craig JJIjfqihc. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Journal for Quality in Health care.* 2007;19(6):349-357.
5. Patton MQ. Qualitative research & evaluation tools. 4th ed. ed. Los Angeles, California SAGE 2015.
6. Carter SM, Little M. Justifying knowledge, justifying method, taking action: Epistemologies, methodologies, and methods in qualitative research. *Qualitative Health Research.* 2007;17(10):1316-1328.
7. Marshall MN. Sampling for qualitative research. *Family Practice.* 1996;13(6):522-526.
8. Galletta A. *Mastering the semi-structured interview and beyond: From research design to analysis and publication.* Vol 18: NYU press; 2013.
9. Rubin HJ, Rubin IS. *Qualitative interviewing: The art of hearing data.* Sage; 2011.
10. Amgarth-Duff I, Hosie A, Caplan G, Agar M. Toward Best Practice Methods for Delirium Biomarker Studies: An International Modified Delphi Study. *International Journal of Geriatric Psychiatry.* 2020.
11. Amgarth-Duff I, Hosie A, Caplan G, Agar M. A systematic review of the overlap of fluid biomarkers in delirium and advanced cancer-related syndromes. *BMC Psychiatry.* 2020;20(1):1-32.
12. Braun V, Clarke V. Using thematic analysis in psychology. *Qualitative Research in Psychology.* 2006;3(2):77-101.
13. Lincoln YS, Guba E. *Naturalistic Inquiry London.* England: SAGE Publications; 1985.
14. Lincoln YS, Guba EG. But is it rigorous? Trustworthiness and authenticity in naturalistic evaluation. *New Directions for Program Evaluation.* 1986;1986(30):73-84.
15. Braun V, Clarke V. *Successful qualitative research: A practical guide for beginners.* SAGE Publications 2013.
16. Guba EG, Lincoln YS. *Fourth generation evaluation.* SAGE Publications; 1989.

17. Heaslop M, Salisbury. Australian Code for the Responsible Conduct of Research. In: Government A, ed. Canberra2007.

18. Waite J, Poland F, Charlesworth G. Facilitators and barriers to co-research by people with dementia and academic researchers: Findings from a qualitative study. *Health Expectations.* 2019;22(4):761-771.

19. Hosie A, Kochovska S, Ries N, et al. Older Persons' and Their Caregivers' Perspectives and Experiences of Research Participation With Impaired Decision-Making Capacity: A Scoping Review. *The Gerontologist.* 2020.

20. Lange PW, Lamanna M, Watson R, Maier AB. Undiagnosed delirium is frequent and difficult to predict: Results from a prevalence survey of a tertiary hospital. *Journal of Clinical Nursing.* 2019;28(13-14):2537-2542.

21. de la Cruz M, Fan J, Yennu S, et al. The frequency of missed delirium in patients referred to palliative care in a comprehensive cancer center. *Supportive Care in Cancer.* 2015;23(8):2427-2433.

22. Mayoral R, Madrigal F, Perez S, Aviles E. Delirium in terminal cancer inpatients: short-term survival and missed diagnosis. *Salud Mental.* 2018;41(1).

23. Davis DH, Muniz Terrera G, Keage H, et al. Delirium is a strong risk factor for dementia in the oldest-old: a population-based cohort study. *Brain.* 2012;135(9):2809-2816.

24. Fong T, Jones R, Shi P, et al. Delirium accelerates cognitive decline in Alzheimer disease. *Neurology.* 2009;72(18):1570-1575.

25. Fick DM, Agostini JV, Inouye SK. Delirium superimposed on dementia: a systematic review. *Journal of the American Geriatrics Society.* 2002;50(10):1723-1732.

26. Inouye SK, Ferrucci L. Introduction: Elucidating the pathophysiology of delirium and the interrelationship of delirium and dementia. *The Journals of Gerontology Series A: Biological Sciences Medical Sciences.* 2006;61(12):1277-1280.

27. Murray C, Sanderson DJ, Barkus C, et al. Systemic inflammation induces acute working memory deficits in the primed brain: relevance for delirium. *Neurobiology of Aging.* 2012;33(3):603-616. e603.

28. Holt R, Siddiqi N, Young J. The ethics of consent in delirium studies. *Journal of Psychosomatic Research.* 2008;65(3):283-287.

29. Adamis D, Devaney A, Shanahan E, McCarthy G, Meagher D. Defining 'recovery'for delirium research: a systematic review. *Age and Ageing.* 2015;44(2):318-321.

30. Blennow K, Hampel H, Weiner M, Zetterberg H. Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. *Nature Reviews Neurology.* 2010;6(3):131.

31. Narchi H, Ghatasheh G, Al Hassani N, Al Reyami L, Khan Q. Why do some parents refuse consent for lumbar puncture on their child? A qualitative study. *Hospital Pediatrics.* 2012;2(2):93-98.

32. Duits FH, Martinez-Lage P, Paquet C, et al. Performance and complications of lumbar puncture in memory clinics: results of the multicenter lumbar puncture feasibility study. *Alzheimer's & Dementia.* 2016;12(2):154-163.

33. Kim EJ, Kim SH. Simplification improves understanding of informed consent information in clinical trials regardless of health literacy level. *Clinical Trials.* 2015;12(3):232-236.

34. Nishimura A, Carey J, Erwin PJ, Tilburt JC, Murad MH, McCormick JB. Improving understanding in the research informed consent process: a systematic review of 54 interventions tested in randomized control trials. *BMC Medical Ethics.* 2013;14(1):28.

35. Haggstrom L, Nelson J, Wegner E, Caplan G. 2-18F-fluoro-2-deoxyglucose positron emission tomography in delirium. *Journal of Cerebral Blood Flow & Metabolism.* 2017;37(11):3556-3567.

36. Schmitt EM, Marcantonio ER, Alsop DC, et al. Novel risk markers and long-term outcomes of delirium: the successful aging after elective surgery (SAGES) study design and methods. *Journal of American Medical Directors Association.* 2012;13(9):818. e811-818. e810.

37. Hall RJ, Watne LO, Cunningham E, et al. CSF biomarkers in delirium: a systematic review. *International Journal of Geriatric Psychiatry.* 2018;33(11):1479-1500.

38. Simera I, Moher D, Hirst A, Hoey J, Schulz KF, Altman DG. Transparent and accurate reporting increases reliability, utility, and impact of your research: reporting guidelines and the EQUATOR Network. *BMC Medicine.* 2010;8(1):24.

39. Plint AC, Moher D, Morrison A, et al. Does the CONSORT checklist improve the quality of reports of randomised controlled trials? A systematic review. *Medical Journal of Australia.* 2006;185(5):263-267.

40. Levine D, Kressel HY. 2016: Reviewing for Radiology—Reporting Guidelines and Why We Use Them. *Radiology* 2016;280.

41. Bracken-Roche D, Bell E, Macdonald ME, Racine E. The concept of 'vulnerability'in research ethics: an in-depth analysis of policies and guidelines. *Health Research Policy and Systems.* 2017;15(1):8.

42. Prusaczyk B, Cherney SM, Carpenter CR, DuBois JM. Informed consent to research with cognitively impaired adults: transdisciplinary challenges and opportunities. *Clinical Gerontologist.* 2017;40(1):63-73.

Chapter 6: REDEEMS Explanation and Elaboration document

6.1 Chapter Preface

Chapter four reported on Stage 1 and 2 of the REDEEMS guideline development, which used a modified Delphi process followed up a consensus meeting to develop a preliminary list of reporting items. This chapter describes Stage 3 of the development process, which involved preparation for dissemination and communication of the REDEEM guidelines via an Explanation & Elaboration paper ('E&E').

The REDEEMS E&E document was submitted for publication to the Journal of the Academy of Consultation-Liaison Psychiatry in June 2021.

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6.2 Introduction

Reporting guidelines are one step towards research reporting that allows reliable and consistent interpretation, application, and synthesis of study results. Current guidelines that focus on different aspects of biomarker research include the REMARK,[1] STARD,[2] STROBE,[3] A guideline for uniform reporting of body fluid biomarker studies in neurologic disorders[4] and the CONSORT statement.[5] These guidelines are concerned with research into prognostic and diagnostic biomarkers, or biomarker studies conducted in the context of a randomised controlled trial. None of these guidelines are specific to delirium. We therefore developed the REDEEMS guideline, which addresses specific areas that international delirium experts deemed useful to address important methodological aspects of in delirium biomarker research.

The recommended process for developing reporting guidelines includes the development of an accompanying Elaboration and Explanation ('E&E') paper, such as was originally undertaken by the CONSORT group to accompany their revised statement.[6,7] Other reporting guidelines such as the STARD, STROBE, and REMARK later adopted this process as a means of informing authors and reviewers about their guidelines and providing detailed rationales for the items included.[1,3,8] Despite recommendations for implementation strategies to increase the uptake of reporting guidelines,[6] a survey of developers of 30 reporting guidelines found that only 43% (n=13) had used an implementation strategy such as an E&E document.[9] The purpose of this accompanying E&E paper is to provide a detailed explanation of each of the REDEEMS guideline items and promote their implementation.[6]

6.2.1 Development of the REDEEMS guideline

As reported in Chapter four, the REDEEMS guideline was developed by delirium researchers via a three-stage process proposed by Moher et al. 2010 (a systematic

review, a three-round modified Delphi consensus process, and an online consensus meeting).[6] The final REDEEMS guideline containing 9 items, resulted. Figure 4.1 (Chapter 4) presents the guideline development process, and Table 4.10 (Chapter 4) lists the guideline items.

6.2.2 How to use the REDEEMS guideline

The REDEEMS guideline items focus on ways that authors can ensure transparent and complete reporting of delirium biomarker studies. It does not intend to be a definitive list covering all aspects of delirium biomarker studies. Rather, it outlines the minimum requirements specific to reporting delirium biomarker studies, with the expectation that authors will provide further information as necessary and according to the specific study design.

The REDEEMS guideline used the REMARK checklist [1] as the initial framework from which to build the modifications required to meet the specific additional considerations for delirium biomarker studies. Therefore, REMARK reporting items that were identified as not necessary for adaptation for delirium biomarker studies were not presented in the Delphi process. These items, which are also deemed important in other reporting guidelines (such as CONSORT and STARD), are considered 'gold standard' in the reporting of research studies, and include i) describing the characteristics of the sample (eligibility criteria), ii) reporting baseline characteristics, iii) recruitment and flow of participants and iv) limitations of the study and directions for future research. Such items have not been repeated in the REDEEMS, as they are already well documented across reporting guidelines in health research[1-3,10] after rigorous development and publication processes. It is therefore recommended that the REDEEMS is used in conjunction with the most appropriate reporting guideline for each individual delirium biomarker study, as can be found on the EQUATOR network

(http.//www.equator-network.org/). Appendix 7 illustrates the use of the REDEEMS guideline for two exemplar papers from the systematic review in Chapter 3.

6.2.3 How to use the E&E document

Each REDEEMS item is presented with a rationale for inclusion and accompanied by an example of good reporting drawn from published delirium biomarker literature. It should be noted that examples represent optimal reporting of the item rather than of the overall paper; and some have been slightly edited to remove citations or spell out abbreviations.

Items are numerically ordered from 1 to 9, although order of presentation may vary according to the individual study or specific journal requirements, while unknown or missing information requires an adequate justification.

6.3 REDEEMS guideline items

Discussion and explanation of the nine items of the REDEEMS guideline (Table 4.10, Chapter 4) are presented below.

Item 1. Study rationale

1. **State the biomarker under study (including the nature of the specimen)**
2. **Describe the biological hypothesis(/es) tested**

Examples

1. *"Previous work in a nested, matched case–control subset of the Successful Aging after Elective Surgery (SAGES) cohort demonstrated that higher CRP levels before surgery and on Postoperative Day 2 (POD2) could predict postoperative delirium in older adults. This research has been extended by examining the associations between C-Reactive Protein and postoperative delirium incidence, duration, and*

feature severity; Length of stay; and discharge disposition in the entire SAGES study cohort." [11]

"A priori, we selected five markers of inflammation and four markers of coagulation—all nine markers are described in the Electronic Supplementary Material (ESM)—based on previous studies examining inflammation and coagulation during critical illness." [12]

2. "*We have investigated a hypothesis that delirium is caused by acute episodes of neuronal cell death using cerebrospinal fluid (CSF) markers of cell death: lactate, neuron-specific enolase (NSE), and S100B, and examined whether there is any relationship between these measures and outcomes of delirium. Additionally, these markers may offer insights into the etiology of increased reactive oxygen species and glucose hypometabolism. which are seen in dementia and mild cognitive impairment*." [13]

Explanation

A biomarker study aims to explore a biological process and its biological contribution to the clinical event of interest (delirium), possibly as part of a risk/predictive factor analysis, or as an effect modifier of outcomes (e.g. mortality). The biomarker under study should be chosen *a priori*, based on previous data or reasoning that supports a biologically plausible rationale i.e. a clear hypothesis[14] and provided early on in the paper. The type of biological specimen chosen should also have adequate specificity and sensitivity.

The importance of taking into consideration the underlying biology of delirium by testing for a plausible hypothesis has been documented,[14] and is perceived as one reason for weak associations and lack of progress in the understanding of delirium

pathophysiology. Given the current status of the biological knowledge of pathophysiological mechanisms underpinning delirium, it is reasonable that the level of justification be hypothetical, until more data on its pathophysiology emerges. It is important to note that not all delirium biomarker studies will be studying a hypothesis, and so it is also reasonable to conduct an exploratory delirium biomarker study. If the study is not testing a specific hypothesis, it should be made clear that the study is undertaking an exploratory (also known as an 'un-biased') approach.

For some research questions a control or comparator group will be needed to test the hypothesis, and if so the choice should be clearly justified. Control or comparator groups to consider in a delirium biomarker study include: participants without delirium, healthy participants, and/or participants with the same underlying diagnosis and/or illness severity without delirium. In longitudinal studies, the group under comparison may include participants with a shorter duration of delirium, a lower delirium severity, or who do not develop delirium.

Item 2. Ascertainment of delirium

1. **Describe the training and/or credentials of personnel who ascertained delirium cases**
2. **Specify the delirium tool and/or diagnostic process that was used to ascertain cases**
3. **Describe frequency, timing and duration of delirium assessment**

Examples

"*All participants were observed daily by the nursing and medical staff and by members of the research team until discharge. To screen for a change in behaviour, the 13-items Delirium Observation Screening scale was used during the first 5 days of*

admission. The diagnosis of delirium was made by a geriatrician, according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV).” [15]

“Delirium assessments for each patient were carried out preoperatively on the day of surgery, followed by a post-operative assessment 3–4 days later. Assessment consisted of mental status assessment with cognitive tests, examination of case notes and discussion with clinical staff, leading to a DSM-IV diagnosis of delirium assessed with the CAM. Delirium cases were defined as delirium present pre-operatively and active at the time of sample collection (prevalent) or delirium not present pre-operatively but developing postoperatively (incident).” [16]

Explanation

A description of the population of interest is needed to place the study in a clinical context.

Currently, there is vast variation in how delirium is assessed, including subjective clinical judgment, various tools, and comprehensive processes supported by cognitive testing.[17] Standardisation of process and reference rater characteristics will help to ensure more reliable assessment of delirium cases and severity,[18] and comparability of results. It is therefore important that delirium is ascertained using a structured tool or process for which psychometric properties have been established (e.g. reliability, validity, discriminatory power, and normative data).[19]

Delirium should also be prospectively evaluated wherever possible. If accessing both adult and paediatric populations, these should be considered separately as the exact mechanisms in both are not yet known. Furthermore, consideration of participants with SSD is needed. In studies which aim to compare participant with delirium (‘full syndromal delirium’) vs no delirium controls SSD is often excluded to define a ‘clear’

group with delirium to compare with controls. It is however possible that SSD group may provide important information about the biomarker under-study and inform the research question, and this should be considered.

Item 3. Outcome measures

Define and justify all clinical endpoint(s) and their measures (including relationship to delirium where relevant)

Example

"Delirium-/coma-free days were defined as the number of days after enrolment, a patient was alive and free of delirium or coma. Delirium-/coma-free days provide an estimate of duration of normal brain function free of coma and delirium and hence function as negative surrogate of delirium duration not confounded by coma or death. Delirium-/coma-free days as an outcome has been used previously in high impact studies and takes into account confounding by death and discharge." [20]

Explanation

By precisely defining (not simply naming) the clinical endpoints relevant to delirium, measures can be replicated and meaningful comparisons can be made between studies. For example, it is not sufficient to refer to the end point as 'delirium severity' without reporting how severity was measured. Wherever possible, standardised definitions are also recommended. Importantly, the choice of a primary clinical endpoint should be stated (see example above) relating this to the primary aim of the study. Blinding is particularly important if the endpoint is potentially subject to measurement bias (e.g. delirium severity), while less important for definitive endpoints (e.g. death).[21] Reporting whether and how the analyser was blinded to patient outcomes, particularly if subjective, allows the reader to assess the risk of measurement bias.

Item 4. Assay procedures

1) **Specify the assay method used with a detailed protocol that includes the reagents/kits used**
2) **Describe the methods of preservation, storage and processing of the biological sample**
3) **Describe the assay validation method for repeatability and robustness, including the sensitivity limits of the assay**
4) **Specify the inter- and intra- assay coefficients of variation**
5) **Specify the method of blinding of outcome assessor to biomarker results**

Examples

1. **"***The concentrations of plasma cortisol and IGF-1 were determined by enzyme-linked immunosorbent assay (ELISA) using colorimetric kits purchased from Alpco (Salem, New Hampshire) and Assay Designs (Ann Harbor, Michigan), respectively. The optical densities were measured using a Bio-Tek Spectrophotometer (Plate Reader) PowerWave XS (Winooski, Vermont). The concentrations were calculated from a best fit standard curve generated by the ELISA kit instructions and using the manufacturer suggested protocols*." [22]

   "Aβ40 and Aβ42 was assayed using MSD electrochemiluminescence assay (Meso Scale Discovery, Rockville, MD, USA), and p-tau and t-tau were assayed using INNOTEST enzyme-linked immunosorbent assays (Fujirebio, Ghent, Belgium) according to the manufacturer's specifications." [23]

2. *"Serum was obtained by centrifugation for 15 minutes at 1780 g at 4°C, and aliquots were stored at -80°C."* [24]

3. "*ELISA was conducted according to the manufacturer's instructions, and the subject samples were assayed in duplicate and values averaged. All duplicates possessed <10% coefficient of variation*." [25]

4. "*CRP before surgery and on post operative day 2 was measured in the entire sample using a high-sensitivity ELISA kit (R&D Systems; Minneapolis, MN), with all standards and samples run in duplicate. Each 96-well plate contained the standard curve and cases and controls at both time points. Coefficient of variations of duplicate measures were generally 5% or less. If any CV was greater than 10%, that plasma sample was repeated."* [11]

   "Intra-assay coefficients of variation were 5.1% for a quality control sample with an Neurofilament light concentration of 10.9 pg/ml and 9.6% for a quality control sample with a concentration of 150 pg/ml. The lower limit of quantification was 6.7 pg/ml." [26]

5. *"The laboratory workers who assayed the cytokines were blinded to all clinical diagnoses of the patients."* [27]

Explanation

These items were derived from the REMARK checklist,[1] but were included in the REDEEEMS guideline as they have been identified as a priority area for improvement in the reporting of delirium biomarker studies.[28]

Detailed reporting of assay methods allows others to assess their adequacy and to replicate it with precision and accuracy, and also to report any potential limitations that may impact interpretation of results. If another widely accessible document which details the exact assay method is used (for example, a commercially available assay protocol), it is acceptable to cite that document without repeating all the details of the process. If a commercially available kit is used for the assay, it is important to state whether the kit instructions were followed exactly and, if not, explain any deviations from the kit's recommended procedures.

Despite complete standardisation of the assay and quality monitoring, random variation (measurement error) in assay results can still occur due to assay imprecision or variations across laboratories. Therefore, reporting strategies used to reduce the measurement error, such as taking the average of two or three results to produce a measurement with less error, is important. Reporting reproducibility assessments provides a sense of the overall variability in the assay. Batch effects also need to be taken into consideration. [29]

It is important to include as much detail as possible about the type of biological sample used in the study and the way it was collected, processed, and stored. The time of specimen collection often will not coincide with the time when the marker assay was performed, as it is common for assays to be performed after the specimens have been stored for some period of time. Therefore, authors should state when the specimens were taken relative to how long they were stored prior to performing the marker assay. Storage conditions relevant to the viability of the assay, e.g. temperature, should also be reported. If the specimen studied is serum or plasma, information should be provided about how the specimen was collected, including anticoagulants used, the temperature at which the specimen was maintained prior to storage, the storage tube type, processing protocols, and preservatives used. The Biospecimen Reporting for Improved Study Quality (BRISQ) guideline provides detailed recommendations on what should be reported in relation to specimen collection, processing and storage when publishing research biospecimens [30].

Objective measures are those that are not subject to a large degree of individual interpretation and are likely to be a reliable measure across patients.[31] However, sometimes a patient's clinical outcome is known by the individual running the assay and analysing the results, which can increase the risk of measurement bias. Reporting

the extent of blinding of the assay assessor to clinical outcomes allows assessment of the risk of this type of bias.

Item 5. Timing of collection of the biological sample

1. **Precisely describe the time of collection of the biological sample in relation to delirium (onset, duration, resolution)**
2. **Provide a rationale for the timing of the sample collection based on the clinical scenario, the hypothesis being tested, and/or the study design**

Example

"*All patients underwent phlebotomy at four time points: preoperative (PREOP), post-anesthesia care unit (PACU), postoperative day 2 (POD2), and 1 month postoperative (PO1MO). Blood collection was incorporated into clinical blood draws taken in the pre-admitting testing center (PREOP), in the PACU, and on the surgical wards (POD2). The PO1MO blood sample was obtained either at the 30-day postoperative follow-up visit or in the patient's home by the study team*." [32]

Explanation

Different phases of delirium have been shown to be associated with varying biomarker findings.[33] Therefore, a thorough description of the timing of specimen collection in relation to onset, presence, and resolution of delirium is particularly important.

The time of specimen collection will often not coincide with the time when the marker assay is performed, as it is common for marker assays to be performed after the specimens have been stored for some period of time. In longitudinal sampling of populations *at risk of delirium*, it is recommended that samples are collected prior to delirium onset, during the delirium episode, and after delirium resolution. In

longitudinal sampling of populations *with delirium*, it is recommended that samples are collected during delirium and again after delirium resolution.

It is also important to justify the timing of the sample collection according to the clinical scenario and/or the hypothesis being tested. For example, clinical insults (surgery, anaesthetic); clinically relevant decision points (e.g. extubation, discharge); when the delirium precipitant is likely to have clinically resolved; or based on the kinetics of the biomarker, such as the time point after sepsis when an inflammatory biomarker is likely to change. This reporting allows the reader to make an informed judgement of the appropriateness of the timing of biomarker collection; while more consistent overall reporting will promote better understanding of associations between clinical, delirium, and biomarker trajectories.

Item 6. Confounding variables

- **State the confounding variables assessed and whether or not they were specified *a priori***
- **Clearly define and justify all confounding variables (including the relationship to delirium where relevant)**

Examples

"To adjust for potential confounders, we selected covariates a priori based on biological plausibility and previous research. These covariates, collected at enrollment, included age, severity of illness, and admission with severe sepsis, which was identified according to treating physicians' diagnosis and confirmed using consensus criteria." [12]

"First, to avoid confounding by coma and death—both of which can truncate delirium duration and which we hypothesized would be associated with the exposures—we used the number of days alive without delirium or coma (i.e., delirium/ coma-free days) during the first 14 days after study enrollment, a period of analysis chosen because

almost all delirium and coma in our cohort occurred within 14 days of enrollment. We considered patients who were discharged from the hospital prior to study day 14 to be delirium/coma-free. In addition, we used days of delirium among survivors over the same 14-day period to focus more specifically on delirium. Patients who died in hospital were excluded from this analysis because early death curtails delirium duration." [34]

Explanation

Delirium has multiple clinical causes, and occurs in and across heterogenous clinical populations which requires careful considerations of the clinical variables to account for in studies exploring delirium biomarkers.[35] Imprecise or unmeasured potential confounders can increase the risk of residual confounding. [36,37]The study report should therefore state and define all variables considered and included in the analysis, including confounding variables.

Confounding variables should be decided *a priori* and should take into account the population being studied/the clinical condition. The confounding variables should be based on known relationships with the outcomes of interest and/or help define subgroups of interest within the population. Dementia status is particularly important to collect as it is the strongest risk factor for delirium and because biomarkers of delirium and dementia overlap. Efforts should therefore be made to report data on dementia status when planning a biomarker study, including how it was ascertained. Other examples of important confounders in delirium biomarkers include: age, baseline cognitive impairment and severity of illness, all of which should all be controlled for in the final analysis.

Item 7. Sample size

Describe how the sample size was determined and provide a rationale

Example

Power analysis, assuming a clinically important difference of 4 mean bilateral bispectral levels between the two groups (non-delirious and delirious), suggested that 114 patients were required for the study (alpha = 0.05; 1-beta = 0.8).[38]

Explanation

Inadequate sample sizes may contribute to falsely negative results leading to a type II error. Underpowered studies limit the ability to detect true differences in biomarker findings and to draw any firm conclusions. For example, if a study with negative findings is not adequately powered, a clinically important but statistically non-significant effect is usually ignored or, even worse, authors conclude that there was no significance difference in their study. [39] Thus, there are important scientific reasons to explain the considerations that led to the sample size, whether based on a formal statistical calculation or determined by practical considerations, such as the availability of samples or cost.[1] Sample size should be determined based on the estimated effect size of the biomarker in predicting the outcome, and the estimated incidence or prevalence of delirium also needs to be taken into consideration. Sample size should be decided *a priori* based on previous studies/pilot data.

Item 8. Statistical analysis

1. **Account for clinical and biomarker missing data in the analysis plan based on the design of the study**
2. **State how confounding variables will be accounted for in the analysis**

Examples

"*In order to reduce bias from missing data, we used multiple imputation to account for missing covariates and outcomes among patients with at least partial outcomes data available at a given time point."* [40]

"Little's MCAR test showed that there was no systematic pattern of missing values (chi-square = 106.010, df = 111, P = 0.616)." [41]

Explanation

Many biomarker studies will have missing biomarker or covariate data. Authors should report the number of patients with missing values for each clinical variable of interest and explain type of missing data (missing at random (MAR), missing completing at random (MCAR) and how the missing data was handled (case-wise deletion, multiple imputation, etc.). The statistical plan should account for biomarker missing data due to clinical attrition from overall deterioration, worsening cognition and death, all of which are common in patients in delirium biomarker studies. Missing data due to the practical challenges of biomarker collection in people with delirium should also be planned for. These include situations where a patient refuses specimen collection, is away for a procedure, or is too sick for collection. The nature and approach to deal with missing data may differ depending on whether the study is cross-sectional or longitudinal.

The clinical covariates should be described and controlled for in the statistical analysis plan. Since delirium is a complex heterogeneous condition with multifactorial risk factors, precipitants and clinical influences, clinical covariates relevant to the scenario and hypothesis should be considered. Important considerations in the selection of covariates include the following: 1) relevancy to the clinical setting and hypothesis; 2)

prioritisation of covariates that are supported in delirium or relevant literature; and 3) implications for the required sample size to avoid overfitting or biasing findings.

Item 9. Univariate and multivariable analysis

1. **Report the estimated effect size or confidence intervals**
2. **Specify whether biomarker result was dichotomized using a cut-point and/or threshold**
3. **Specify the number of included participants and reasons for attrition or missing data**
4. **Describe how model assumptions were verified (multivariable)**

Example

"In regression analyses, tryptophan, tyrosin, phenylalanine, methionine and 5-HIAA remained significantly associated with delirium status in patients free from dementia when adjusting for age, gender, ADL, Charlson and APACHE II" [42]

Explanation

Item 9 is also derived from the REMARK checklist,[1] but was included in the REDEEMs guideline because the complex nature of delirium requires that the analytical approach take into account and explicitly report its multifactorial risks, precipitants and clinical influences. .

The association of the biomarker with the clinical endpoint is of key. Results should be reported for all primary and secondary endpoints to avoid selective reporting, not just for those that were statistically significant, or those that will draw interest to the paper.

The unadjusted and adjusted results should both be reported together, allowing the readers to interpret the data behind the measures of association. For adjusted analyses,

the number of included participants in the analysis should be reported, as this may differ because of missing values in covariates. Readers can compare unadjusted measures of association with those adjusted for confounding variables and assess how much and in what direction they changed.

For each outcome, study results should be reported as a summary of the outcome in each group together with the contrast between the groups (the estimated effect size). For binary outcomes, the estimated effect size could either be the risk ratio (relative risk), odds ratio, or risk difference. Confidence intervals (CI) should also be presented for all outcomes in addition to estimates, to indicate the precision of the estimate. A 95% CI is standard; however, other levels can be used. [43,44] CIs are particularly important in relation to differences that did not meet a statistical significance, for which they often indicate that the result does not rule out an important clinical difference.[7] P values can also be provided, but they should not be reported in the absence of CI's.

Although univariate analyses are useful, they are generally insufficient due to the possible relationship of the biomarker under study and confounding variables are adjusted for in a multivariate analysis. It is helpful to report on both univariate and multivariate results, allowing for a direct assessment of how the biomarker is altered by inclusion of standard covariates in the multivariate model. Types of multivariate analysis will depend on the study, and so the details of the different types of multivariate the models available is beyond the scope of this chapter.

Authors should report all potential confounding variables and the criteria for including or excluding variables in multivariate models. Decisions about excluding or including variables should be guided by knowledge or explicit assumptions about causal relations. Careful consideration of biomarkers that are confounders versus those that

are mediators is important. Inappropriate decisions may introduce bias; for example, by including confounding variables that are in the causal pathway (i.e. mediators) that occur due to an underlying illness such as sepsis. Inappropriate adjustment for sepsis in this example may lead to an adjustment for variables in the causal pathway.[14]

6.4 Concluding remarks

The REDEEMS guideline and E&E document was developed to guide authors in reporting delirium biomarker studies in a transparent fashion. Good reporting of studies will increase the potential for synthesis of studies through meta-analysis. The resources will help researchers to be more informed of the critical elements of a delirium biomarker study, so that these can be applied from the initial process of study design through to the conduct, analysis, and ultimately reporting. While it may not be possible for authors to report every item in every study, they are E&E documents are encouraged to assess the impact of missing information and report the rationale for its absence.

The REDEEMS guideline and E&E document were developed as a collaborative effort of delirium researchers committed to improving understanding of delirium pathophysiology, whose contributions are gratefully acknowledged.

Several groups may potentially benefit from using the REDEEMS guideline, including authors, researchers, peer reviewers, journal editors and consumers of research. For authors and researchers planning a delirium biomarker study, the REDEEMS guideline can be used as both a guide during the planning and design phase of the study and a reporting checklist. For researchers planning a systematic review or meta-analyses in the delirium biomarker field, the REDEEMS can be used to create a template for the data extraction phase. In the future, inclusion of the REDEEMS in the

reporting requirements for authors submitting manuscripts could guide peer reviewers and journal editors in their assessment of delirium biomarker study manuscripts.

The next step for this project is dissemination to promote uptake of the guideline, and evaluation of the influence on improved study rigor and capacity to fully answer study hypotheses.[6] Authors of future delirium biomarker studies can contribute to transparent and complete reporting by using the REDEEMS guideline and recommending it to others in the field. As new evidence emerges and critical feedback is obtained, the REDEEMS will be updated in the future, such as has occurred for other reporting guidelines such as the CONSORT.[5]

6.5 References

1. Altman DG, McShane LM, Sauerbrei W, Taube SE. Reporting recommendations for tumor marker prognostic studies (REMARK): explanation and elaboration. *BMC Medicine.* 2012;10(1):51.
2. Bossuyt PM, Reitsma JB, Bruns DE, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *Radiology.* 2015;277(3):826-832.
3. Vandenbroucke JP, Von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *PLoS Medicine.* 2007;4(10):e297.
4. Gnanapavan S, Hegen H, Khalil M, et al. Guidelines for uniform reporting of body fluid biomarker studies in neurologic disorders. *Neurology.* 2014;83(13):1210-1216.
5. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *International Journal of Surgery.* 2012;10(1):28-55.
6. Moher D, Schulz KF, Simera I, Altman DG. Guidance for developers of health research reporting guidelines. *PLoS Medicine.* 2010;7(2).
7. Moher D, Schulz KF, Altman D, Group C. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *Jama.* 2001;285(15):1987-1991.
8. Cohen JF, Korevaar DA, Altman DG, et al. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. *BMJ (open).* 2016;6(11).
9. Simera I, Altman DG, Moher D, Schulz KF, Hoey J. Guidelines for reporting health research: the EQUATOR network's survey of guideline authors. *PLoS Medicine.* 2008;5(6):e139.
10. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *International Journal of Surgery.* 2014;12(12):1495-1499.
11. Vasunilashorn SM, Dillon ST, Inouye SK, et al. High C-Reactive Protein Predicts Delirium Incidence, Duration, and Feature Severity After Major Noncardiac Surgery. *Journal of the American Geriatrics Society.* 2017.
12. Girard TD, Ware LB, Bernard GR, et al. Associations of markers of inflammation and coagulation with delirium during critical illness. *Intensive Care Medicine.* 2012;38(12):1965-1973.
13. Caplan GA, Kvelde T, Lai C, Yap SL, Lin C, Hill MA. Cerebrospinal fluid in long-lasting delirium compared with Alzheimer's dementia. *Journals of Gerontology Series A-Medical Sciences.* 2010;65(10):1130-1136.
14. Amgarth-Duff I, Hosie A, Caplan G, Agar M. Delirium researchers' perspectives of the challenges in delirium biomarker research: a qualitative study *PLoS ONE.* 2020.

15. Egberts A, Wijnbeld EH, Fekkes D, et al. Neopterin: a potential biomarker for delirium in elderly patients. *Dementia & Geriatric Cognitive Disorders.* 2015;39(1-2):116-124.

16. Cape E, Hall RJ, van Munster BC, et al. Cerebrospinal fluid markers of neuroinflammation in delirium: a role for interleukin-1beta in delirium after hip fracture. *Journal of Psychosomatic Research.* 2014;77(3):219-225.

17. Neufeld KJ, Nelliot A, Inouye SK, et al. Delirium Diagnosis Methodology Used in Research: A Survey-Based Study. *American Journal of Geriatric Psychiatry.* 2014.

18. Tieges Z, Evans JJ, Neufeld KJ, MacLullich AM. The neuropsychology of delirium: advancing the science of delirium assessment. *International Journal of Geriatric Psychiatry.* 2018;33(11):1501-1511.

19. Oh ES, Akeju O, Avidan MS, et al. A roadmap to advance delirium research: Recommendations from the NIDUS Scientific Think Tank. *Alzheimer's & Dementia.* 2020;16(5):726-733.

20. Khan BA, Perkins AJ, Prasad NK, et al. Biomarkers of Delirium Duration and Delirium Severity in the ICU. *Read Online: Critical Care Medicine| Society of Critical Care Medicine.* 2020;48(3):353-361.

21. Day SJ, Altman DG. Blinding in clinical trials and other studies. *BMJ (Online).* 2000;321(7259):504.

22. Cerejeira J, Batista P, Nogueira V, Vaz-Serra A, Mukaetova-Ladinska EB. The stress response to surgery and postoperative delirium: evidence of hypothalamic-pituitary-adrenal axis hyperresponsiveness and decreased suppression of the GH/IGF-1 Axis. *Journal of Geriatric Psychiatry and Neurology.* 2013;26(3):185-194.

23. Oh ES, Blennow K, Bigelow GE, et al. Abnormal CSF amyloid-β42 and tau levels in hip fracture patients without dementia. *PLoS ONE.* 2018;13(9):e0204695.

24. van Munster BC, Korse CM, de Rooij SE, Bonfrer JM, Zwinderman AH, Korevaar JC. Markers of cerebral damage during delirium in elderly patients with hip fracture. *BMC Neurology.* 2009;9:21.

25. Yen TE, Allen JC, Rivelli SK, et al. Association between Serum IGF-I levels and Postoperative Delirium in Elderly Subjects Undergoing Elective Knee Arthroplasty. *Scientific Reports.* 2016;6:20736.

26. Casey CP, Lindroth H, Mohanty R, et al. Postoperative delirium is associated with increased plasma neurofilament light. *Brain.* 2020;143(1):47-54.

27. Van Munster BC, Korevaar JC, Zwinderman AH, Levi M, Wiersinga WJ, De Rooij SE. Time-course of cytokines during delirium in elderly patients with hip fractures. *Journal of the American Geriatrics Society.* 2008;56(9):1704-1709.

28. Amgarth-Duff I, Hosie A, Caplan G, Agar M. A systematic review of the overlap of fluid biomarkers in delirium and advanced cancer-related syndromes. *BMC Psychiatry.* 2020;20(1):1-32.

29. Leigh D, Lischer H, Grossen C, Keller L. Batch effects in a multiyear sequencing study: False biological trends due to changes in read lengths. *Molecular Ecology Resources.* 2018;18(4):778-788.

30. Moore HM, Kelly AB, Jewell SD, et al. Biospecimen reporting for improved study quality (BRISQ). *Journal of Proteome Research.* 2011;10(8):3429-3438.

31. Velentgas P, Dreyer NA, Wu AW. Outcome definition and measurement. *Developing a protocol for observational comparative effectiveness research: a user's guide*: Agency for Healthcare Research and Quality (US); 2013.

32. Dillon ST, Vasunilashorn SM, Ngo L, et al. Higher C-Reactive Protein Levels Predict Postoperative Delirium in Older Patients Undergoing Major Elective Surgery: A Longitudinal Nested Case-Control Study. *Biological Psychiatry.* 2017;81(2):145-153.

33. Hall RJ, Watne LO, Cunningham E, et al. CSF biomarkers in delirium: a systematic review. *International Journal of Geriatric Psychiatry.* 2018;33(11):1479-1500.

34. Hughes CG, Pandharipande PP, Thompson JL, et al. Endothelial activation and blood-brain barrier injury as risk factors for delirium in critically ill patients. *Critical Care Medicine.* 2016;44(9):e809.

35. Maldonado JR. Delirium pathophysiology: An updated hypothesis of the etiology of acute brain failure. *International Journal of Geriatric Psychiatry.* 2017;33(11):1428-1457.

36. Becher H. The concept of residual confounding in regression models and some applications. *Statistics in Medicine.* 1992;11(13):1747-1758.

37. Brenner H, Blettner M. Controlling for continuous confounders in epidemiologic research. *Epidemiology.* 1997:429-434.

38. Plaschke K, Fichtenkamm P, Schramm C, et al. Early postoperative delirium after open-heart cardiac surgery is associated with decreased bispectral EEG and increased cortisol and interleukin-6. *Intensive Care Medicine.* 2010;36(12):2081-2089.

39. Moher D, Dulberg CS, Wells GA. Statistical power, sample size, and their reporting in randomized controlled trials. *Jama.* 1994;272(2):122-124.

40. Hughes CG, Patel MB, Brummel NE, et al. Relationships between markers of neurologic and endothelial injury during critical illness and long-term cognitive impairment and disability. *Intensive Care Medicine.* 2018;44(3):345-355.

41. Adamis D, Lunn M, Martin FC, et al. Cytokines and IGF-I in delirious and non-delirious acutely ill older medical inpatients. *Age and Ageing.* 2009;38(3):326-251.

42. Watne LO, Idland A-V, Fekkes D, et al. Increased CSF levels of aromatic amino acids in hip fracture patients with delirium suggests higher monoaminergic activity. *BMC Geriatrics.* 2016;16(1):149.

43. Altman D. Clinical trials and meta-analyses. *Statistics with Confidence: Confidence Intervals and Statistical Guidelines 2nd ed London: BMJ Books.* 2000:120-138.

44. Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. *British medical journal (Clinical research ed)*. 1983;286(6376):1489.

Chapter 7: Conclusion and Recommendations

This doctoral research project identified significant gaps in the reporting rigor of delirium biomarker studies and developed reporting guidelines specific to this field of research (the REDEEMS).[1] Through a development process that included a systematic review, a Delphi and consensus process, and an accompanying Explanation and Elaboration ('E&E') document, REDEEMS aims to standardize and strengthen the conduct and reporting of delirium biomarker studies as a means to improving their scientific rigor, dissemination, and impact on knowledge and clinical practice.

This concluding chapter summarises the findings of the doctoral research project by answering the research questions; presents a synthesis of the findings; describes how the results will contribute to the field of delirium pathophysiology; and discusses the overall strengths and limitations. Six recommendations for future research that arose from this thesis are also described.

7.1 Summary of findings

The three research questions of the doctoral research project are re-visited and answered in the following sections.

7.1.1 Research question 1: What is the overlap in the biomarkers in delirium and advanced cancer-related syndromes?

Chapter three reported a systematic review of the overlap of biomarkers with advanced cancer-related syndromes; namely, cancer pain, fatigue, anorexia cachexia, sickness behavior, and cancer-related cognitive impairment. Review of 151 studies identified a considerable overlap in the biomarkers of delirium and advanced cancer. Overall, 41 biomarkers had been studied in relation to both delirium and either an advanced cancer-related syndrome or prognosis. Of these, 24 biomarkers (59%) were positively

associated with either delirium or advanced cancer syndromes/prognosis in at least one study. No cancer studies reported having any participants with delirium, and of the delirium studies, six studies reported participants with cancer. However, it is unclear whether the biomarkers identified were predominantly associated with delirium or the underlying cancer, as three of the six oncology studies grouped the delirium participants together, irrespective of their cancer comorbidity.

In addition to the limited capacity of these studies to answer research question 1, the overall poor quality of reporting of the included studies further reduced confidence in the findings as well as the potential utility of future evidence syntheses. Thus, an incidental but important finding of the systematic review was that there was a systematic problem in the consistency and quality of reporting of delirium biomarker studies, which furthermore raised doubts about the quality of their methods (see Figures 3.3 and 3.4, Chapter three).

Hence, the incidental finding of systemic poor quality reporting of delirium biomarkers studies warranted a change in the direction of the doctoral research. From this point onwards, the doctoral research focused on developing reporting guidelines for delirium biomarker studies and understanding the challenges and opportunities to strengthening the field of research.

7.1.2 Research question 2: What are the critical elements of high quality conduct and reporting for delirium biomarker studies?

A total of nine items were deemed critical elements for reporting high quality delirium biomarker studies by the consensus of delirium researchers, and were included in the REDEEMS guideline. The items classified into the following nine categories: 1. Study rationale, 2. Ascertainment of delirium, 3. Outcome measures, 4. Assay procedures, 5. Timing of collection of the biological sample, 6. Confounding variables, 7. Sample

size, 8. Statistical analysis, and 9. Univariate and multivariate analyses. The guideline, along with the Explanatory document (Chapter six), seeks to inform delirium biomarker researchers of the critical elements of high quality conduct and reporting for their studies.

7.1.3 Research question 3: What are the key methodological challenges in conducting delirium biomarker research?

Findings of the qualitative study in Chapter 5 identified a range of factors that contribute to the challenges and overall quality of delirium biomarker research. Delirium researchers acknowledged that biomarker research in the field is in its infancy and that the quality of reporting current delirium biomarker research is poor, adding to the lack of scientific understanding. Overall, they concurred that delirium biomarker research is, in practical terms, an extremely difficult and complex field. According to this international group of researchers, the key methodological challenges in delirium biomarker research were:

i. The inaccuracy of diagnostic assessment of delirium
ii. Delirium superimposed on dementia (DSD)
iii. The lack of studies with a pre-determined biological hypothesis
iv. Limited infrastructure and resource investment
v. The fluctuating nature of delirium meaning that time point of biomarker collection is crucial
vi. The ethical and practical issues with collecting CSF by lumbar puncture and imaging in people with delirium
vii. Accounting for the complexity/biology of the whole person
viii. Lack of standardisation of delirium biomarker research
ix. Ethical committee barriers

x. The need for transdisciplinary collaboration between scientists and clinician

Interpretation of overall findings

Drawing upon the discrete findings of each study together at the conclusion of this doctoral research project enabled a higher-level interpretation of the overall project to be made. Thus, Figure 7.1 presents a proposed model of the complex inter-relationship of the diverse key factors relating to the challenges, complexities, and considerations in delirium biomarker research. The model categorises these factors at the macro (systems), meso (organisational) and micro (individual) levels, highlighting the importance of transdisciplinary collaboration, education and training, and standardization of research methods and reporting to inform and improve the understanding of delirium pathophysiology.

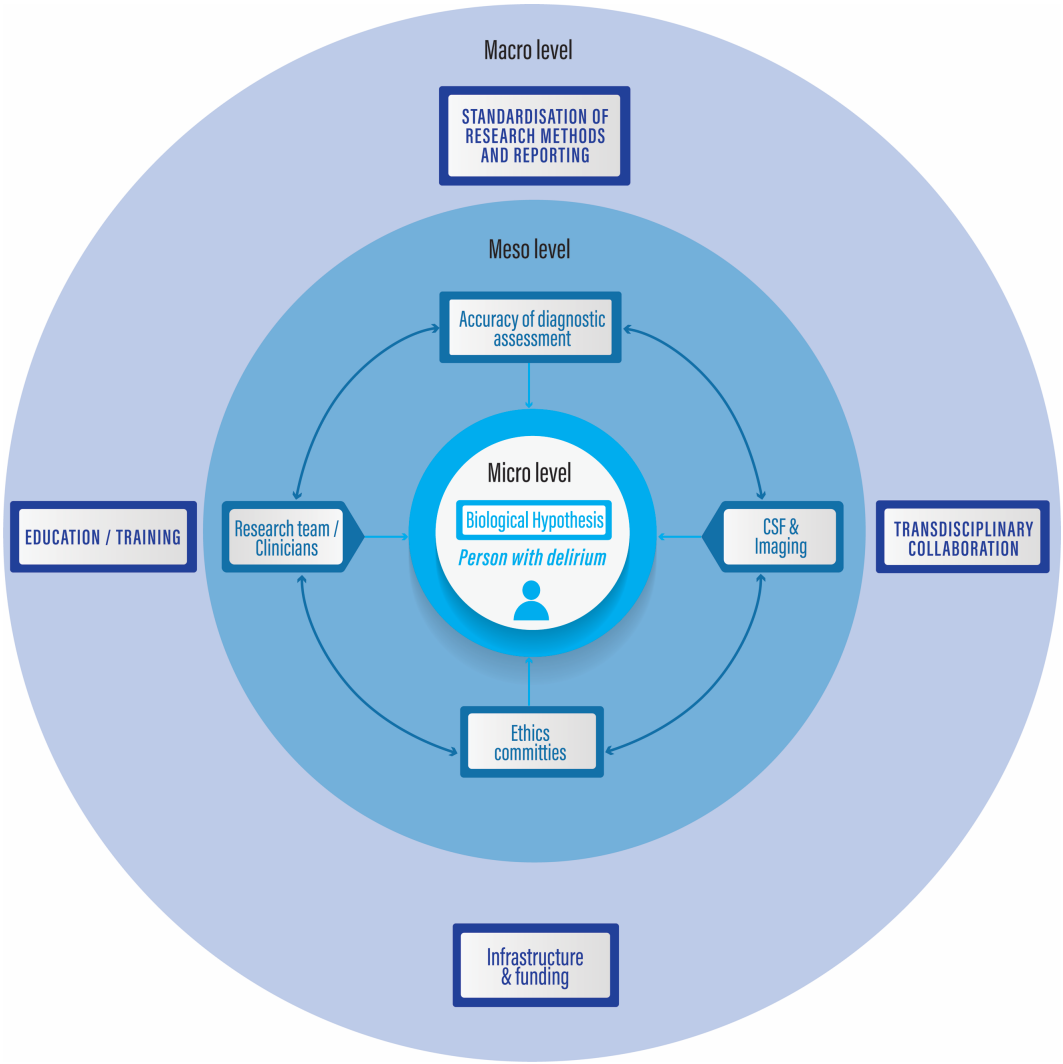

Figure 7.1 Proposed model of the inter-related key challenges, complexities, and considerations in delirium biomarker research

The supporting evidence derived from this doctoral work underpinning interpretations at the macro, meso and micro levels are further discussed below.

Macro (systems) level

Here, the macro (systems) level was defined as pertaining to standardisation of research methods and reporting, education and training, infrastructure and funding and transdisciplinary collaboration.

Delirium researchers acknowledged that delirium biomarker research is predominantly being conducted by clinicians with minimal background in basic science. To address this gap, interdisciplinary collaborative efforts are needed to enhance research quality in the field. Instigating international training and educational workshops on the methodology for delirium biomarker research would support researchers to develop high-quality study protocols. Interdisciplinary collaboration would focus on encouraging teams of scientists, clinicians, researchers and biostatisticians to work together in a united way to and integrate their knowledge and skills to improve methods for delirium biomarker studies. This includes standardisation of research protocols such as specimen collection, analysis, data reporting, imaging sequences and biomarker assessment to allowing for future collaborations and sharing of samples between laboratories. A proposed solution cited in the literature is to utilise a platform such as a international biomarker consortium for such activities, an approach which is currently used for other conditions such as dementia.[2] Such an effort has the potential to build large-scale data and specimen banks to conduct systems biology, -omics (e.g. proteomics, metabolomics), and machine learning studies to accelerate the advancement of scientific knowledge in the field.[2] This will also help alleviate the challenges of limited infrastructure for clinicians undertaking delirium biomarker studies.

Increased awareness through public education is needed to improve research funding in the field of delirium. Improving public awareness and funding has been successful through public health campaign models in Alzheimer's disease prevention. The International Drive to Illuminate Delirium (IDID)[3] seeks to advance the field of delirium along five pillars: awareness, policy, diagnosis, burden, and biology, drawing on the same methods and procedures used to increase public awareness and research

funding for Alzheimer's disease. The campaign includes work groups with international experts from multiple disciplines to develop plans that will lessen the burden of delirium.[2]

Meso (organisational) level

The meso (organisational) factors comprise interrelations between the research team/clinicians, accuracy of diagnostic assessment, collection of CSF and imaging studies, and ethics committees. Findings confirmed that ethical committee interpretation of current research regulations in delirium are stringent. This is driven by several factors: the perception that patients are unlikely to profit directly from being involved in a delirium biomarker study, concerns about potential harms to a vulnerable population, perceived burden of specimen collection and the quality of informed consent. Those with impaired capacity tend to be either excluded from delirium research, or less frequently recruited, to circumvent the challenges of tailoring methods and study measures.[4] Improving communication processes by clinicians/the research team with potential participants and proxies particularly with regards to the specimen collection process is essential to increase their understanding of the proposed research and improve person-centeredness of information given to potential participants. Better communication and explanation of study rationales to ethical committees, and in grant applications could also help in alleviating these challenges.

Although the systematic review found that 99% of studies reported the population, the qualitative findings revealed that purely stating the population is not sufficient. It appeared from the qualitative findings that the poor identification of delirium contributes researchers' uncertainty about whether delirium was indeed present, or not, at the time of biomarker collection. The uncertainty concerning the conceptualization

and measurement of delirium has had important implications for the delirium reference standard used in research, as there are currently no definitive diagnostic tests that can identify delirium, meaning that the diagnosis of delirium relies on clinical examination of people using the DSM-V or the ICD-10. Findings from the qualitative study flags the urgent need for more systematic and reliable research processes for identification of patient with delirium. Such a process could be elucidated by clinicians, scientists and researchers working in a more united way to improve methods and generalizability across delirium biomarker studies.[2] Detailed and standardised documentation of the reference standard in all studies is necessary, including specification of the methods used to assess the individual features of delirium.

Micro (individual) level

The person with delirium is importantly and deliberately placed at the centre of the proposed model. Factors relevant to the person include: the biological hypothesis, and the interpersonal approaches required by researchers to support patient participation in delirium biomarker studies. Equally each delirium study specifically aims to improve our understanding for a particular population (group of individuals).

Findings from the systematic review in Chapter three confirmed that a high percentage (82%) of delirium biomarker studies stated a pre-defined hypothesis, however, the qualitative findings highlighted that a pre-defined hypothesis must be supported by a strong biological underpinning and a justification for the hypothesis, considering this in the context of the individuals in whom it is aiming to build our understanding of delirium. One of the most complex issues which still needs resolution, is development of methodological approaches which can account for and understand the complexity

and biology of the whole person, and take this heterogeneity into account when studying biomarkers in a population of interest.

The impact on people with delirium participating in delirium biomarker studies is not insignificant. The invasiveness of CSF collection by lumbar puncture and the difficulties of getting an agitated patient to lie still in a PET scan were two challenges that were highlighted in the qualitative study. Greater consumer input (e.g. people who have previously experienced delirium and their caregivers) into delirium biomarker study development, as well as involving families and/or proxies in specimen collection procedures would help to ensure improved value proposition and communication so they can better weigh the risks and benefits of delirium studies. Equally their views on the research questions of interest, and what involving them in the design phases of research will ensure their views underpin the research priorities going forward; and model which is becoming usual practice in many areas of research, including cancer and dementia research.

7.2 Recommendations of this doctoral research

This thesis concludes with six recommendations for future delirium biomarker research.

Recommendation 1

That delirium biomarker researchers use the REDEEMS guideline to improve the transparency, standardisation, and completeness of study reporting.

Recommendation 2

That education and training resources and workshops in delirium biomarker research methodology are developed.

Recommendation 3

That delirium biomarker researchers engage in multi-institutional and transdisciplinary collaborations involving clinicians and scientists.

Recommendation 4

That delirium biomarker researchers obtain consumer input into study development to improve the value proposition and the communication of study rationales and processes, to both ethical committees and potential participants/proxies.

Recommendation 5

That consensus is developed for the key characteristics of a universal delirium reference standard and its operationalisation across settings and populations.

Recommendation 6

That practical tools (e.g. a protocol template) to aid delirium biomarker researchers develop rigorous study protocols be created and disseminated.

Figure 7.2 (below) illustrates the relationship between the three studies of this doctoral research project that led to the standardisation of research methods (denoted in blue) and provides the high-level recommendations for future research (shown in green).

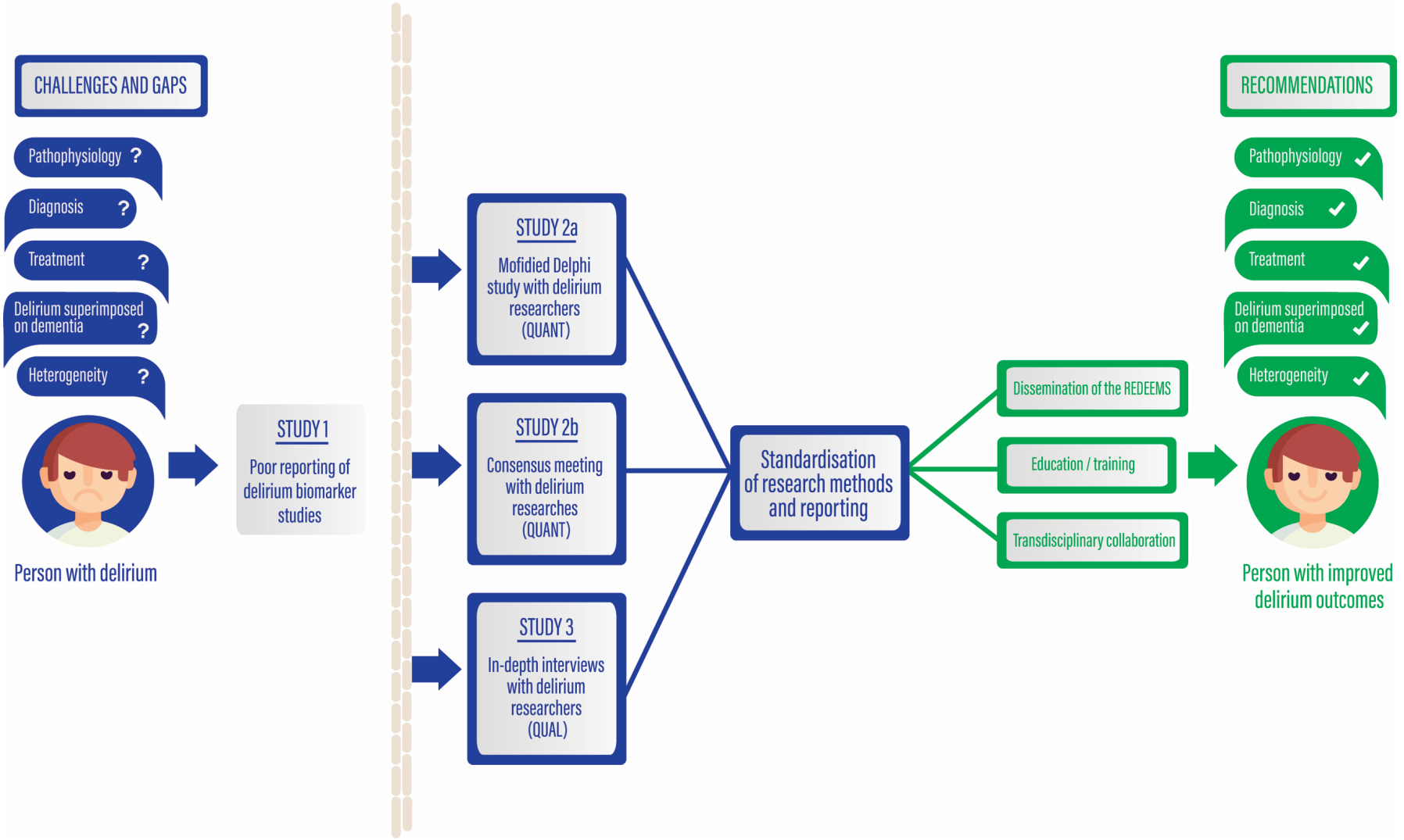

Figure 7.2 Summary of the doctoral research project

7.3 Strengths and limitations

7.3.1 Strengths

Strengths were that multiple methods were used, comprising both qualitative and quantitative research methods allowing for an in-depth exploration into the nuances and challenges and the reasons underpinning participant views.

A systematic approach to developing the REDEEMS reporting guideline was used which was based on a well-established process in health research.[5]

Another key strength was the breadth of expertise and number of years' experience of the international participants involved in the development of the REDEEMS.

7.3.2 Limitations

While the limitations of each study have been described in the relevant chapters, there are a number of overall limitations to this doctoral research project that are highlighted in this section.

Firstly, majority of participants were from high income countries therefore further engagement and promotion of delirium biomarker research in low and middle income countries is needed. Also, the current research included only the views of delirium researchers and did not include clinician or patient/consumer perspectives.

The guidance statement by Moher el al. (2010) recommends a pilot testing stage to determine the overall clarity and usability of the guidelines.[5] A specific piloting phase was not undertaken as part of the development process, however the clarity of items were discussed in detail in the consensus meting and several iterations of the REDEEMS were developed before the final version. For this reason, it is unlikely that the outcomes of the REDEEMS would have been different if the checklist would have

been piloted, however it is a potential limitation. Lastly, as new evidence emerges and critical feedback is obtained, the REDEEMS will need be modified and updated in the future, such as has occurred for other reporting guidelines such as the CONSORT.

7.4 Summary

The findings from this doctoral research project point to specific ways to improve the robustness of scientific research on the pathophysiological mechanisms of delirium. The project used a multiple methods approach to address three research questions that resulted in the development of the first reporting guideline specific for delirium biomarker studies.

Firstly, developing a reporting guideline is an essential step to improving reporting quality in delirium biomarker research. By elucidating the critical elements of reporting, this project also has potential to inform researcher knowledge and practice in delirium biomarker study methodology. Dissemination of the REDEEMS guideline will support improved consistency of the reporting of delirium biomarker studies and permit greater replication and potential for synthesis in the field, thereby improving scientific understanding.

Greater international, multisite and transdisciplinary collaboration, along with concept development workshops focused on methodology of conducing delirium biomarker research at international delirium society meetings, are worthy future endeavours. Better explanation of study rationales to ethical committees, as well as involvement of consumers, are called for. A collaborative effort to increase awareness of, and improve research funding for delirium is also needed. Such advancements will lead to significant improvement of the understanding of delirium pathophysiology and, it is hoped, ultimately improve outcomes for people with delirium.

7.5 References

1. Amgarth-Duff I, Hosie A, Caplan G, Agar M. A systematic review of the overlap of fluid biomarkers in delirium and advanced cancer-related syndromes. *BMC psychiatry.* 2020;20(1):1-32.
2. Oh ES, Akeju O, Avidan MS, et al. A roadmap to advance delirium research: Recommendations from the NIDUS Scientific Think Tank. *Alzheimer's & Dementia.* 2020;16(5):726-733.
3. Khachaturian AS, Hayden KM, Devlin JW, et al. International drive to illuminate delirium: A developing public health blueprint for action. *Alzheimer's & Dementia.* 2020;16(5):711-725.
4. Hosie A, Kochovska S, Ries N, et al. Older Persons' and Their Caregivers' Perspectives and Experiences of Research Participation With Impaired Decision-Making Capacity: A Scoping Review. *The Gerontologist.* 2020.
5. Moher D, Schulz KF, Simera I, Altman DG. Guidance for developers of health research reporting guidelines. *PLoS Medicine.* 2010;7(2).

Appendix 1: Publications

Appendix 1.1

Study 1

Amgarth-Duff, I., Hosie, AM., Caplan, G., Agar, M. A systematic review of the overlap of fluid biomarkers in delirium and advanced cancer-related syndromes. *BMC Psychiatry.* 2020; 20:182. doi: 10.1186/s12888-020-02584-2.

Amgarth-Duff et al. BMC Psychiatry (2020) 20:182
https://doi.org/10.1186/s12888-020-02584-2

BMC Psychiatry

RESEARCH ARTICLE Open Access

A systematic review of the overlap of fluid biomarkers in delirium and advanced cancer-related syndromes

Ingrid Amgarth-Duff[1*], Annmarie Hosie[1], Gideon Caplan[2,3] and Meera Agar[1,4,5]

Abstract

Background: Delirium is a serious and distressing neurocognitive disorder of physiological aetiology that is common in advanced cancer. Understanding of delirium pathophysiology is largely hypothetical, with some evidence for involvement of inflammatory systems, neurotransmitter alterations and glucose metabolism. To date, there has been limited empirical consideration of the distinction between delirium pathophysiology and that of the underlying disease, for example, cancer where these mechanisms are also common in advanced cancer syndromes such as pain and fatigue. This systematic review explores biomarker overlap in delirium, specific advanced cancer-related syndromes and prediction of cancer prognosis.

Methods: A systematic review (PROSPERO CRD42017068662) was conducted, using MEDLINE, PubMed, Embase, CINAHL, CENTRAL and Web of Science, to identify body fluid biomarkers in delirium, cancer prognosis and advanced cancer-related syndromes of interest. Studies were excluded if they reported delirium tremens only; did not measure delirium using a validated tool; the sample had less than 75% of participants with advanced cancer; measured tissue, genetic or animal biomarkers, or were conducted post-mortem. Articles were screened for inclusion independently by two authors, and data extraction and an in-depth quality assessment conducted by one author, and checked by two others.

Results: The 151 included studies were conducted in diverse settings in 32 countries between 1985 and 2017, involving 28130 participants with a mean age of 69.3 years. Seventy-one studies investigated delirium biomarkers, and 80 studies investigated biomarkers of an advanced cancer-related syndrome or cancer prognosis. Overall, 41 biomarkers were studied in relation to both delirium and either an advanced cancer-related syndrome or prognosis; and of these, 24 biomarkers were positively associated with either delirium or advanced cancer syndromes/prognosis in at least one study. The quality assessment showed large inconsistency in reporting.

Conclusion: There is considerable overlap in the biomarkers in delirium and advanced cancer-related syndromes. Improving the design of delirium biomarker studies and considering appropriate comparator/controls will help to better understanding the discrete pathophysiology of delirium in the context of co-existing illness.

Keywords: Delirium, Biomarker, Advanced cancer, Review

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Background

Delirium is a very common cause of acute cognitive change in people with advanced cancer [1] and is associated with increased morbidity and mortality [2, 3]. Delirium is a serious and complex neurocognitive disorder characterized by acute deterioration in attention, awareness and cognition, variously affecting memory, language and visuospatial ability, orientation and perception [4].

Delirium occurs in people who are medically unwell, due to the underlying disease which has put them at risk (e.g. dementia, cancer, infection, renal impairment) or intercurrent problems, and the subsequent medical treatment (e.g. surgery, medication) . Delirium can occur for any person, with those who are older, have advanced illness, and/or prior cognitive impairment most at risk [5]. The prevalence of delirium in patients with advanced cancer in oncology and palliative care settings is higher than that in most other settings, including geriatrics [1, 6–9]. A systematic review of palliative care patients (with 98.9% of participants with advanced cancer), reported delirium incidence rates between 3% and 45%. Delirium prevalence ranged from 13.3% to 42.3% at admission to hospital, and 25% to 62% during admission. Delirium prevalence increased up to 88% in the hours to days before death [1].

The pathophysiology of delirium is poorly understood, and largely hypothetical. Current hypotheses include: neuronal ageing, neuroinflammation, oxidative stress, neuroendocrine dysregulation, disruption to the circadian rhythm, and neurotransmitter dysregulation [10, 11]. A reduction in glucose metabolism seen in people with delirium is a model with developing evidence [12, 13]. Collectively, the biological correlates of delirium are referred to as 'delirium biomarkers'. A biomarker is a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease [14]. Biomarkers are most commonly studied to investigate their correlation with a disease in order to better understand its underlying pathophysiology, and subsequently inform prevention and treatment strategies for that disease. A challenge for the field of delirium research is that correlation may exist between biomarkers of delirium and those of the patient's disease or injury which placed them at increased risk of delirium, or which precipitated it (for example sepsis or hip fracture). Such correlation should be factored into delirium biomarker research, yet rarely has been. Better understanding of the interplay between delirium pathophysiology and that of correlated conditions and diseases, for example, cancer (the focus of this review), is crucial to develop more effective prevention and treatment of delirium.

We therefore conducted a systematic review of the literature to explore the overlap between biomarkers that have been studied in delirium and biomarkers that have been studied in cancer-related syndromes. Our aim was to identify biomarkers associated with delirium and with specific clinical situations in advanced cancer (namely prognosis; cognitive impairment, anorexia cachexia, cancer pain, cancer-related fatigue, and sickness behavior); and to evaluate the nature and extent of overlap of the findings.

Methods

A systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [15] was conducted. In July 2017, two separate searches were conducted in MEDLINE, PubMed, Embase, CINAHL, CENTRAL, and Web of Science. The first was for literature of delirium biomarkers; the second was for literature of biomarkers in advanced cancer-related syndromes. Primary terms for the delirium search were 'delirium' and 'biomarker'. Search terms for the cancer search were: 'cancer', 'neoplasms', 'metastasis', 'fatigue', 'sickness behavior', 'cancer pain', 'cachexia', and 'prognosis'. Additional terms which encompassed commonly researched biomarkers were also included. Filters in Medline were: 1: Humans; 2. English language and 3. Published from 1980 onward (when delirium was first included in the *DSM, Third Edition (DSM-III)*). Search terms and filters were tailored to each subsequent database, as required. The full search strategy is provided in Additional file 1. Reference lists of included studies and relevant systematic reviews and meta-analyses identified in the search were examined for additional eligible studies.

We included English language studies published in peer-reviewed journals that reported body fluid biomarkers in adult participants with delirium, cancer prognosis or an advanced cancer-related syndrome of interest. Studies were excluded if they reported delirium tremens only; did not measure delirium using a validated tool; the sample had less than 75% of participants with advanced cancer; measured tissue, genetic or animal biomarkers, or were conducted post-mortem. Protocols and ongoing studies were also excluded. Based on the expert knowledge of the authors in both delirium and cancer, the advanced cancer-related syndromes and prognosis were chosen based on the potential biological plausibility that the pathophysiological mechanisms could overlap with that of delirium. We limited the search to advanced cancer as this is the cancer population with the highest prevalence of both delirium and the cancer-related syndromes of interest.

The following definitions were used in this review:

Anorexia cachexia: A complex metabolic syndrome of involuntary weight loss associated with cancer and some other palliative conditions [16].

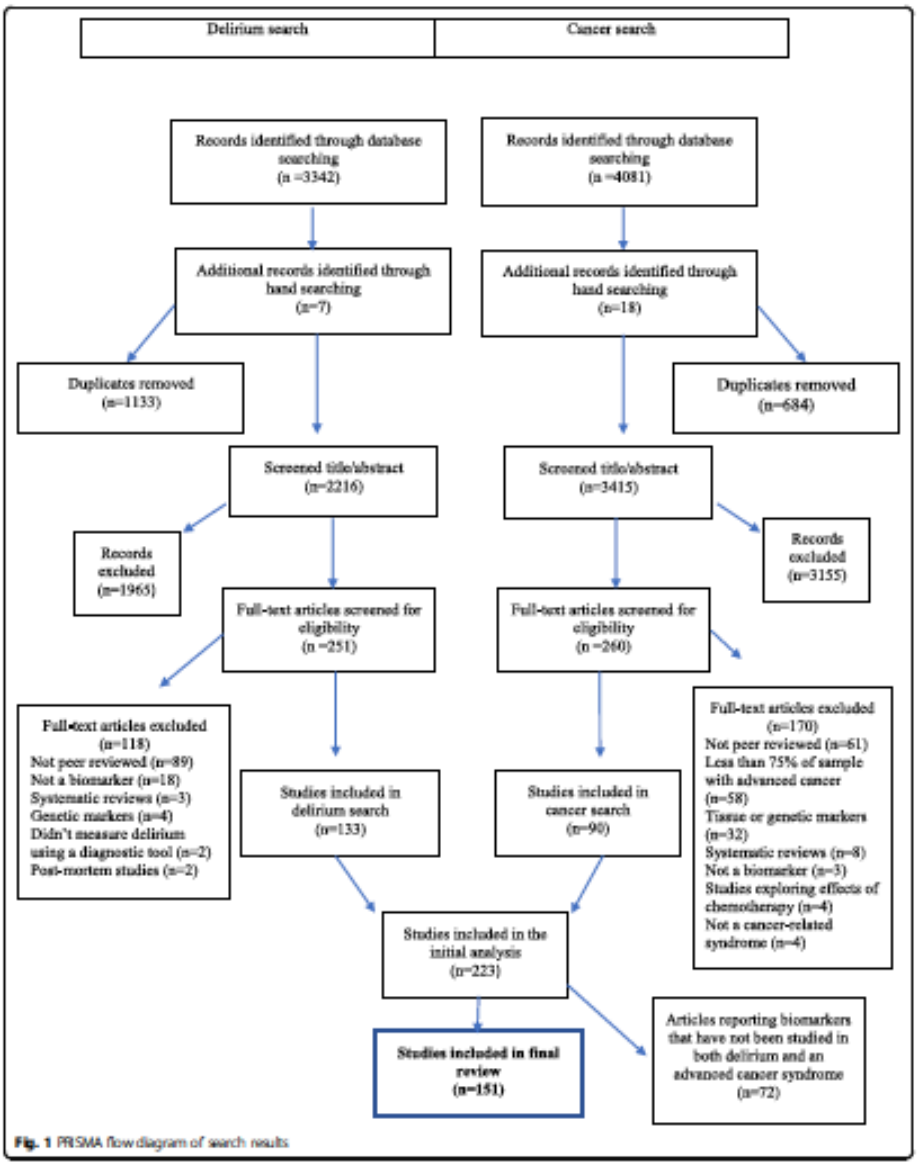

Fig. 1 PRISMA flow diagram of search results

Table 1 Characteristics of assays and main findings of included delirium studies[a]

Author and year	Participants				Endpoints	Biomarkers studied	Biological material	Assay method	Covariates accounted for in multivariate analysis	Results	
	Total (N)	Sample	Total participants with cancer/total participants in the study	Number of delirium with cancer/total number delirium (%)						Positive association with at least one delirium endpoint [**]	Negative association
Egberts et al. (2017) [24]	86	Aged ≥65 admitted to geriatrics	Not measured/NR	Not measured/NR	Delirium presence	CRP, NLR	Blood	Flow cytometry	Age, gender, the CCI score, CRP level, and WBC counts	NLR	CRP
Kozak et al. (2017) [25]	60	Patients with acute ischemic stroke	Not measured/NR	Not measured/NR	Delirium presence	TNF-α, IL-1β, IL-18, BDNF, NSE	Serum	ELISA	No multivariate analysis	None	TNF-α, IL-1β, IL-18, BDNF, NSE
Tomasi et al. (2017) [26]	38	Patients with sepsis associated delirium and non-sepsis associated delirium[a]	Not measured/NR Not measured/NR	Not measured/NR	Delirium presence	IL-1, IL-6, IL-10, BDNF, VCAM-1, ICAM-1, MPO, cathepsin, PDGF-AA, PDGF-AB/BB, RANTES, PAI, NCAM	Plasma	ELISA	No multivariate analysis	IL-1, IL-10, RANTES, VCAM-1, ICAM-1, PDGF-AB/BB	IL-6, MPO, BDNF, NCAM, PDGF-AA, PAI, Cathepsin D
Mauridhashom et al. (2017) [11]	560	Patients ≥70 undergoing major non-cardiac surgery[a]	Not measured/NR	Not measured/NR	-Delirium incidence -Delirium duration -Delirium severity	CRP	Plasma	ELISA	Age, sex, surgical procedure, anesthesia route, CCI and POST-OP infectious complications	CRP	None
Chu et al. (2016) [27]	103	Patients aged ≥70 admitted for acute or elective vertebral, knee, or hip surgery	Not measured/NR	Not measured/NR	Delirium incidence	IGF-1	Serum	ELISA	MMSE and age	None	IGF-1
Dillon et al. (2016) [28]	Entire sample (n=566); pooled sample (n=150)	Dementia-free adults ≥70 years old undergoing major scheduled non-cardiac surgery[a]	Advanced cancer excluded, other cancer stages NR	Advanced cancer excluded, other cancer stages NR	Delirium incidence	Proteomic[b]	Plasma	ELISA	No multivariate analysis	CRP (PRE-OP, PACU, POD2)	CRP (POD1MO)
Guo et al. (2016) [29]	572	Aged ≥65 with hip fractures undergoing THA[a]	Not measured/NR	Not measured/NR	-Delirium presence -Delirium prevalence	CRP, Alb, Hb	Blood	NR	NR	CRP, Alb, Hb	None
Kalabic et al. (2016) [30]	120	Patients with delirium in the psychiatric ICU	None	Cancer excluded	Lethal outcome	CRP	NR	NR	Age, pneumonia and CRP	CRP	None
Neerland et al. (2016) [31]	149	Patients with acute hip fracture[a]	Advanced cancer excluded, other cancer stages NR	Advanced cancer excluded, other cancer stages NR	Delirium presence	CRP, IL-6, sIL-6R	CSF	ELISA	No multivariate analysis	CRP[b]	sIL-6R, IL-6
Shen et al. (2016) [32]	140	Patients ≥65 undergoing elective gastrointestinal tumor resection[a]	140/140 (100)	36/36 (100)	-Delirium incidence -Delirium severity	IGF-1, CRP, IL-6	Serum	ELISA	NR	IGF-1, CRP, IL-6	None
Sun et al. (2016) [33]	112	Oral cancer patients[a]	112/112 (100)	56/56 (100)	Delirium incidence	IL-6, CRP, PCT, cortisol, Aβ1-40	Blood	ELISA	No multivariate analysis	IL-6, CRP, PCT, cortisol, Aβ1-40	None
Yen et al. (2016) [34]	98	Patients undergoing elective knee replacement surgery	Not measured/NR	Not measured/NR	Delirium incidence	IGF-1	Serum	ELISA	Obstructive sleep apnea, IGF-1 and diabetes	None	IGF-1
Avila-Funes et al. (2015) [35]	141	Patients aged ≥70 admitted to tertiary care hospital	37/141 (26.2)	6/23 (26)	Delirium incidence	Cortisol, E2	Blood	Radioimmunoassay	Age, BMI, comorbidity, MMSE, previous history of delirium, BUN/Cr ratio, and cortisol levels	E2	Cortisol
Brum et al. (2015) [36]	70	Oncology inpatients[a]	45/70 (64.3)	17/17 (100)	Delirium presence	BDNF, TNF-α	Serum	ELISA + Flow cytometry	No multivariate analysis	None	BDNF, TNF-α
Egberts et al.	86	Patients admitted	Not measured/NR	Not	Delirium	NP, IL-6, IGF-1	Plasma	HPLC	Age, gender and the CCI,	NP, IL-6, IGF-1	None

Table 1 Characteristics of assays and main findings of included delirium studies[a] *(Continued)*

Author and year	Participants: Total (N)	Participants: Sample	Participants: Total participants with cancer/total participants in the study	Participants: Number of delirium with cancer/ total number delirium (%)	Endpoints	Biomarkers studied	Biological material	Assay method	Covariates accounted for in multivariate analysis	Results: Positive association with at least one delirium endpoint [**]	Results: Negative association
(2015) [37]		to Internal Medicine and Geriatrics[a]		measured/ NR	presence				and those including NP were adjusted for age, gender, CCI, tertiles of eGFR and CRP		
Ronaughan et al. (2015) [38]	200	Elderly patients admitted to general hospital	18/200 (9)	13/44 (27)	Delirium presence	CRP, Hb	Blood	NR	NR	CRP, Hb	None
Skrede et al. (2015) [39]	10	Patients with hip fracture	Not measured/NR	Not measured/ NR	Delirium incidence	MCP-1	Serum	ELISA	No multivariate analysis	MCP-1	None
Vasunilashorn et al. (2015) [40]	566	Patients ≥70 undergoing major non-cardiac surgery[a]	Not measured/NR	Not measured/ NR	Delirium incidence	IL-1B, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IFN-γ, GM-CSF, TNF-α, VEGF	Plasma	Luminex assay	No multivariate analysis	IL-1B, IL-2, IL-4, IL-6, IL-12, VEGF, IL-5, TNF-α	GM-CSF, IFN-γ, IL-10, IL-4
Alexander et al. (2014) [41]	77	ICU patients requiring mechanical ventilation	Not measured/NR	Not measured/ NR	-Delirium presence -Delirium duration	IL-6, IL-8, IL-10, APOE	Serum	ELISA	Age, sex, APACHE III, CCI, 24-hour propofol dose, 24-hour narcotic dose, and 24-hour benzodiazepine dose.	APOE	IL-10, IL-8, IL-6
Baranyi et al. (2014) [42]	34	Patients undergoing surgery for CPB[a]	Not measured/NR	Not measured/ NR	Delirium incidence	sIL-2R	Serum	ELISA	No multivariate analysis	sIL-2R	None
Cape et al. (2014) [43]	43	Patients >60 years old with hip fracture	Not measured/NR	Not measured/ NR	-Delirium incidence -Delirium prevalence	IL-1β, IFNγ, GFAP, IGF-1, IL-1RA	CSF	ELISA	Presence of prior dementia	IL-1β, IL-1RA[c]	GFAP, IFN-γ, IGF-1
Capri et al. (2014) [44]	351	Patients admitted for any kind of emergency or elective surgery[a]	Comorbidity measured, cancer NR	Comorbidity measured, cancer NR	Delirium presence	IL-1β, IL-2, IL-6, IL-8, IL-10, TNF-α	Plasma	ELISA	Age, comorbidity, ADL, IADL, HADS and pre-op benzodiazepines intake	IL-6, IL-2	IL-8, IL-10, IL-1β (IJDL), TNF-α (IJDL)
Chen et al. (2014) [45]	372	Patients aged ≥65 who underwent surgery for a femoral neck fracture or an intertrochanteric fracture[a]	Not measured/NR	Not measured/ NR	Delirium presence	LP	Plasma	ELISA	Age, ASA, type of surgery and plasma leptin level	LP	None
Hatta et al. (2014) [46]	29	Patients aged 65-89 admitted to hospital due to an emergency	Not measured/NR	Not measured/ NR	Delirium incidence	NK cell activity, IL-1β	Blood	ELISA	No multivariate analysis	NK cell activity	IL-1β
Kazmierski et al. (2014) [47]	113	ICU patients scheduled for CABG surgery with CPB[a]	Not measured/NR	Not measured/ NR	Delirium incidence	Cortisol, IL-2, TNF-α, HCY, cobalamin	Serum	CLIA	NR	Cortisol, IL-2, TNF-α, HCY	Cobalamin
Ritchie et al. (2014) [48]	710	Patients admitted to a Medical Acute Admission Unit	Not measured/NR	Not measured/ NR	-Delirium incidence -Delirium severity	CRP	NR	NR	NR	CRP	None
Ritter et al. (2014) [49]	78	ICU patients	Not measured/NR	Not measured/ NR	Delirium presence	TNF-α, STNFR-1, STNFR2, APN, IL-1β, IL-6, IL-10	Plasma	ELISA	Sedation and sepsis	STNFR-1, STNFR2, IL-1β	TNF-α, IL-6, IL-10
Zhang et al. (2014) [50]	223	ICU patients	Not measured/NR	Not measured/ NR	Delirium presence	CRP	Plasma	I-CHROMA™	Age, sex, APACHE II, intubation status, living alone, physical restraint, alcohol drinking, smoking, type of medical condition, and hospital LOS before ICU admission	CRP	None

Table 1 Characteristics of assays and main findings of included delirium studies[a] *(Continued)*

Author and year	Participants: Total (N)	Participants: Sample	Participants: Total participants with cancer/total participants in the study	Participants: Number of delirium with cancer/ total number delirium (%)	Endpoints	Biomarkers studied	Biological material	Assay method	Covariates accounted for in multivariate analysis	Results: Positive association with at least one delirium endpoint [**]	Results: Negative association
Cerejeira et al. (2013) [51]	101	Patients ≥60 years without dementia undergoing elective hip arthroplasty[a]	Not measured/NR	Not measured/ NR	Delirium incidence	Cortisol, IGF-1, CRP, IL-4, IL-6, IL-10	Plasma	ELISA	No multivariate analysis	Cortisol	CRP, IL-6, IL-4, IL-10, IGF-1
Colkesen et al. (2013) [52]	52	Patients with ACS admitted to coronary ICU[a]	Not measured/NR	Not measured/ NR	Delirium presence	Cortisol, troponin I, MB-CK	Serum	CLIA	NR	Cortisol	Troponin I, MB-CK
Kazmierski et al. (2013) a [53]	113	ICU patients scheduled for CABG surgery with CPB	Not measured/NR	Not measured/ NR	Delirium incidence	Cortisol, IL-2	Plasma	CLIA	NR	Cortisol[a], IL-2	None
Kazmierski et al. (2014) b [54]	113	ICU patients scheduled for CABG surgery with CPB	Not measured/NR	Not measured/ NR	Delirium incidence	IL-2, TNF-α	Plasma	CLIA	NR	IL-2, TNF-α	None
Liu et al. (2013) [55]	338	Patients aged ≥65 undergoing major non-cardiac surgery[a]	Not measured/NR	Not measured/ NR	Delirium incidence	IL-6	Blood	ELISA	Age, education, history of coronary artery disease, alcoholism, PRE-OP ASA ≥ 3, PRE-OP NYHA ≥ 3, PRE-OP MMSE score ≤ 24, PRE-OP serum IL-6 ≥ 7.5 pg/mL, POST-OP serum IL-6, POST-OP VAS pain level	IL-6	None
Plaschke et al. (2010) [56]	114	1. Patients following heart surgery[a] 2. Patients on the non-cardiac ICU[a]	Not measured/NR	Not measured/ NR	Delirium incidence	IL-6	Plasma	ELISA	No multivariate analysis	None	IL-6
Skrobik et al. (2013) [57]	99	ICU patients[a]	Not measured/NR	Not measured/ NR	Drug-induced coma and delirium	TNF-α, IL-1β, IL-1RA, IL-4, IL-6, IL-8, IL-10, IL-17, MIP-1B, MCP-1	Blood	BCA	Fentanyl, midazolam, CYP3A4/5, P-gp inhibitors	IL-6	TNF-α, IL-17, IL-8, MCP-1, IL-1RA, MIP-1B, IL-10, IL-1β
Westhoff et al. (2013) [58]	61	Patients ≥75 admitted for surgical repair of acute hip fracture[a]	Not measured/NR	Not measured/ NR	Delirium incidence	EGF, eotaxin, FGF-2, Flt-3L, Fractalkine, G-CSF, GM-CSF, IFN-α2, IFN-γ, IL-1RA, IL-1α, IL-1β, IL-2, sIL-2Ra, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12p40, IL-12p70, IL-13, IL-15, IL-17, IP-10, MCP-1, MCP-3, MDC, MIP-1α, MIP-1β, PDGF-AA, PDGF-AB/BB, RANTES, sCD40L, TGF-α, TNF-α, TNF-β, VEGF	Blood + CSF	Lumbar punctures and Luminex assays	No multivariate analysis	Flt-3L, IL-1RA, IL-6	EGF, eotaxin, FGF-2, fractalkine, G-CSF, GM-CSF, IFN-α2, IFN-γ, IL-1α, IL-1β, IL-2, sIL-2Ra, IL-3, IL-4, IL-5, IL-7, IL-8, IL-9, IL-10, IL-12p40, IL-12p70, IL-13, IL-15, IL-17, IP-10, MCP-1, MCP-3, MDC, MIP-1α, MIP-1β, PDGF-AA, PDGF-AB/BB, RANTES, sCD40L, TGF-α, TNF-α, TNF-β, VEGF
Bakker et al. (2012) [59]	201	Patients undergoing cardiac surgery	Not measured/NR	Not measured/ NR	Delirium incidence	Cre	Plasma	NR	NR	Cre	None
Baranyi et al. (2012) [60]	34	Patients undergoing surgery for cardiopulmonary bypass[a]	Not measured/NR	Not measured/ NR	Delirium incidence	Alb, CRP	Serum	NR	No multivariate analysis	Alb	CRP
Cerejeira et al. (2012) [61]	101	Patients aged ≥60 undergoing elective total hip arthroplasty[a]	Not measured/NR	Not measured/ NR	Delirium incidence	IL-6, IL-1β, IL-4, IL-10, TNF-α, CRP, AChE, BuChE	Blood	ELISA (Multiplex assay)	No multivariate analysis	AChE, BuChE	CRP, IL-1β, TNF-α, IL-4, IL-10
Girard et al. (2012) [62]	138	Mechanically ventilated ICU patients[a]	Not measured/NR	Not measured/ NR	Delirium incidence	CRP, MMP-9, MPO, NGAL, sTNFR1, D-dimer, protein C, PAI-1, VWF	Plasma	ELISA	Age, severity of illness, and severe sepsis	MMP-9, Protein C, sTNF-R1	CRP, MPO, NGAL, D-dimer, PAI-1, VWF
Osse et al. (2012) [63]	125	Patients ≥70 undergoing elective cardiac	Not measured/NR	Not measured/ NR	Delirium incidence	NP, BH4, HVA, Glu, Ser, Gly, Cit, Tau, Arg, Met, Trp, Tyr, Phe, Leu, Ile, Val, Trp/LNAA, Tyr/LNAA, Phe	Plasma	HPLC	BH4, total biopterin, HVA, ratios of Trp/LNAA, tyr: LNAA, phe: LNAA, phe: Tyr, Cit/Arg,	NP, HVA	BH4, Glu, Ser, Gly, Cit, Tau, Arg, Met, Trp, Tyr, Phe, Leu, Ile, Val, Trp/LNAA, Tyr/LNAA, Phe/LNAA,

Table 1 Characteristics of assays and main findings of included delirium studies[a] *(Continued)*

Author and year	Participants: Total (N)	Participants: Sample	Participants: Total participants with cancer/total participants in the study	Participants: Number of delirium with cancer/ total number delirium (%)	Endpoints	Biomarkers studied	Biological material	Assay method	Covariates accounted for in multivariate analysis	Results: Positive association with at least one delirium endpoint [**]	Results: Negative association
		surgery				LNAA, Phetyr, Grang Tau Ser 9 met			TSH ratio, baseline CRP, plasma urea, cre, age, sex, type of surgery, acute cardiac surgical risk factors, EuroSCORE, MMSE, pre-op anxiety and depression, and chronic medical comorbidity		Phetyr, Grang Tau Ser 9 met
Bisschop et al. (2011) [64]	143	Patients undergoing surgery for hip fracture	Not measured/NR	Not measured/ NR	-Delirium presence -Delirium severity	Cortisol, insulin, glucose	Blood	NR	Sex, age, pre-existing cognitive impairment, pre-existing functional impairment, cortisol, glucose, insulin, insulin glucose	Cortisol	Glucose, insulin
Holmes et al. (2011) [65]	222	Patients with mild to severe AD	Not measured/NR	Not measured/ NR	-Presence of sickness behaviour -Delirium incidence	IL-6, TNF-α, CRP	Blood	ELISA	Baseline ADAS score, age, gender, and the presence of delirium	None	IL6, TNF-α, CRP
Lee et al. (2011) [66]	65	Patients ≥65 who had undergone hip surgery[a]	Not measured/NR	Not measured/ NR	Delirium incidence	CRP	Blood	NR	No multivariate analysis	None	CRP
McGrane et al. (2011) [67]	87	Mechanically ventilated, medical and surgical ICU patients[a]	Not measured/NR	Not measured/ NR	Delirium/ coma-free days	PCT, CRP	Blood	TRACE Assay analysis	Age, APACHE II, sedation group (dexmedetomidine vs. lorazepam), and sepsis	PCT	CRP
Morandi et al. (2011) [68]	110[f]	Mechanically ventilated medical ICU patients	Not measured/NR	NR	Delirium presence	IGF-1	Blood	Radioimmunoassay	Age, severe sepsis and APACHE II		IGF-1
Van der Boogaard et al. (2011) a [69]	100	ICU patients[a]	Not measured/NR	Not measured/ NR	Delirium presence	TNF-α, IL-1β, IL-6, IL-8, IL-17, IL-18, MIF, IL-1RA, IL-10, MCP-1, HMP-1, CRP, PCT, Aβ1-40, Aβ1-42, S100B, cortisol	Plasma	Luminex assay, immunologic detection, and an immunometric assay	NR	**Delirium vs non-delirium:** IL-6[?], IL-18[?], Ratio Aβ[illegible], TNF-α, IL-6, MIF, IL-1RA, MCP-1, PCT, cortisol, Aβ1-42 **Inflamed delirium vs non-inflamed delirium:** IL-6, TNF-α, IL-1β, IL-1RA, MCP-1, PCT, CRP, ratio Aβ[illegible], ratio Aβ[illegible]	**Delirium vs non-delirium:** IL-1β, IL-17, IL-18, HMP, CRP, S100B, Tau, Ratio Tau/Aβ[illegible], Aβ[illegible], Aβ[illegible], Aβ[illegible], Aβ[illegible], Ratio Aβ[illegible], Ratio Aβ[illegible], Ratio Aβ[illegible] **Inflamed delirium vs non-inflamed delirium:** IL-1β, IL-4, MIF, IL-8, cortisol, Aβ1-42, IL-18, IL-17, HMP, S100B, Tau, tau/Aβ1-42, Ratio Tau/Aβ[illegible], Aβ[illegible], Ratio Aβ[illegible]/Aβ[illegible], Ratio Aβ[illegible], Aβ[illegible], Aβ[illegible]
Van der Boogaard et al. (2011) b [70]	20	ICU patients	Not measured/NR	Not measured/ NR	Delirium presence	Proteomic[g]	Urine + Blood	NR	No multivariate analysis		CRP, Cre
Burkhart et al. (2010) [71]	113	Patients aged ≥65 undergoing elective cardiac surgery with CPB	Not measured/NR	Not measured/ NR	Delirium presence	CRP	NR	NR	EuroSCORE, Leucocytes, CRP max, Fentanyl intraoperatively, duration of mechanical ventilation, pooled RBC, and treated PONV	CRP	None
Mu et al. (2010) [72]	243	Patients undergoing elective CABG surgery	Not measured/NR	Not measured/ NR	Delirium incidence	Cortisol	Serum	CLIA	Age, history of diabetes mellitus, PRE-OP LVEF, PRE-OP NYHA, pre-op EuroSCORE score, duration of surgery, POST-OP APACHE II, serum cortisol, POST-OP LVEF, POST-OP complications (within 1 day)	Cortisol	None

Table 1 Characteristics of assays and main findings of included delirium studies[a] *(Continued)*

Author and year	Participants: Total (N)	Participants: Sample	Participants: Total participants with cancer/total participants in the study	Participants: Number of delirium with cancer/total number delirium (%)	Endpoints	Biomarkers studied	Biological material	Assay method	Covariates accounted for in multivariate analysis	Results: Positive association with at least one delirium endpoint [bb]	Results: Negative association
Pearson et al. (2010) [73]	20	Patients ≥60 with acute hip fracture awaiting surgery[e]	Not measured/NR	Not measured/NR	Delirium presence	Cortisol	CSF + serum	ELISA	No multivariate analysis	Cortisol	None
Plaschke et al. (2010) [74]	114	Patients undergoing elective CABG[e]	Not measured/NR	Not measured/NR	Delirium incidence	Cortisol, IL-6	Plasma	ELISA	No multivariate analysis	IL-6, cortisol	None
Tsuruta et al. (2010) [75]	103	ICU patients[e]	Not measured/NR	Not measured/NR	•Delirium incidence •Delirium prevalence	CRP	Serum	Immunoturbidimetry	Age, APACHE II, coexistence of infection, use of a mechanical ventilator and length of ICU stay	CRP	None
Van Munster et al. (2010) [76]	120	Patients ≥65 admitted for hip fracture surgery	Not measured/NR	Not measured/NR	Delirium presence	Cortisol, IL-6, IL-8, S100B	Plasma	CLIA	Age, infection, pre-existent cognitive and functional impairment	Cortisol, IL-6, IL-8, S100B	None
Adamis et al. (2009) [77]	67	Patients aged ≥70 admitted to elderly care unit	Not measured/NR	Not measured/NR	•Delirium incidence •Delirium severity	APOE, IL-1α, IL-1β, IL-1RA, IL-6, TNF-α, IGF-1, IFN-γ, LIF	Serum	ELISA	No Multivariate analysis	IGF-1, IFN-γ, IL-1RA,	APOE, IL-1α, IL-1β, IL-6, TNF-α, LIF
Van Munster et al. (2009) [78]	120	Patients ≥65 admitted for hip fracture surgery	Not measured/NR	Not measured/NR	Delirium incidence	S100B, NSE	Blood	ECLIA	No multivariate analysis	S100B	NSE
Lemstra et al. (2008) [79]	68	Patients undergoing surgery for hip fracture	Not measured/NR	Not measured/NR	Delirium incidence	CRP, IL-6, IGF-1	Blood	ELISA	No multivariate analysis	None	CRP, IL-6, IGF-1
Pfister et al. (2008) [80]	16[f]	Patients with sepsis	Not measured/NR	Not measured/NR	Sepsis-related delirium presence	CRP, IL-6, S100B, cortisol	Serum	Solid-phase enzyme-labelled chemiluminescent sequential immunometric assay	No multivariate analysis	CRP, S100B, Cortisol	IL-6
Rudolph et al. (2008) [81]	42	Patients undergoing cardiac surgery	Not measured/NR	Not measured/NR	Delirium incidence	IL-1β, IL-1RA, IL-6, IFN-α, TNF-α, TNF-R1, TNF-R2, IL-2, IL-2R, IL-7, IL-12 p40, p70, IL-15, IFN-γ, IP-10, IL-4, IL-5, IL-10, IL-13, MIP-1α, MIP-1b, MIG, Eotaxin, RANTES, CCL-2, IL-8, GM-CSF, IL-17, DR5	Serum	ELISA	No multivariate analysis	MIP-1α, MIP-1b, MIG, Eotaxin, RANTES, CCL-2	IL-1β, IL-1RA, IL-6, IFN-α, TNF-α, TNF-R1, TNF-R2, IL-2, IL-2R, IL-7, IL-12p40, p70, IL-15, IFN-γ, IP-10, IL-4, IL-5, IL-10, IL-13, IL-8, GM-CSF, IL-17, DR5
Van Munster et al. (2008) [82]	98	Patients ≥65 admitted for hip fracture surgery	Not measured/NR	Not measured/NR	Delirium presence	IL-6, IL-8, IL-12 (TNF-α, IL-1β, and IL-10 excluded from analysis)	Plasma	CLIA	No multivariate analysis	IL-6, IL-8	IL-12
Adamis et al. (2007) [83]	164	Acutely ill patients admitted to elderly care unit	Not measured/NR	Not measured/NR	•Delirium presence •Delirium resolution	APOE, IL-1α, IL-1β, IL-1RA, IL-6, TNF-α, IGF-1, IFN-γ, LIF, CRP	Serum	ELISA	LogAPACHE II, DRS, CRP, Gender, TNF-α, IFN-γ, IGF-1, IL-1RA, and possession of APOE epsilon 4 allele	IGF-1, APOE, IFN-γ	IL-6, IL-1α, IL-1β, IL-1RA, TNF-α, LIF, CRP
de Rooij et al. (2007)[e] [84]	185	Patients aged ≥65 admitted to the Department of Medicine	18/185 (9.7)	5/64 (34)	Delirium presence	IL-1β, IL-6, IL-8, IL-10, TNF-α, CRP	Serum	CLIA	Age, cognitive impairment, and infection	IL-6, IL-8	IL-1β, IL-10, TNF-α, CRP
Plaschke et al. (2007) [85]	37	ICU patients	Not measured/NR	Not measured/NR	Delirium presence	SAA, IL-6	Blood	ELISA	No multivariate analysis for IL-6	None	SAA, IL-6
White et al. (2005) [86]	283	Patients ≥75 from emergency medical admissions	Not measured/NR	Not measured/NR	•Delirium prevalence •Delirium incidence	CRP, Alb, AChE, BuChE, Aspirin esterase, Benzoylcholinesterase	Plasma	ELISA	No multivariate analysis	CRP, Alb, AChE, BuChE, Aspirin esterase, Benzoylcholinesterase	None
Wilson et al. (2005) [87]	100	Patients ≥75 suffering from significant	Not measured/NR	Not measured/NR	Delirium incidence	IGF-1	Plasma	CLIA	Depression, IGF-1 levels and IQCODE scores	IGF-1	None

Table 1 Characteristics of assays and main findings of included delirium studies[a] *(Continued)*

Author and year	Participants: Total (N)	Participants: Sample	Participants: Total participants with cancer/total participants in the study	Participants: Number of delirium with cancer/ total number delirium (%)	Endpoints	Biomarkers studied	Biological material	Assay method	Covariates accounted for in multivariate analysis	Results: Positive association with at least one delirium endpoint **	Results: Negative association
		physical illness									
Beloosesky et al. (2004) [illegible]	32	Patients undergoing surgery for hip fracture	Not measured/NR	Not measured/ NR	-Cognition -Post-operative complications (including delirium) -Post-operative function -Mortality	CRP, FBG	Blood	Nephelometric assay	Unclear	CRP	FBG
Robertsson et al. (2001) [illegible]	172	Patients <80 referred to the neuropsychiatric diagnostic unit with suspected dementia	Not measured/NR	Not measured/ NR	Delirium presence	Cortisol	Serum	NR	Age, severity of dementia and severity of delirium	Cortisol	None
Van der Mast et al. (2000) [illegible]	296[l]	Patients admitted for elective cardiac surgery	Not measured/NR	Not measured/ NR	Delirium incidence	Trp, Ile, Val, Met, Leu, Tyr, Phe, Ser, cortisol	Plasma	HPLC	Plasma amino acids; the ratios of Trp/ΣLNAA, Tyr/ΣLNAA, and Phe/ΣLNAA; albumin; cortisol; and thyroid functions	Trp, Trp/LNAA	Cortisol, Ile, Val, Met, Leu, Tyr, Phe, Ser
Van der Mast et al. (1999) [illegible]	296	Patients admitted for elective cardiac surgery	Not measured/NR	Not measured/ NR	Delirium incidence	Alb, cortisol, 5-HT, trp, phe, val, leu, Ile, tyrosine	Plasma	HPLC	Age, inclusion as an in-patient, use of nifedipine, MMSE score, GHQ score, DAL score, Albumin, ratio rT3/T3, ratio Phe:ΣLNAA	Alb, phe:ile, Phe:leu, Phe:val, Phe:tyr, Phe: trp	Cortisol, 5-HT
Gustafson et al. (1993) [illegible]	155	Stroke patients	Not measured/NR	Not measured/ NR	Delirium presence	Cortisol	Plasma	Radioimmunoassay	Intercept, basal plasma cortisol, paresis, age, left-sided brain lesion, sex, anti-cholinergic medication, post-dexamethasone plasma cortisol	Cortisol	None
McIntosh et al. (1985) [illegible]	7	Male patients admitted to hospital for elective surgery	Not measured/NR	Not measured/ NR	Delirium incidence	Cortisol, B-endorphin	Plasma	Radioimmunoassay	No multivariate analysis	Cortisol, B-endorphin	None

[a] Studies with both delirium and cancer participants are bolded; red coloured biomarkers indicate significance in multivariate analysis
[b] Dementia was an exclusion criteria
[c] Only CRP is reported from this study
[d] Only between incident and prevalent delirium
[e] Pre-operative and post-operative cortisol remained significantly increased in delirium, however, after controlling for pre-operative depression, only preoperative cortisol concentration remained significant, irrespective of the cortisol level after surgery.
[f] Only 66 included in the primary analysis
[g] In inflamed patients only
[h] In non-inflamed patients only
[i] Only CRP and Cre are reported
[j] Same cohort as Plaschke et al. 2007
[k] Only 18 were analysed
[l] same cohort as Van Der Mast et al. 1999

Abbreviations: [illegible], 5HT Serotonin, 6-SMT 6-sulfatoxymelatonin, 8-iso-PGF2α 8-iso-prostaglandin F2α, A1M Alpha-1 antitrypsin, α-1-AGP α-1-acid glycoprotein, AA Anticholinergic activity, AB Amyloid-β, ACHE Acetylcholinesterase, ACS Acute Coronary Syndrome, ADAS Alzheimer's Disease Assessment Scale, ADL Activities of daily living, Ala Alanine, Alb Albumin, AD Alzheimer's Disease, APACHE Acute Physiology and Chronic Health Evaluation, APN Adiponectin, ANG Angiopoietin, APOA1 Apolipoprotein A1, APOE Apolipoprotein E, Arg Arginine, APS Acute Physiology Score, ASA American Society of Anaesthesiologists Scale, BCA The bicinchoninic acid assay, BDNF Brain-Derived Neurotrophic Factor, BH4 Tetrahydrobiopterin, BLI B-Endorphin-Like Immunoreactivity, BuChE Butyrylcholinesterase, C3 Complement C3, CABG Coronary Artery Bypass Graft, CBA Cytometric bead array immunoassay, CCI Charlson Comorbidity Index, Cit Citrulline, CK Creatine Kinase, CK-MB Creatine Kinase-MB, CLIA Chemiluminescence Immunoassay, CNTN-1 Contactin-1, CPB Cardiopulmonary Bypass, Cre Creatinine, CRP C-Reactive Protein, [illegible], FBG Fibrinogen, FBLN1 Fibulin-1, ECLIA Electrochemiluminescence Immunoassay, EGF Epidermal Growth Factor, FGF-2 Fibroblast Growth Factor, [illegible], GABA Gamma-aminobutyric Acid, G-CSF Granulocyte-Colony Stimulating Factor, GFAP Glial Fibrillary Acidic Protein, GHQ General Health Questionnaire, Glu Glutamic acid, Gly Glycine, GM-CSF Granulocyte-Macrophage Colony-Stimulating Factor, HADS Hospital Anxiety and Depression Scale, Hb Haemoglobin, HCY Homocysteine, HNP-1 Defensin, HP Haptoglobin, HPLC High-performance liquid chromatography, HVA Homovanillic Acid, IADL Instrumental activities of daily living, ICU Intensive care unit, Ile Isoleucine, ICAM-1 Intercellular Adhesion Molecule 1, IDO Indoleamine 2, 3-dioxygenase, IFN Interferon, IGF Insulin-Like Growth Factor, IL Interleukin, IL-1RA Interleukin-1 Receptor Antagonist, [illegible], IP-10 Interferon gamma-induced protein 10, IQCODE The Informant Questionnaire on Cognitive Decline in the Elderly, KYN Kynurenine, Leu Leucine, LIF Leukaemia Inhibitory Factor, LNAA Large Neutral Amino Acids, LOS Length of stay, LPT Leptin, Met Methionine, MB-CK MB-isoform of Creatinine Kinase, MCP Monocyte Chemotactic Protein, MDC Human Macrophage-derived Chemokine, MIF Macrophage Migration Inhibitory Factor, MIG Monokine Induced by Gamma Interferon, MIP Macrophage Inflammatory Protein, MMP-9 Matrix Metalloproteinase-9, MMSE Mini-mental state examination, MPO Myeloperoxidase, MT Melatonin, NCAM Neural Cell Adhesion Molecule, NGAL Neutrophil Gelatinase-Associated Lipocalin, NLR Neutrophil-Lymphocyte ratio, NK cells Natural killer cells, NP Neopterin, NR Not reported, NSE Neuron Specific Enolase, Orn Ornithine, NYHA New York Heart Association, PACU Post-anaesthesia care unit, PAI-1 Plasminogen activator inhibitor-1, PCT Procalcitonin, PDGF Platelet-Derived Growth Factor, Phe Phenylalanine, [illegible] Plasma free 3-methoxy-4-hydroxyphenylglycol, pNF-H The Phosphorylated Neurofilament H, POD1MO 1 month post-operative, POD2 Post-operative day 2, PONV Post-operative nausea and vomiting, POST-OP Post-operative, PRE-OP Pre-operative, [illegible], RANTES Chemokine (C-C motif) ligand 5, RBC Red blood cell, S100B S100 calcium-binding protein B, sCD40L Soluble CD40 ligand, Ser Serine, sIL-2R Soluble IL-2 receptor, SLI Somatostatin-Like Immunoreactivity, sTNFR Soluble Tumor Necrosis Factor Receptor, Tau Taurine, T-tau Total tau, TGF-α Transforming Growth Factor Alpha, THA Total Hip Arthroplasty, TRACE Time Resolved Amplified Cryptate Emission, TSH Thyroid Stimulating Hormone, TNF Tumor Necrosis Factor, Trp Tryptophan, TXB Thromboxane, Tyr Tyrosine, UDL Under detection limit, Val Valine, VCAM-1 Vascular Cell Adhesion protein 1, VEGF Vascular Endothelial Growth Factor, vWF Von Willebrand Factor, ZAG Zinc-α-2-glycoprotein

Table 2 Characteristics of assays and main findings of included cancer studies[a]

Author and year	Participants		Endpoints	Biomarkers studied	Biological material	Assay method	Covariates adjusted for in multivariate analysis	Results		
	Total participants (N)	Cases; control						Positive association with at least one endpoint[b]		Negative association
Amano et al. (2017)[a] [94]	1702	Advanced cancer patients; no control	-Anorexia -Weight loss -Fatigue -Dyspnea -Dysphasia -Edema -Pressure ulcer -ADL disabilities	CRP	NR	NR	Age, gender, primary tumor site, distant metastasis, chemotherapy, ECOG PS, and setting of care	CRP		None
Demirkay et al. (2017) [92]	87	Participants with advanced cancer; healthy participants without a known chronic disease	-Cachexia -Weight loss -PPS -OS	LP, resistin	Serum	ELISA	NR	Multivariate results NR	LP	Resistin* Multivariate results NR
Fogelman et al. (2017) [96]	69	Participants with advanced cancer; healthy controls with no cancer diagnosis	Either 10% weight loss or death at 60 days from the start of therapy	APN, bFGF, CXCL-16, PSN, Ghrelin, IGF-1, IL-1β, IL-6, IL-8, Nidhs, LP, MCP-4, MK, MSTN, PIF, sTNFR1, sTNFR2, TARC, TNF-α, VEGF, ZAG	NR	NR	Smoking status, best response, pain, difficulty swallowing	MK, IL-1β, CXCL-16, IL-6, IL-8, TNF-α Multivariate results NR		APN, bFGF, PSN, Ghrelin, IGF-1, Nidhs, LP, MCP-4, MSTN, MK, PIF, sTNFR1, sTNFR2, TARC, VEGF, ZAG Multivariate results NR
Luo et al. (2017) [97]	217	Participants with advanced cancer; no control	-PPS -OS	PBG, CA-125, NLR, PLR	Serum + Plasma	NR	NR		PBG	CA-125, NLR, PLR
Reuben et al. (2017) [98]	49	Participants with cancer; no control	-Pain -Appetite -Fatigue	CRP, ESR, sTNF-RI, IL-1RA, IL-6, MCP-1, IL-1β, MIF, TGF-β1	Serum	ELISA (multiplex assay)	Sex, BMI and age	sTNF-r1, MCP-1, MIF, CRP, IL-6, IL-1RA		IL-1β, TGF-β1, ESR
Amano et al. (2016) [99]	1511	Advanced cancer patients; no control	-Survival rate -Mortality rate	CRP	Plasma	Latex-enhanced immunoturbidimetric assay	Age, gender, primary tumor site, distant metastasis, chemotherapy, ECOG PS, and setting of care	CRP		None
Bye et al. (2016)	60	Participants	-Cachexia	IL-1β, IFN-γ, LP, APN,	Serum	ELISA	No multivariate	IL-6		IL-1β, IFN-γ,

Table 2 Characteristics of assays and main findings of included cancer studies* *(Continued)*

Author and year	Participants		Endpoints	Biomarkers studied	Biological material	Assay method	Covariates adjusted for in multivariate analysis	Results	
	Total participants (N)	Cases; control						Positive association with at least one endpoint**	Negative association
[100]		with advanced cancer; healthy controls with normal weight	-Survival	TNF-α, IL-6, IGF-1			analysis		TNF-α, APN, IGF-1
Mitsunga *et al.* (2016) [101]	421	Participants with advanced cancer with low, intermediate and high CRP levels	OS	CRP, NLR	Blood	ELISA (Multiplex assay)	**Retrospective cohort:** Sex, age, ECOG-PS, UICC stage, CA 19-9, prognostic CRP classification; **Prospective cohort:** Sex, age, ECOG-PS, UICC stage, CA 19-9, NLR classification, mGPS, prognostic CRP classification	CRP, NLR	None
Morgado *et al.* (2016) [102]	49	Participants with advanced cancer and fatigue with and without weight loss	-Weight loss -Fatigue	Hb, LDH, Alb, CRP, Cre	Serum + Urine	NR	No multivariate analysis	Alb, CRP	Hb, LDH, Cre
Rodrigues *et al.* (2016) [103]	51	Participants with advanced cancer; no control	Fatigue	IL-1, IL-6, TNF-α, α-1-AGP, GPS (Alb+CRP)	Blood	NR	No multivariate analysis	TNF-α, GPS (Alb+CRP)	None
Srdic *et al.* (2016) [104]	100	Participants with advanced cancer with and without cachexia	-Cachexia -Chemotherapy toxicity -Survival	CRP, IL-6, Alb, Hb	NR	The Bromocresol Purple method	NR	CRP, IL-6, Alb, Hb	None
Wu *et al.* (2016) [105]	55	Participants with advanced cancer; no control	-OS -PFS	NLR, PLR, ALP, LDH	Blood	NR	NR	PLR, NLR, LDH	ALP
Bilir *et al.* (2015)	80	Participants	-OS	Il-1β, IL-1α, IL-6, TNF-α,	Serum	ELISA	NR	CRP, TRAF-6, Alb, LDH, IL-1a, IL-6,	IL-1β,

Table 2 Characteristics of assays and main findings of included cancer studies[a] (Continued)

Author and year	Participants		Endpoints	Biomarkers studied	Biological material	Assay method	Covariates adjusted for in multivariate analysis	Results	
	Total participants (N)	Cases; control						Positive association with at least one endpoint[b,c]	Negative association
[106]		with advanced cancer and cachexia; healthy controls with no known chronic disease or weight loss	-Cachexia	orexin-A, galanin, TWEAK, TNF-6, NPY, CRP, Testosterone, AE, LDH				TNF-α, TWEAK, orexin-A, NPY, testosterone	galanin
Moura et al. (2015) [107]	79	Participants with advanced cancer; no control	-Body composition -Fatigue	IL-6	Serum	ELISA (multiplex assay)	NR	IL-6	None
Moura et al. (2015) b [108]	1160	Participants with advanced cancer; no control	Survival	mGPS (Alb+CRP)	NR	NR	Primary tumor site, age and gender	mGPS (Alb+CRP)	None
Barrera et al. (2014) [109]	135	Participants with advanced cancer; healthy controls	-Quality of life (fatigue, PS, hyporexia, BMI) -Survival	IL-31, IL-33, IL-27, IL-29, IL-1β, IL-2, IL-6, IL-8, IL-1 2p70, IL-17A, IFN-γ, TNF- α, IL-4, IL-10	Plasma	CBA	No multivariate analysis	IL-6, IL-8, IFN-γ, IL-33, IL-10, IL-29[b], IL-1 2p70[b], IL17A[b]	IL-31, IL-27, IL-1β, IL-2, TNF-α, IL-4
Blakely et al. (2014) [110]	90	Participants with advanced cancer with normal CRP and elevated CRP	-OS -Morbidity rate -gastrointestinal obstruction -Pain -Bleeding -Other symptoms (NR) -Major complications	CRP	Serum	NR	NR	CRP	None
Fujiwara et al. (2014) [111]	21	Participants with advanced cancer with and without cachexia	Cachexia	LP, IL-6, TNF-α	Serum	ELISA	No multivariate analysis		LP, IL-6, TNF-α
Lindelmann et al. (2014)	218	Participants with	-Survival -Weight loss	CRP, Alb	Plasma	Immunoturbidimetry	No multivariate analysis	CRP, Alb	None

Table 2 Characteristics of assays and main findings of included cancer studies* (Continued)

Author and year	Participants		Endpoints	Biomarkers studied	Biological material	Assay method	Covariates adjusted for in multivariate analysis	Results	
	Total participants (N)	Cases; control						Positive association with at least one endpoint**	Negative association
[112]		advanced cancer; no control							
Mondello *et al.* (2014) [113]	170	Participants with advanced cancer; healthy controls	-Survival -Cachexia	LP, ghrelin, obestatin	Serum	ELISA	Age, ghrelin, obestatin, leptin, metastatic disease and chronic kidney disease	LP, Ghrelin, obestatin	None
Moriwaki *et al.* (2014) [114]	62	Patients with advanced cancer with GPS 0, GPS 1 or GPS 2	OS	GPS (Alb+CRP), ALP, LDH, Bilirubin, CEA, CA 19-9	NR	NR	GPS, median ALP, median LDH, number of metastatic organs, liver metastasis, peritoneal metastasis, other metastasis	GPS (Alb+CRP)	ALP, Bilirubin, LDH, CEA, CA 19-9
Szkandera *et al.* (2014) [115]	474	Participants with cancer; no control	Cancer-specific survival	CRP, NLR, PLR	Plasma	NR	Age, gender, tumour grade, tumour stage, administration of chemotherapy, surgical resection, NLR, PLR, bilirubin levels and plasma CRP levels	CRP, NLR	PLR
Zhang *et al.* (2014) [116]	200	Participants with cancer; no control	-Fatigue -Chemotherapy adverse effects	TNF-α, IL-1 α, IL-1 β, 17-HCS	Plasma + urine	ELISA	No multivariate analysis	TNF-α, IL-1α, IL-1β	17-HCS
Jafri *et al.* (2013) [117]	173	Participants with advanced cancer with high inflammation and with low inflammation	-PPS -OS	ALI (Alb+NLR)	Serum	NR	Sex, race, PS and histology	ALI (Alb+NLR)	None
Laird *et al.* (2013) [118]	1466	Participants with advanced cancer with low and high CRP levels	-Symptoms of the ECTC (pain, appetite loss, cognitive function, dyspnea, fatigue, physical function,	CRP	Blood	NR	No multivariate analysis	CRP	None

Table 2 Characteristics of assays and main findings of included cancer studies* *(Continued)*

Author and year	Participants		Endpoints	Biomarkers studied	Biological material	Assay method	Covariates adjusted for in multivariate analysis	Results	
	Total participants (N)	Cases; control						Positive association with at least one endpoint**	Negative association
			role function, social function, QoL, nausea/ vomiting, diarrhea, sleep, constipation) -Survival						
Laird *et al.* (2013) b [119]	2456	Participants with advanced cancer; no control	-Symptoms of the EORTC (pain, appetite loss, cognitive function, dyspnea, fatigue, physical function, role function, social function, QoL, nausea/ vomiting, diarrhea, sleep, constipation) -Survival	mGPS (Alb+CRP)	Blood	NR	NR	mGPS (Alb+CRP)	None
Paiva *et al.* (2013) [120]	223	Participants with cancer with and without fatigue	-Fatigue -OS	CRP, Hb, LDH, Alb	Blood	NR	Age, KPS, type of treatment, breast cancer, upper gastrointestinal cancer, head and neck cancer, lower gastrointestinal cancer, lung cancer, urologic cancer, and CRP	CRP, Hb, LDH, Alb, WBC	None
Suh *et al.* (2013) [121]	98	Participants with advanced cancer; no control	Survival	IL-6, TNF-α	Plasma	ELISA (multiplex assay)	Gender (male), fatigue (BFI-K score), ECOG (3–4), IL-6 (High, ≥9.06 pg/mL)	IL-6	TNF-α
De Raaf *et al.* (2012) [122]	92	Participants with advanced cancer; cancer survivors	Physical and mental fatigue	CRP, IL-1-RA, NP, IL-6 and IL-8	Plasma	CBA	No multivariate analysis	CRP, IL-6, IL-1-ra, NP	IL-8
Gioulbasanis *et al.* (2012)	114	Participants with	-Nutritional status (cachexia)	IL-8	Plasma	CLIA	PS, histology, BMI, gender, age,	IL-8	None

Table 2 Characteristics of assays and main findings of included cancer studies* *(Continued)*

Author and year	Participants		Endpoints	Biomarkers studied	Biological material	Assay method	Covariates adjusted for in multivariate analysis	Results	
	Total participants (N)	Cases; control						Positive association with at least one endpoint**	Negative association
[123]		advanced cancer with malnutrition, with a risk of malnutrition, and who were well nourished	-Survival				smoking status, weight loss history		
Gulen *et al.* (2012) [124]	88	Participants with advanced cancer with and without weight loss; age- and sex-matched controls	Weight loss (>5%)	LP, APN, TNF-α, CRP	Serum	ELISA	No multivariate analysis	LP	APN, TNF-α, CRP
Heitzer *et al.* (2012) [125]	65	Advanced cancer patients with cancer pain; healthy controls without pain	Pain intensity	IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, TNF-α, TNF-β, IFN-γ, IL-1α, IL-7, IL-13, IL-18, MCP-1, MIP-1a, MIP-1B, OPG	Serum	ELISA	NI	Unclear	Unclear
Minton *et al.* (2012) [126]	720	Participants with advanced cancer with and without fatigue	Fatigue	CRP, Alb, Hb	Blood	NR	Hb, current treatment with chemo, QOL score, depression, pain dyspnoea, cognitive function, insomnia and loss of appetite	CRP, Alb, Hb	None
Partridge *et al.* (2012) [127]	102	Patients with advanced cancer with GPS 0, GPS 1 or GPS 2 ; no control	Survival	mGPS (Alb+CRP)	Blood	NR	Sex, primary cancer site, age, Hb and WBC	mGPS (Alb+CRP)	None
Pond *et al.* (2012) [128]	220	Participants with advanced cancer; no control	-OS -PPS	CRP	NR	NR	NR	CRP	None
Wang *et al.*	177	Participants	Survival	CRP, Alb, mGPS	NR	NR	PS, pretherapeutic	CRP, mGPS (Alb+CRP), NLR	Alb

Table 2 Characteristics of assays and main findings of included cancer studies[a] (Continued)

Author and year	Participants		Endpoints	Biomarkers studied	Biological material	Assay method	Covariates adjusted for in multivariate analysis	Results	
	Total participants (N)	Cases; control						Positive association with at least one endpoint[b]	Negative association
(2012) [129]		with cancer; no control		(Alb+CRP), NLR			weight, WBC, neutrophil count, NLR, CRP, mGPS, PI, the 7th TNM staging, surgery, degree of differentiation, palliate chemotherapy		
Aydin et al. (2011) [130]	61	Advanced cancer patients; no control	Survival	CRP, Alb, TPN	Serum	Nephelometric assay	No multivariate analysis	CRP, Alb, TPN	None
Dev et al. (2011) [131]	77	Participants with advanced cancer; no control	Symptom distress (pain, fatigue, nausea, depression, anxiety, drowsiness, appetite, well-being, dyspnea, sleep)	Cortisol	Serum	NR	NR	Cortisol	None
Gioulbasanis et al. (2011) [132]	115	Participants with advanced cancer with malnutrition, with a risk of malnutrition, and who were well nourished	-Nutritional status (cachexia) -Survival	Alb, CRP, ghrelin, LP, APN, IGF-1	Plasma	Reiken immunoassay	Number of metastatic sites, PS, weight loss <5%, MNA groups, age, and major histological type	CRP, LP, Alb	Ghrelin, APN, IGF-1
Hwang et al. (2011) [133]	402	Participants with cancer; no control	-PFS -OS	Alb, CRP	Serum	Latex turbidimetric immunoassay	Peritoneal metastasis, bone metastasis, albumin, CRP, ECOG PS, GPS	Alb, CRP	None
Kwak et al. (2011) [134]	90	Participants with advanced cancer; no control	Fatigue	IL-6, TNF-α	Blood	NR	BFI score, age, gender, BMI, blood pressure, heart rate, cancer site, previous treatment, comorbidity,	None	IL-6, TNF-α

Table 2 Characteristics of assays and main findings of included cancer studies* (Continued)

Author and year	Participants		Endpoints	Biomarkers studied	Biological material	Assay method	Covariates adjusted for in multivariate analysis	Results	
	Total participants (N)	Cases; control						Positive association with at least one endpoint**	Negative association
							medication, pain score, sleep disorder, dyspnea, ECOG PS, WBC, Hb, BUN, creatinine, albumin, AST, ALT, total bilirubin, CRP, IL-6, and TNF-α		
Lee et al. (2011) [135]	126	Participants with advanced cancer; no control	14 day mortality	CRP	Serum	NR	CRP, chemotherapy, age, dyspnea, altered mental status, hypotension, and leukocytosis	CRP	None
Schmidt-Bergsdahl et al. (2011) [136]	83	Participants with advanced cancer; no control	- Clinical features of cachexia (weakness, loss of appetite, fatigue, QOL, weight loss) -Survival	IL-6, IL-1β, IL-8, TNF-α	Plasma	BCA	Sex, age, diagnosis, oncological treatment, CCI and medications	IL-6, IL-1β, IL-8, TNF-α	None
Machostergios et al. (2011) [137]	77	Participants with advanced cancer; no control	-TTP -OS	IGF-1, GHP, Alb	Serum	Radioimmunoassay	Sex, current smoker, albumin, IGF-1	IGF-1, GHP, Alb	None
Dalewska et al. (2010) [138]	218	Participants with cancer with and without cachexia; healthy blood donors; and patients with non-malignant diseases of alimentary tract	Cachexia	LP, CRP, IL-1, IL-6, IL-8, TNF-α, Alb, Hb.	Serum	ELISA	NR	LP, IL-6, Alb, TNF-α	IL-1, IL-8, Hb, CRP*
Mrek et al. (2010) [139]	56	Participants with advanced cancer; no	Cancer-specific survival	IGF-1, IGFBP-3, CRP, mGPS (Alb=CRP); LP	Serum	NR	BMI, cancer stage, Hb, WBC, mGPS	mGPS (Alb=CRP)	IGF-1, IGFBP-3, LP, CRP

Table 2 Characteristics of assays and main findings of included cancer studies[a] (Continued)

Author and year	Participants		Endpoints	Biomarkers studied	Biological material	Assay method	Covariates adjusted for in multivariate analysis	Results	
	Total participants (N)	Cases; control						Positive association with at least one endpoint**	Negative association
		control							
Ishaka et al. (2008) [140]	112	Participants with advanced cancer; no control	Mortality	CRP, Alb, mGPS (Alb>CRP), Neutrophil ratio	Serum	NR	Neutrophil ratio, CA 19-9, CRP, albumin, and mGPS	mGPS (Alb>CRP)	None
Karapanagiotou et al. (2009) [141]	161	Participants with advanced cancer; healthy controls	-Weight loss -TTP -OS	Ghrelin, LP	Serum	ELISA	Sex, age, BMI, Ghrelin	Ghrelin Multivariate results NR	LP Multivariate results NR
Paddison et al. (2009) [142]	44	Participants with advanced cancer; healthy controls	Fatigue	Hb, WBC, Neutrophil, Monocyte, Lymphocyte	Blood	NR	Age, gender, time until treatment termination, and fatigue	Hb, WBC, Neutrophil count, monocyte count	None
Talaksheh et al. (2009) [143]	26	Participants with cancer cachexia; healthy controls	Anorexia (cachexia and BMI)	TNF-α, IFN-γ, IL-6, IL-1RA, LP, ghrelin	Plasma	ELISA	No multivariate analysis	TNF-α, IL-6, IL-1RA, LP	IFN- γ, ghrelin
Inagaki et al. (2008) [144]	46	Participants with advanced cancer with and without fatigue	Fatigue	IL-6	Plasma	ELISA	Logistic regression: IL-6, gender, weight and clinical fatigue Multiple regression gender, weight, IL-6 and total score of the CFS	IL-6	None
Karapanagiotou et al. (2008) [145]	152	Participants with advanced cancer; healthy controls	-Weight loss -TTP -OS	LP, ARN, resistin	Serum	ELISA	Sex, age, BMI, resistin	Resistin	LP, ARN
Sharma et al. (2008) [146]	52	Participants with advanced cancer; no control	-OS -Toxicity	IL-1β, IL-2, IL-4, IL-5, IL-8, IL-10, IL-12, GM-CSF, IFN-γ, TNF-α, sIL-6R, sgp130, VEGF, eotaxin, MCP-1, MIP-	Serum	NR	Tumour site (colonic primary), GPS, CEA, and albumin	GPS (Alb>CRP), Hb, Alb	CRP, IL-1β, IL-2, IL-4, IL-5, IL-8, IL-6, IL-10, IL-12, GM-CSF, IFN-

Table 2 Characteristics of assays and main findings of included cancer studies* (Continued)

Author and year	Participants		Endpoints	Biomarkers studied	Biological material	Assay method	Covariates adjusted for in multivariate analysis	Results	
	Total participants (N)	Cases; control						Positive association with at least one endpoint**	Negative association
				Ra, MIP-1β, Alb, CRP, GPS (Alb+CRP)					
Wanyrika et al. (2008) [147]	40	Participants with advanced cancer with and without cachexia	-Cachexia -Nutritional status	LP	Serum	ELISA	No multivariate analysis	LP	None
Rowsell et al. (2007) [148]	101	Participants with cancer; no control	-REE -Weight loss -Nutritional intake	IL-1RA, IL-6, TNF-α, IL-10, IFN-γ, VEGF	Serum	ELISA	Cancer histology and stage, nutritional intake	IL-1RA, IL-6, TNF-α, IFN-γ, VEGF	IL-10
Richey et al. (2007) [149]	24	Participants with cancer with and without cachexia	Cachexia	GPS (Alb+CRP), Alb, IL-1a, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, TNF-α, IFN-γ, VEGF, GM-CSF, MCP-1, MIP-1a, MIP-1β, RANTES, FGF, Hb, CRP, CEA	Serum	Dry-slide method with the VITROS Fusion Series analyser	No multivariate analysis	GPS (Alb+CRP), Alb, CEA	IL-1a, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, TNF-α, IFN-γ, VEGF, GM-CSF, GM-CSF, MCP-1, MIP-1a, MIP-1β, RANTES, FGF, Hb, CRP, CEA
Suh et al. (2007) [150]	44	Participants with advanced cancer; no control	Survival	CRP	Serum	NR	NR	CRP	None
Al Murri et al. (2006) [151]	96	Breast cancer patient's no control	Survival	CRP, Alb, GPS (Alb+CRP)	NR	NR	GPS and treatment	CRP, GPS (Alb + CRP)	None
Kayacan et al. (2006) [152]	56	Participants with advanced cancer with and without cachexia; healthy smokers for the control	-Cachexia -PS -Survival	TNF-α, IL-6	Serum	ELISA	NR	None	TNF-α, IL-6

Table 2 Characteristics of assays and main findings of included cancer studies* *(Continued)*

Author and year	Participants		Endpoints	Biomarkers studied	Biological material	Assay method	Covariates adjusted for in multivariate analysis	Results	
	Total participants (N)	Cases; control						Positive association with at least one endpoint**	Negative association
Ramsey *et al.* (2008) [153]	119	Participants with advanced cancer; no control	-Cancer-specific survival -Cancer-specific mortality	GPS (Alb+CRP)	NR	NR	GPS, Hb, calcium, WBC, neutrophil count, Alb, CRP	GPS (Alb+CRP)	None
Di Nisio *et al.* (2005) [154]	141	Participants with advanced cancer; no control	Survival	IL-6, IL-10, IFN-γ, P-selectin	Plasma	BCA	Life expectancy, WHO performance status, concomitant treatment, type of carcinoma, and histology	IL-10, IL-6, P-selectin	IFN-γ
Rich *et al.* (2005) [155]	80	Participants with advanced cancer with good and dampened circadian rhythms	-Extent of metastatic disease -PS -QOL	IL-6, TGF-a, TNF-α, cortisol	Serum	ELISA	NR	IL-6, TGF-a, TNF-α	Cortisol
Bolukbas *et al.* (2004) [156]	69	Participants with advanced cancer; healthy controls with stable weight	Weight loss	LP	Serum	ELISA	NR	LP	None
De Vita *et al.* (2004) [157]	68	Participants with advanced cancer; no control	-TTP -OS	IL-6	Serum	ELISA	NR	Il-6	None
Dulger *et al.* (2004) [158]	54	Participants with advanced cancer with and without cachexia; healthy gender- and age-matched adults	Cachexia	TNF-α, IL-1β, IL-6, CRP, LP, GH, TG, insulin, glucose, triglyceride, total protein, ESR	Serum	Solid-phase, two-site chemiluminescent immunometric assays	No multivariate analysis	Alb, total protein, GH, TNF-α, IL-1β, IL-6, insulin, LP, ESR[b]; CRP[b]	Glucose, TG
Elahi *et al.*	165	Participants	Survival	Alb, CRP	NR	Fluorescence	NR	Alb, CRP	None

Table 2 Characteristics of assays and main findings of included cancer studies* *(Continued)*

Author and year	Participants		Endpoints	Biomarkers studied	Biological material	Assay method	Covariates adjusted for in multivariate analysis	Results	
	Total participants (N)	Cases; control						Positive association with at least one endpoint**	Negative association
(2004) [159]		with advanced cancer; no control				polarization immunoassay			
Jamieson *et al.* (2004) [160]	33	Participants with advanced cancer; healthy controls	Weight loss	Hb, Alb, CRP, APN, LP, IL-6	Serum	ELISA	No multivariate analysis	Hb, Alb, CRP, APN, LP, IL-6	None
Songur *et al.* (2004) [161]	91	Participants with advanced cancer; healthy controls	-Malnutrition -Survival	IL-6, Alb, CRP, TFN, LDH	Serum	NR	NR	IL-6, Alb, CRP, TFN, LDH	None
Scott *et al.* (2003) [162]	106	Participants with advanced cancer with and without weight loss	-Weight loss	Hb, Alb, CRP	Blood	NR	No multivariate analysis	Hb, Alb, CRP	None
Aleman *et al.* (2002) [163]	106	Patients newly diagnosed with NSCL vs patients with no cancer	-Nutritional status -Survival	IL-6, IL-12, IL-10, IL-2, LP, α -1A, ferritin, CRP, TNF-α, s-TNFR2, sIL-2R, IFN-γ	Serum	CLIA	NR	IL-6, IL-12, IL-2, sTNFR2, IFN-γ, sIL-2R, LP, α-1 A, CRP, ferritin Multivariate results unclear	IL-10, TNF-α Multivariate results unclear
Orditura *et al.* (2002) [164]	85	Participants with advanced cancer; healthy controls	-OS -TTF	IL-8, IL-10, IL-2	Serum	ELISA	NR	IL-10, IL-2, IL-8	None
Scott *et al.* (2002) [165]	106	Participants with advanced cancer; no control	Survival	Alb, CRP	Blood	NR	Age, sex, stage, histological type, weight loss, haemoglobin, albumin, CRP, KPS and EORTCV QLQ-C30 subscale	CRP, Alb	None
Jatoi *et al.* (2001) [166]	73	Participants with	Anorexia and/or weight loss	NPY, LP, CCK-8	Serum	Radioimmunoassay	No multivariate analysis	NPY	LP, CCK-8

Table 2 Characteristics of assays and main findings of included cancer studies* *(Continued)*

Author and year	Participants		Endpoints	Biomarkers studied	Biological material	Assay method	Covariates adjusted for in multivariate analysis	Results	
	Total participants (N)	Cases; control						Positive association with at least one endpoint**	Negative association
		advanced cancer; healthy controls							
Mantovani *et al.* (2001) [167]	58	Participants with advanced cancer; normal weight healthy controls	-BMI -Cachexia -ECOG PS -Survival	LP, IL-6, TNF-α	Serum	ELISA	No multivariate analysis	Unclear	Unclear
Mantovani *et al.* (2000) [168]	32	Participants with advanced cancer; normal weight healthy controls	-cachectic symptoms (BMI)	LP, IL-1a, IL-6, and TNF-α	Serum	ELISA	No multivariate analysis	Unclear	Unclear
Nerova *et al.* (2000) [169]	87	Participants with advanced cancer; healthy controls	-Cachexia -Prognosis	TNF-α	Serum	ELISA	No multivariate analysis	Unclear	Unclear
O'Gorman *et al.* (1999) [170]	50	Participants with advanced cancer with weight loss or weight gain; weight stable controls	-Weight loss -Appetite -PS -Inflammation	Alb, CRP	Blood	NR	No multivariate analysis	Alb, CRP	None
Okada *et al.* (1998) [171]	100	Participants with cancer; healthy controls	Weight loss	IL-6	Serum	ELISA	No multivariate analysis	IL-6	None
Wallace *et al.* (1998) [172]	54	Participants with advanced cancer; healthy	Weight loss	LP	Serum	Radioimmunoassay	No multivariate analysis	LP	None

Table 2 Characteristics of assays and main findings of included cancer studies* *(Continued)*

Author and year	Participants		Endpoints	Biomarkers studied	Biological material	Assay method	Covariates adjusted for in multivariate analysis	Results	
	Total participants (N)	Cases; control						Positive association with at least one endpoint**	Negative association
		controls							
Maltoni *et al.* (1997) [173]	530	Participants with advanced cancer; no control	Survival	Neutrophil, lymphocyte & monocyte %, basophil + eosinophil %, Hb, TFN, Alb, total WBC, Pseudocholinesterase, proteinuria, TFN, transport iron	Blood	NR	No multivariate analysis	Neutrophil %, lymphocyte %, total WBC, CHE, Alb	basophil + eosinophil %, Hb, TFN
Simons *et al.* (1997) [174]	21	Participants with cancer and weight loss; no control	-Weight loss -Body composition -Appetite -REE	LP	Plasma	ELISA	No multivariate analysis	LP	None

Note: Cancer prognosis was not separated from the other syndromes in the table
* Red coloured biomarkers indicate significance in multivariate analysis
**Secondary analysis of Amano, 2016
†In cancer vs no cancer only
Abbreviations: *17-HCS* 17-hydroxycorticosteroids, *α-1-AGP* α-1-acid glycoprotein, *α-1A* alpha-1 antitrypsin, *Alb* Albumin, *ALP* Alkaline phosphatase, *APN* Adiponectin, *APOA2* Apolipoprotein A2, *BCA* The bicinchoninic acid assay, *bFGF* Basic fibroblast growth factor, *CA 19-9* Cancer antigen, *CBA* Cytometric bead array immunoassay, *CCK* Cholecystokinin, *CEA* Carcinoembryonic antigen, *CK* Creatine Kinase, *CLIA* Chemiluminescence Immunoassay, *Cre* Creatinine, *CRP* C-Reactive Protein, *CXCL* Soluble CXC chemokine ligand, *ESR* Erythrocyte sedimentation rate, *FBG* Fibrinogen, *FSN* Follistatin, *GH* Growth Hormone, *GM-CSF* Granulocyte-Macrophage Colony-Stimulating Factor, *HA* Hyaluronic Acid, *Hb* Haemoglobin, *IGF* Insulin-Like Growth Factor, *IGFBP* Insulin-like Growth Factor Binding Protein, *IL* Interleukin, *IFN* Interferon, *LDH* Lactate Dehydrogenase, *LP* Leptin, *MCP* Monocyte Chemotactic Protein, *MIP* Macrophage Inflammatory Protein, *MK* Midkine, *NI* Not enough Information, *NR* Not reported, *MSTN* Myostatin, *NLR* Neutrophil-lymphocyte ratio, *NP* Neoptetin, *NPY* Neuropeptide Y, *OPG* Osteoprotegrin, *PLR* Platelet-lymphocyte ratio, *RANTES* Chemokine (C–C motif) ligand 5, *sTNFR* SolubleTumor Necrosis Factor Receptor, *Sgp130* Soluble glycoprotein 130, *TARC* Thymus and Activation-Regulated Chemokine, *TFN* Transferrin, *TG* Triglyceride, *TNF* Tumor Necrosis Factor, *TRAF-6* Tumor Necrosis Factor Receptor associated factor-6, *TTF* Time to treatment failure, *TWEAK* TNF-like weak inducer of apoptosis, *VEGF* Vascular Endothelial Growth Factor, *ZAG* Zn-alpha2 glycoprotein

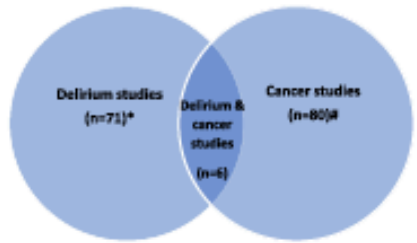

Fig. 2 Conceptual model illustrating the 'true overlap' of delirium and advanced cancer biomarker studies. * Cancer as a comorbidity not measured/reported # Delirium as a concurrent illness or comorbidity not measured/reported

participants who had delirium also had cancer, in another two, 26% and 27% of the delirium cohorts had cancer, and in the remaining study 14% of the delirium participants had cancer (Table 1). Although only six delirium studies reported co-existing cancer, there is still uncertainty as to how many participants in both groups of studies had both delirium and cancer. The two most common biomarkers in these six studies that reported a positive association with delirium were CRP (n=3) and IL-6 (n=3). It is unclear however whether these biomarkers were predominantly associated with delirium or the cancer, as three of the six studies grouped the delirium participants together, irrespective of their cancer comorbidity.

The quality assessment showed a large variability in the reporting of included studies. 150 (99%) studies had a clear aim statement which included their outcome of interest. One study did not report a clear aims statement [175]. One hundred and nineteen studies (79%) did not explicitly state the hypothesis; however, in most (n=94; 62%) the hypothesis could be interpreted by the study aim. All 151 studies stated the participant population in detail. No study reported all elements of the assay methods in the REMARK checklist [23]. One hundred and thirty one studies (87%) did not report whether assays were blinded to the study endpoint, however 59 (45%) of those studies were objective assessments. Further, 14 studies (9%) reported a power calculation to justify their sample size. Most (n=125; 83%) of studies defined all clinical endpoints examined. Ninety seven (64%) studies undertook multivariate analysis, and of these 67 (69%) described the multivariate model and the covariates included in the model, and 23 (23%) explained the rationale for inclusion of the covariates in the models. (Additional files 4 and 5). Furthermore, 27 delirium studies (38%) did not report the reason for admission. Of the 44 studies that did report the reason for admission, these were predominantly for surgery-elective and acute (n=40). Most studies in the non-surgical population did not report a reason for admission, with the exception of 4 studies where the medical condition of interest occurred on admission (e.g stroke). See additional files 4 and 5 for the complete quality assessments.

The methodological quality of the assay procedures only is depicted in Figure 3, with reporting of type of biological material mostly provided but much lower frequency of reporting for other critical descriptors.

Discussion

This is the first systematic review to our knowledge, to demonstrate the high degree of overlap in biomarkers in delirium, cancer prognosis and advanced cancer syndromes. This systematic review of 151 studies found that 41 biomarkers were independently investigated in studies of both delirium and prognosis/advanced cancer syndromes; with over half having a positive association in at least one study.

Biomarkers fall into three categories (though not mutually exclusive); those which present before disease onset that can help identify individuals who are most at risk of a particular disease (for example, genetic markers), those which are disease markers and as such, increase during disease progression and decrease after resolution, and thirdly, biomarker as an end-product of a disease for which levels are proportionate to 'damage' due to the disease [176]. The findings of this systematic review suggest that categorization along these lines is less understood in delirium. For example, there is evidence to show that conditions such as sepsis and hip fracture cause changes in inflammatory markers [177, 178], however, there is little evidence about whether delirium self-propagates. Some animal model data in delirium suggests that there might be a direct impact of inflammatory markers on brain dysfunction [179]. To our knowledge there was no published relationship between tumor markers and neurological brain dysfunction. Although clinical evidence suggests long term impacts on brain function, the exact pathophysiological mechanisms are poorly understood, and biomarkers to measure this are also unclear.

The issue of biomarker overlap between associated conditions has been researched in women with pre-eclampsia and polycystic ovary syndrome [180], however the overlap with respect to delirium and its associated conditions has not been well addressed. Of the 71 delirium studies, only five studies sought to determine the association with the participants' common primary condition in their analysis. Tomasi et al. (2017) found that biomarkers differed between patients in the three groups in those with sepsis alone and those who developed sepsis-associated encephalopathy, or delirium,

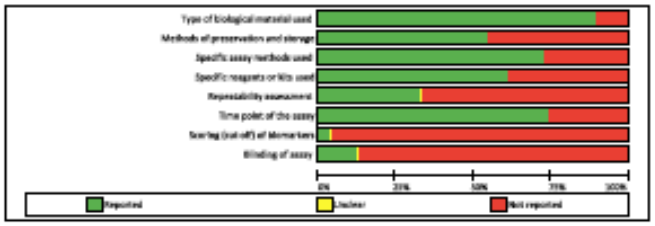

Fig. 3 Quality assessment graph of the assay procedures review author's judgements about each assay domain of the REMARK checklist, presented as percentages across studies

suggesting different mechanisms of sepsis-associated encephalopathy, delirium in people with sepsis, and sepsis itself. Likewise, Pfister et al. (2008) found differences in CRP, s100 calcium binding protein B (s100B) and cortisol in patients with sepsis-associated delirium, compared to non-sepsis associated delirium. In two studies, delirium in stroke was examined [25, 92] but these studies did not identify differences in cortisol [92] or TNF- α, IL- 1β, IL-18, Brain-derived neurotrophic factor (BDNF) and Neuron specific enolase (NSE) [25] between patients who developed delirium after stroke compared to those who did not develop delirium. Moreover, Sun et al. (2016) attempted to explore the overlap of biomarkers in delirium and dementia in patients with cancer, however, no multivariate analysis was undertaken, therefore results of this study are inconclusive.

Although the aim of this systematic review was to explore the overlap of biomarkers in delirium and advanced cancer syndromes, the findings highlighted a bigger problem in the methodology of delirium biomarker research. The quality assessment in this systematic review found that many of the included studies were of poor methodological quality, inadequately reported, or were influenced by potential confounding factors. A potential barrier to the complete understanding of delirium pathophysiology is the lack of guidelines for conducting and reporting delirium biomarker studies. Results from this review indicate that the absence of such guidelines has likely impeded the quality of individual studies and the overall quality of this critical field of delirium research. Reporting guidelines for delirium biomarker research are an essential step to improving methodological and reporting rigor, and will increase the potential for synthesis of future studies through meta-analyses.

Several studies have previously been performed to determine biomarkers associated with delirium, however potential confounding factors could be the underlying precipitants of delirium; ie risk factors (sepsis), or underlying conditions present (for example cancer or dementia). The top five most commonly studies biomarkers in this review were inflammatory biomarkers, namely, CRP, IL-6, TNF- α, IL-10 and IL-8. The challenge with inflammatory markers is that they are non-specific and the inflammatory pathways are similar to those implicated in other conditions such as sepsis and depression [181, 182]. Likewise, of the six delirium studies where there was concomitant cancer, it is very difficult to determine whether those biomarkers found were related to the cancer or the delirium itself, considering alterations in inflammatory pathways are implicated in both. Therefore, future delirium biomarker studies need to be prospectively evaluated and take into account and assess robustly other active co-morbidities such as cancer that could plausibly impact on the pathophysiological and/or biological findings. Similarly, future cancer biomarker studies must also take into account how delirium may clinically or biologically confound biomarker studies in cancer, considering the high prevalence of delirium in this population. Of the six delirium studies with cancer, three did not report the type of cancer, and of the remaining three studies, none were primary brain tumours or brain metastases. Understanding the spread of brain cancer is important in delirium studies, and is an important consideration for future delirium biomarker studies.

Majority of the studies in this review (n=98; 65%) undertook a multivariate analysis, taking into account confounding variables. Where studies only undertook univariate analysis, it is uncertain whether any observed changes in biomarkers were related to the delirium itself, or whether these changes may have been lost when adjusted for confounding factors (such as prior cognitive impairment) in a multivariate analysis. Furthermore, there is likely to be a higher proportion of participants with both delirium and cancer in both groups of studies for which this clinical information was not assessed or that were not reported. Key methodological issues which need to be addressed in future delirium studies include

adjusting for confounders such as age, gender, concurrent medication, comorbidities, prior cognitive impairment, frailty and other neurological conditions. These clinical covariates must also be clearly defined and justified. Assay procedures ought to be reported in detail, including a detailed protocol of the reagents/kits used, repeatability assessments, methods of preservation and storage, assay validity, sensitivity limits of the assay and a scoring and reporting protocol. The timing of the assay is crucial in delirium studies, and the fluctuating pathophysiological processes occurring during delirium, after delirium resolution, and in those who have not yet developed delirium, must be taken into consideration, and be separated in future studies. More standardised and detailed methods of delirium biomarker studies is a crucial step in carrying out future subgroup analyses within this cohort and improving the overall understanding of delirium pathophysiology.

Limitations are that only English language and published studies were included. It is possible that articles were missed; however, two reviewers independently screened all citations derived from a search of six relevant and diverse databases, and all reference lists of included articles were also searched. Another limitation of our study is the lack of a risk of bias tool for biomarker studies, therefore we used an adaptation of tumor marker reporting guidelines, the REMARK checklist [23]. Lastly, the heterogeneity of the data precluded the conduct of a meta-analysis, and precluded any firm conclusions about the biomarkers in delirium and cancer, thus, limiting the rigor of this review. Strengths of this review however, were that we undertook a systematic approach adhering to the PRISMA [15] and an extensive quality assessment of the included studies was undertaken.

Conclusion

This review found that there is large overlap in the biomarkers in delirium and in advanced cancer-related syndromes, although because of the heterogeneity of the studies firm conclusions about the true overlap of delirium and advanced cancer syndrome biomarkers was not possible. More robust conduct and reporting of delirium biomarker studies will help to better understand the pathophysiology of delirium in the context of co-existing pathophysiology. An improved understanding of the clinical and biological associations of delirium and advanced cancer syndromes in future prospective studies will provide and inform the directions of research into delirium in people with advanced cancer.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12888-020-02584-2.

Additional file 1: MEDLINE search strategies MEDLINE search strategies for delirium and cancer studies.

Additional file 2: Participant characteristics- delirium studies Characteristics of participants in the included delirium studies.

Additional file 3: Participant characteristics- cancer studies Characteristics of participants in the included cancer studies.

Additional file 4: Quality assessment of included delirium studies using the REMARK checklist The quality assessment for all included delirium studies.

Additional file 5: Quality assessment of included cancer studies using the REMARK checklist The quality assessment for all included cancer studies.

Additional file 6: PRISMA checklist.

Abbreviations

BDNF: Brain-derived neurotrophic factor; CRP: C-reactive protein; CSF: Cerebrospinal fluid; ELISA: Enzyme-linked immunosorbent assay; IL-: Interleukin; NSE: Neuron specific enolase; S100B: S100B calcium binding protein B; TNF: Tumor necrosis factor

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Ethics approval and consent to participant

Not applicable.

Authors' contributions

IAD undertook the literature search, identified potential articles, extracted data, interpreted results, performed a quality assessment, drafted and revised all versions of the manuscript. MA and AH contributed to study selection and screening, interpreting results, revised manuscript drafts and supervised the study. All authors (IAD, AH, MA and GC) contributed to the interpretation of results, manuscript preparation and read and approved the final manuscript.

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Availability of data and materials

All data generated or analysed in this systematic review are included within this published article and its additional files.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. Hosie A, Davidson P, Agar M, Sanderson C, Phillips J. Delirium prevalence, incidence, and implications for screening in specialist palliative care inpatient settings: a systematic review. Palliat Med. 2013;27(6):486–98.
2. Davis DH, Skelly DT, Murray C, Hennessy E, Bowen J, Norton S, et al. Worsening cognitive impairment and neurodegenerative pathology progressively increase risk for delirium. Am J Geriatr Psychiatry. 2015;23(4):403–15.

3. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet. 2014;383(9920):911–22.
4. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, fifth edition (DSM-5). Arlington: American Psychiatric Publishing; 2013.
5. National Clinical Guideline Centre for Acute and Chronic Conditions. Delirium: diagnosis, prevention and management: NICE clinical guideline 103; 2010. Available from: https://www.nice.org.uk/guidance/cg103.
6. Neefjes EC, van der Vorst MJ, Verdegaal BA, Beelman AT, Berkhof J, Verheul HM. Identification of patients with cancer with a high risk to develop delirium. Cancer Med. 2017;6(8):1869–70.
7. Uchida M, Okuyama T, Ito Y, Nakaguchi T, Miyaoka M, Sakamoto M, et al. Prevalence, course and factors associated with delirium in elderly patients with advanced cancer: a longitudinal observational study. Jpn J Clin Oncol. 2015;45(10):984–90.
8. Grandahl MG, Nielsen SE, Kraemer EA, Schultz HH, Arnfred SM. Prevalence of delirium among patients at a cancer ward: clinical risk factors and prediction by bedside cognitive tests. Nordic J Psychiatry. 2016;70(6):413–7.
9. Bush SH, Lawlor PG, Ryan K, Centeno C, Lucchesi M, Kanji S, et al. Delirium in adult cancer patients: ESMO clinical practice guidelines. Ann Oncol. 2018; 29(Supplement_4):iv143–iv65.
10. Maldonado JR. Delirium pathophysiology: an updated hypothesis of the etiology of acute brain failure. Int J Geriatr Psychiatry. 2017;33(11):1428–57.
11. Ber C. Cognitive impairment and oxidative stress in the elderly: results of epidemiological studies. Biofactors. 2000;13(1–4):205–9.
12. Heggstrom L, Nelson J, Wegner E, Caplan G. 2-18F-fluoro-2-deoxyglucose positron emission tomography in delirium. J Cereb Blood Flow Metab. 2013; 33(11):1656–67.
13. Caplan GA, Kwekkeboom T, Lai C, Yap SL, Lin C, Hill MA. Cerebrospinal fluid in long-lasting delirium compared with Alzheimer's dementia. J Gerontol Series A-Med Sci. 2010;65(10):1130–6.
14. National Cancer Institute. NCI Dictionary of Cancer Terms [Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/?CdrID=45561 8.
15. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6(7):e1000100.
16. Blum D, Omlin A, Fearon K, Baracos V, Radbruch L, Kaasa S, et al. Evolving classification systems for cancer cachexia: ready for clinical practice? Support Care Cancer. 2011;19(3):273–9.
17. Bower JE. Cancer-related fatigue—mechanisms, risk factors, and treatments. Clin Oncol. 2014;11(10):597.
18. International Association for the Study of Pain. IASP terminology Washington, USA; 2017. Available from: https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698&navItemNumber=576-Pain.
19. Bray V, Dhillon H, Vardy J. Cancer-related cognitive impairment in adult cancer survivors: a review of the literature cancer forum; 2017. Available from: https://cancerforum.org.au/forum/2017/march/cancer-related-cognitive-impairment-in-adult-cancer-survivors-review-of-the-literature/.
20. Dantzer R. Cytokine-induced sickness behaviour: a neuroimmune response to activation of innate immunity. Eur J Pharmacol. 2004;500(1–3):399–411.
21. Dantzer R. Cytokine-induced sickness behavior: where do we stand? Brain Behav Immun. 2001;15(1):7–24.
22. National Cancer Institute. Understanding cancer prognosis; 2018. Available from: https://www.cancer.gov/about-cancer/diagnosis-staging/prognosis.
23. Altman DG, McShane LM, Sauerbrei W, Taube SE. Reporting recommendations for tumor marker prognostic studies (REMARK): explanation and elaboration. BMC Med. 2012;10(1):51.
24. Egberts A, Mattace-Raso F. Increased neutrophil–lymphocyte ratio in delirium: a pilot study. Clin Interv Aging. 2017;12:1115.
25. Kocak MH, Uygur F, Kilinc I, Uca AU, Serhat Toligozr O, Alpinar Z, et al. Delirium in patients with acute ischemic stroke admitted to the non-intensive stroke unit: incidence and association between clinical features and inflammatory markers. Neurol Neurochir Pol. 2017;51(1):38–44.
26. Tomasi CD, Vuolo F, Generoso J, Soares M, Barichello T, Quevedo J, et al. Biomarkers of delirium in a low-risk community-acquired pneumonia-induced sepsis. Mol Neurobiol. 2017;54(1):720–6.
27. Vasunilashorn SM, Dillon ST, Inouye SK, Ngo LH, Fong TG, Jones RN, et al. High C-reactive protein predicts delirium incidence, duration, and feature severity after major noncardiac surgery. J Am Geriatr Soc. 2017;65(8):e109.
28. Dillon ST, Vasunilashorn SM, Ngo L, Otu HH, Inouye SK, Jones RN, et al. Higher C-reactive protein levels predict postoperative delirium in older patients undergoing major elective surgery: a longitudinal nested case-control study. Biol Psychiatry. 2017;81(2):140–53.
29. Guo Y, Jia P, Zhang J, Wang X, Jiang H, Jiang W. Prevalence and risk factors of postoperative delirium in elderly hip fracture patients. J Int Med Res. 2016;44(2):317–27.
30. Kerkic IS, Stanevic M, Jankovic S, Dejanovic SD, Milovanovic S. Markers of inflammation as risk predictors of lethal outcome in patients diagnosed with delirium. Vojnosanit Pregl. 2016;73(9):838–43.
31. Newland BE, Hall RJ, Seljeflot I, Frihagen F, MacLullich AMJ, Raeder J, et al. Associations between delirium and preoperative cerebrospinal fluid C-reactive protein, Interleukin-6, and Interleukin-6 receptor in individuals with acute hip fracture. J Am Geriatr Soc. 2016;64(7):1456–63.
32. Shen H, Shao Y, Chen J, Guo J. Insulin-like growth factor-1, a potential predictive biomarker for postoperative delirium among elderly patients with open abdominal surgery. Curr Pharm Design. 2016;22(38):5879–83.
33. Sun L, Jia P, Zhang J, Zhang X, Zhang Y, Jiang H, et al. Production of inflammatory cytokines, cortisol, and Abeta1-40 in elderly oral cancer patients with postoperative delirium. Neuropsychiatr Dis Treat. 2016;12:789–95.
34. Yen JE, Allen JC, Abell SK, Patterson SC, Metcalf MR, Flink BJ, et al. Association between serum IGF-1 levels and postoperative delirium in elderly subjects undergoing elective knee arthroplasty. Sci Rep. 2016;6:20736.
35. Avila-Funes JA, Ledesma-Heyer JP, Navarrete-Reyes AP, Chavira-Ramirez R, Boeck-Quiroz I, Aguilar-Navarro S. Association between high serum estradiol levels and delirium among hospitalized elderly women. Rev Investig Clin. 2015;67(1):20–4.
36. Brum C, Stertz L, Bobbe E, Rumi D, Kapczinski F, Cereser-Jr A. Association of serum brain-derived neurotrophic factor (BDNF) and tumor necrosis factor-alpha (TNF-alpha) with diagnosis of delirium in oncology inpatients. Rev Bras Psiquiatr. 2015;37(3):197–202.
37. Egberts A, Wijnbeld EH, Fekkes D, van der Ploeg MA, Zhew G, Hooijkaas H, et al. Neopterin: a potential biomarker for delirium in elderly patients. Dement Geriatr Cogn Disord. 2015;39(1–2):116–24.
38. Foroughan M, Delbari A, Said SE, Akbari Kamrani AA, Rashedi V, Zandi T. Risk factors and clinical aspects of delirium in elderly hospitalized patients in Iran. Aging Clin Exp Res. 2016;28(2):313–9.
39. Skrede K, Wyller TB, Watne LO, Seljeflot I, Juliebo V. Is there a role for monocyte chemoattractant protein-1 in delirium? Novel observations in elderly hip fracture patients. BMC Res Notes. 2015;8:186.
40. Vasunilashorn SM, Ngo L, Inouye SK, Libermann TA, Jones RN, Alsop DC, et al. Cytokines and postoperative delirium in older patients undergoing major elective surgery. J Gerontol Series A-Med Sci. 2015;70(10):1289–95.
41. Alexander SA, Ren D, Gunn SR, Kochanek PM, Tate J, Bercovici M, et al. Interleukin 6 and apolipoprotein E as predictors of acute brain dysfunction and survival in critical care patients. Am J Crit Care. 2014;23(1):49–57.
42. Barany A, Rothenhausler HB. The impact of soluble interleukin-2 receptor as a biomarker of delirium. [erratum appears in psychosomatics. 2014 Jul-Aug 55(4):418-9]. Psychosomatics. 2014;55(1):51–60.
43. Cape E, Hall RJ, van Munster BC, de Vries A, Howie SE, Pearson A, et al. Cerebrospinal fluid markers of neuroinflammation in delirium: a role for interleukin-1beta in delirium after hip fracture. J Psychosom Res. 2014;77(3): 219–25.
44. Capri M, Yani SL, Chattat R, Fortuna D, Bucci L, Lanzarini C, et al. Preoperative, high IL-6 blood level is a risk factor of postoperative delirium onset in old patients. Front Endocrinol. 2014;5:173 (EPJ) (no pagination).
45. Chen XW, Shi JW, Yang PS, Wu ZQ. Preoperative plasma leptin levels predict delirium in elderly patients after hip fracture surgery. Peptides. 2014;57:51–5.
46. Hatta K, Kishi Y, Takeuchi T, Wada K, Odawara T, Usui C, et al. The predictive value of a change in natural killer cell activity for delirium. Prog Neuro-Psychopharmacol Biol Psychiatry. 2014;48:26–31.
47. Kazmierski J, Banys A, Latek J, Bourke J, Jaszewski R, Sobow T, et al. Mild cognitive impairment with associated inflammatory and cortisol alterations as independent risk factor for postoperative delirium. Dement Geriatr Cogn Disord. 2014;38(1–2):65–78.
48. Ritchie CW, Newman TH, Leurent B, Sampson EL. The association between C-reactive protein and delirium in 710 acute elderly hospital admissions. Int Psychogeriatr. 2014;26(5):717–24.
49. Ritter C, Tomasi CD, Dal-Pizzol F, Pinto BB, Dyson A, de Miranda AS, et al. Inflammation biomarkers and delirium in critically ill patients. Crit Care. 2014;18(5):R106.

50. Zhang Z, Pan L, Deng H, Ni H, Xu X. Prediction of delirium in critically ill patients with elevated C-reactive protein. J Crit Care. 2014;29(1):88–92.
51. Cerejeira J, Batista P, Nogueira V, Vaz-Serra A, Mukaetova-Ladinska EB. The stress response to surgery and postoperative delirium: evidence of hypothalamic-pituitary-adrenal axis hyperresponsiveness and decreased suppression of the GH/IGF-1 Axis. J Geriatr Psychiatry Neurol. 2011;24(3):172–94.
52. Collinsen Y, Gray S, Oswil Y, Swagin N, Coskun I. Relation of serum cortisol to delirium occurring after acute coronary syndromes. Am J Emerg Med. 2013;31(1):168–5.
53. Karmiński J, Banys A, Lubik J, Bourke J, Jaszewski R. Cortisol levels and neuropsychiatric diagnosis as markers of postoperative delirium: a prospective cohort study. Crit Care. 2013;17(2):R38.
54. Karmiński J, Banys A, Lubik J, Bourke J, Jaszewski R. Raised IL-2 and TNF-alpha concentrations are associated with postoperative delirium in patients undergoing coronary-artery bypass graft surgery. Int Psychogeriatr. 2014;26(5):845–55.
55. Liu P, Li YW, Wang XS, Zou X, Zhang DZ, Wang DX, et al. High serum interleukin-6 level is associated with increased risk of delirium in elderly patients after noncardiac surgery: a prospective cohort study. Chin Med J. 2013;126(19):3621–7.
56. Plaschke K, Hauth S, Jansen C, Bruckner T, Schramm C, Karck M, et al. The influence of preoperative serum anticholinergic activity and other risk factors for the development of postoperative cognitive dysfunction after cardiac surgery. J Thorac Cardiovasc Surg. 2013;145(3):805–11.
57. Skrobik Y, Leger C, Cossette M, Michaud V, Turgeon J. Factors predisposing to coma and delirium: fentanyl and midazolam exposure, CYP3A5, ABCB1, and ABCG2 genetic polymorphisms, and inflammatory factors. Crit Care Med. 2013;41(4):999–1008.
58. Westhoff D, Witlox J, Koenderman L, Kalkwaat KJ, de Jonghe JF, van Stijn MF, et al. Preoperative cerebrospinal fluid cytokine levels and the risk of postoperative delirium in elderly hip fracture patients. J Neuroinflammation. 2013;10:122.
59. Bekker RC, Osse RJ, Tulen JH, Kappetein AP, Bogers AJ. Preoperative and operative predictors of delirium after cardiac surgery in elderly patients. Eur J Cardiothorac Surg. 2012;41(3):544–9.
60. Beloosesky A, Rothenhausler HB. The impact of intra- and postoperative albumin levels as a biomarker of delirium after cardiopulmonary bypass: results of an exploratory study. Psychiatry Res. 2012;200(2-3):857–63.
61. Cerejeira J, Nogueira V, Luis P, Vaz-Serra A, Mukaetova-Ladinska EB. The cholinergic system and inflammation: common pathways in delirium pathophysiology. J Am Geriatr Soc. 2012;60(4):669–75.
62. Girard TD, Ware LB, Bernard GR, Pandharipande PP, Thompson JL, Shintani AK, et al. Associations of markers of inflammation and coagulation with delirium during critical illness. Intensive Care Med. 2012;38(12):1965–73.
63. Osse RJ, Fekkes D, Tulen JH, Wierdsma AI, Bogers AJ, van der Mast RC, et al. High preoperative plasma neopterin predicts delirium after cardiac surgery in older adults. J Am Geriatr Soc. 2012;60(8):1581–8.
64. Bisschop PH, de Rooij SE, Zwinderman AH, van Dorsten HE, van Munster BC. Cortisol, insulin, and glucose and the risk of delirium in older adults with hip fracture. J Am Geriatr Soc. 2011;59(6):1152–6.
65. Holmes C, Cunningham C, Zotova E, Culliford D, Perry VH. Proinflammatory cytokines, sickness behavior, and Alzheimer disease. Neurology. 2011;77(3):212–8.
66. Lee HJ, Hwang DS, Wang SK, Chae IS, Bang S, Kim JL. Early assessment of delirium in elderly patients after hip surgery. Psychiatry Investig. 2013;10(4):360–7.
67. McGaire S, Girard TD, Thompson JL, Shintani AK, Woodworth A, Ely EW, et al. Procalcitonin and C-reactive protein levels at admission as predictors of duration of acute brain dysfunction in critically ill patients. Crit Care. 2011;15(2):R78.
68. Morandi A, Gunther ML, Pandharipande PP, Jackson JC, Thompson JL, Shintani AK, et al. Insulin-like growth factor-1 and delirium in critically ill mechanically ventilated patients: a preliminary investigation. Int Psychogeriatr. 2011;23(7):1175–81.
69. van den Boogaard M, Kox M, Quinn K, van Achterberg T, van der Hoeven J, Schoonhoven L, et al. Biomarkers associated with delirium in critically ill patients and their relation with long-term subjective cognitive dysfunction; indications for different pathways governing delirium in inflamed and non-inflamed patients. Crit Care. 2011;15:R297.
70. van den Boogaard M, van Swelm RPL, Russel FGM, Heemskerk S, van der Hoeven JG, Maessenaar R, et al. Urinary protein profiling in hyperactive delirium and non-delirium cardiac surgery ICU patients. Proteome Sci. 2011;9:13 no pagination.
71. Burkhart C, Dell-Kuster S, Gamberini M, Moercki A, Siegrow M, Filipovic M, et al. Modifiable and non-modifiable risk factors for postoperative delirium after cardiac surgery with cardiopulmonary bypass. J Cardiothorac Vasc Anesth. 2010;24(4):555–9 Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/538/CN-00781538/frame.html.
72. Mu DL, Wang DX, Li LH, Shan GJ, Li J, Yu QJ, et al. High serum cortisol level is associated with increased risk of delirium after coronary artery bypass graft surgery: a prospective cohort study. Crit Care. 2010;14:R6.
73. Pearson A, de Vries A, Middleton S, Gillies F, White T, Armstrong I, et al. Cerebrospinal fluid cortisol levels are higher in patients with delirium versus controls. BMC Res Notes. 2010;3(1):333.
74. Plaschke K, Fichtenkamm P, Schramm C, Hauth S, Martin E, Verch M, et al. Early postoperative delirium after open-heart cardiac surgery is associated with decreased bispectral EEG and increased cortisol and interleukin-6. Intensive Care Med. 2010;36(12):2081–9.
75. Tsuruta R, Nakahara T, Miyauchi T, Kutsuna S, Ogino Y, Yamamoto T, et al. Prevalence and associated factors for delirium in critically ill patients at a Japanese intensive care unit. Gen Hosp Psychiatry. 2010;32(6):607–11.
76. van Munster BC, Bisschop PH, Zwinderman AH, Korevaar JC, Endert E, Wiersinga WJ, et al. Cortisol, interleukins and S100B in delirium in the elderly. Brain Cogn. 2010;74(1):18–23.
77. Adamis D, Lunn M, Martin FC, Treloar A, Gregson N, Hamilton G, et al. Cytokines and IGF-I in delirious and non-delirious acutely ill older medical inpatients. Age Ageing. 2009;38(3):326–251.
78. van Munster BC, Korse CM, de Rooij SE, Bonfrer JM, Zwinderman AH, Korevaar JC. Markers of cerebral damage during delirium in elderly patients with hip fracture. BMC Neurol. 2009;9:21.
79. Lermiss AW, Kalkwaart KJ, Vreeswijk R, van Gool WA, Eikelenboom P. Pre-operative inflammatory markers and the risk of postoperative delirium in elderly patients. Int J Geriatr Psychiatry. 2008;23(9):943–8.
80. Pfister D, Siegemund M, Dell-Kuster S, Smielewski P, Ruegg S, Strebel SP, et al. Cerebral perfusion in sepsis-associated delirium. Crit Care. 2008;12(3):R63.
81. Rudolph JL, Ramlawi B, Kuchel GA, McElhaney JE, Xie D, Sellke FW, et al. Chemokines are associated with delirium after cardiac surgery. J Gerontol Series A-Med Sci. 2008;63(2):184–9.
82. Van Munster BC, Korevaar JC, Zwinderman AH, Levi M, Wiersinga WJ, De Rooij SE. Time-course of cytokines during delirium in elderly patients with hip fractures. J Am Geriatr Soc. 2008;56(9):1704–9.
83. Adamis D, Treloar A, Martin FC, Gregson N, Hamilton G, Macdonald AJD. APOE and cytokines as biological markers for recovery of prevalent delirium in elderly medical inpatients. Int J Geriatr Psychiatry. 2007;22(7):688–94.
84. de Rooij SE, van Munster BC, Korevaar JC, Levi M. Cytokines and acute phase response in delirium. J Psychosom Res. 2007;62(5):521–5.
85. Plaschke K, Hill H, Engelhardt R, Thomas C, von Heken R, Scholz M, et al. EEG changes and serum anticholinergic activity measured in patients with delirium in the intensive care unit. Anaesthesia. 2007;62(12):1217–28.
86. White S, Calver BL, Newsway V, Wade R, Patel S, Bayer A, et al. Enzymes of drug metabolism during delirium. Age Ageing. 2005;34(6):603–8.
87. Wilson K, Beadhurst C, Dowe M, Jackson M, Mottram P. Plasma insulin growth factor-1 and incident delirium in older people. Int J Geriatr Psychiatry. 2005;20(2):154–9.
88. Beloosesky Y, Grinblat J, Pirotsky A, Weiss A, Hendel D. Different C-reactive protein kinetics in post-operative hip-fractured geriatric patients with and without complications. Gerontology. 2004;50(4):216–22.
89. Robertsson B, Blennow K, Basun G, Edman A, Karlsson I, Wallin A, et al. Hyperactivity in the hypothalamic-pituitary-adrenal axis in demented patients with delirium. Int Clin Psychopharmacol. 2001;16(1):59–67.
90. van der Mast RC, van den Broek WW, Fekkes D, Pepplinkhuizen L, Habbema JD. Is delirium after cardiac surgery related to plasma amino acids and physical condition? J Neuropsychiatr Clin Neurosci. 2000;12(1):57–63.
91. van der Mast RC, van den Broek WW, Fekkes D, Pepplinkhuizen L, Habbema JDF. Incidence of and preoperative predictors for delirium after cardiac surgery. J Psychosom Res. 1999;46(5):479–83.
92. Gustafson Y, Olsson T, Asplund K, Hägg E. Acute confusional state (delirium) soon after stroke is associated with hypercortisolism. Cerebrovasc Dis. 1992;2(1):33–8.
93. McIntosh TK, Bush HL, Yeston NS. Beta-endorphin, cortisol and postoperative delirium: a preliminary report. Psychoneuroendocrinology. 1985;10(3):303–13.
94. Amano K, Maeda I, Morita T, Baba M, Miura T, Hama T, et al. C-reactive protein, symptoms and activity of daily living in patients with advanced cancer receiving palliative care. J Cachexia Sarcopenia Muscle. 2017;8(3):487.

95. Demiray G, DeGirmenciGlu S, Ugurlu E, Yaren A. Effects of serum leptin and resistin levels on cancer cachexia in patients with advanced-stage non-small cell lung cancer. Clin Med Insights. 2017;11:1 (no pagination) (1179556917690344).
96. Fogelman DR, Morris J, Xiao L, Hassan M, Vadhan S, Overman M, et al. A predictive model of inflammatory markers and patient-reported symptoms for cachexia in newly diagnosed pancreatic cancer patients. Support Care Cancer. 2017;25(6):1809–17.
97. Luo Y, Kim HS, Kim M, Lee M, Song YS. Elevated plasma fibrinogen levels and prognosis of epithelial ovarian cancer: a cohort study and meta-analysis. J Gynecol Oncol. 2017;28(3.
98. Paulsen O, Laird B, Aass N, Lea T, Fayers P, Kaasa S, et al. The relationship between pro-inflammatory cytokines and pain, appetite and fatigue in patients with advanced cancer. PLoS One. 2017;12(5):e0177920 no pagination.
99. Amano K, Maeda I, Morita T, Miura T, Inoue S, Hiroaga M, et al. Clinical implications of C-reactive protein as a prognostic marker in advanced cancer patients in palliative settings. Eur J Cancer. 2016;55:207.
100. Bye A, Wensaas-Rao N, Iversen PO, Skjegstad G, Holven KB, Ulven S, et al. Alterations in inflammatory biomarkers and energy intake in cancer cachexia: a prospective study in patients with inoperable pancreatic cancer. Med Oncol. 2016;33(6):54.
101. Mitsunaga S, Ikeda M, Shimizu S, Ohno I, Takahashi H, Okuyama H, et al. C-reactive protein level is an indicator of the aggressiveness of advanced pancreatic cancer. Pancreas. 2016;45(1):110–6.
102. Margedo PC, Gioriando A, Gesto M, Navigante A. Relationship between weight loss and parameters of skeletal muscle function in patients with advanced cancer and fatigue. Support Care Cancer. 2016;24(6):3861–6.
103. Rodrigues AR, Trufelli DC, Fonseca F, de Paula LC, Giglio ad. Fatigue in patients with advanced terminal cancer correlates with inflammation, poor quality of life and sleep, and anxiety/depression. Am J Hosp Palliat Med. 2016;33(10):962–7.
104. Sidic D, Plestina S, Sverko-Peternac A, Nikolac N, Simundic AM, Samardzija M. Cancer cachexia, sarcopenia and biochemical markers in patients with advanced non-small cell lung cancer-chemotherapy toxicity and prognostic value. Support Care Cancer. 2016;24(11):4495–502.
105. Wu Y, Li C, Zhao J, Yang L, Liu F, Zheng H, et al. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios predict chemotherapy outcomes and prognosis in patients with colorectal cancer and synchronous liver metastasis. World J Surg Oncol. 2016;14(1):289.
106. Bilir C, Engin H, Can M, Temi YB, Demirtas D. The prognostic role of inflammation and hormones in patients with metastatic cancer with cachexia. Med Oncol. 2015;32(3):56.
107. Miura T, Mitsunaga S, Ikeda M, Shimizu S, Ohno I, Takahashi H, et al. Characterization of patients with advanced pancreatic cancer and high serum interleukin-6 levels. Pancreas. 2015;44(5):756–63.
108. Miura T, Matsumoto Y, Hama T, Amano K, Tei Y, Kikuchi A, et al. Glasgow prognostic score predicts prognosis for cancer patients in palliative settings: a subanalysis of the Japan–prognostic assessment tools validation (J-ProVal) study. Support Care Cancer. 2015;23(11):3349–56.
109. Barrera L, Montes-Servin E, Barrera A, Ramirez-Tirado L, Salinas-Parra F, Bandala-Mendez J, et al. Cytokine profile determined by data-mining analysis set into clusters of non-small-cell lung cancer patients according to prognosis. Ann Oncol. 2014;26(2):428–35.
110. Blakely AM, Heffernan DS, McPhillips J, Ciolfi WG, Miner TJ. Elevated C-reactive protein as a predictor of patient outcomes following palliative surgery. J Surg Oncol. 2014;110(6):651–5.
111. Fujiwara Y, Kobayashi T, Chayahara N, Imamura Y, Toyoda M, Kiyota N, et al. Metabolomics evaluation of serum markers for cachexia and their intra-day variation in patients with advanced pancreatic cancer. PLoS One. 2014;9(11):e113259.
112. Lindenmann J, Neuboeck N, Smolle J, Maier A, Smolle-Juttner FM. The influence of elevated levels of C-reactive protein and hypoalbuminemia on survival in patients with advanced inoperable oesophageal cancer undergoing palliative treatment. Eur Surg. 2014;46:267.
113. Mondello P, Lacquaniti A, Mondello S, Bolignano D, Pitini V, Alcisi C, et al. Emerging markers of cachexia predict survival in cancer patients. BMC Cancer. 2014;14(1):828.
114. Morinaki T, Ishige K, Araki M, Yoshida S, Nishi M, Sato M, et al. Glasgow prognostic score predicts poor prognosis among advanced biliary tract cancer patients with good performance status. Med Oncol. 2014;31(11):287.
115. Szkandera J, Stotz M, Absenger G, Stojakovic T, Samonigg H, Kompan P, et al. Validation of C-reactive protein levels as a prognostic indicator for survival in a large cohort of pancreatic cancer patients. Br J Cancer. 2014;110(1):183.
116. Zhang SY, Zeng D, Peng YH, Yang YX, Zhuang XW, Li ZT, et al. Cancer-related fatigue and chemotherapy-associated adverse effects: correlation with TNF-alpha, IL-1 and 17-hydroxycorticosteroids. Future Oncol. 2014;10(9):1619–26.
117. Jafri SH, Shi R, Mills G. Advance lung cancer inflammation index (ALI) at diagnosis is a prognostic marker in patients with metastatic non-small cell lung cancer (NSCLC): a retrospective review. BMC Cancer. 2013;13(1):158.
118. Laird BJ, McMillan DC, Fayers P, Fearon K, Kaasa S, Fallon MT, et al. The systemic inflammatory response and its relationship to pain and other symptoms in advanced cancer. Oncologist. 2013;18(9):1050–5.
119. Laird BJ, Kaasa S, McMillan DC, Fallon MT, Hjermstad MJ, Fayers P, et al. Prognostic factors in patients with advanced cancer: a comparison of clinicopathological factors and the development of an inflammation-based prognostic system. Clin Cancer Res. 2013;19(19):5456–64.
120. Paiva CE, Paiva BSR. Prevalence, predictors, and prognostic impact of fatigue among Brazilian outpatients with advanced cancers. Support Care Cancer. 2013;21(4):1053–60.
121. Suh SY, Choi YS, Yeom CH, Kwak SM, Yoon HM, Kim DG, et al. Interleukin-6 but not tumour necrosis factor-alpha predicts survival in patients with advanced cancer. Support Care Cancer. 2013;21(11):3071–7.
122. de Raaf P, Sleijfer S, Lamers C, Jager A, Gratama J, van der Rijt C. The association between inflammation and fatigue dimensions in advanced cancer patients and cancer survivors. Palliat Med. 2012;26(4):449–50.
123. Gioulbasanis I, Patrikidou A, Kitikidou K, Papadimitriou K, Vlachostergios PJ, Tsatsaris C, et al. Baseline plasma levels of interleukin-8 in stage IV non-small-cell lung cancer patients: relationship with nutritional status and prognosis. Nutr Cancer. 2012;64(1):41–7.
124. Gulen ST, Karadag F, Karul AB, Kilicarslan N, Ceylan E, Kuman NK, et al. Adipokines and systemic inflammation in weight-losing lung cancer patients. Lung. 2012;190(3):327–32.
125. Heitzer E, Sandner-Kiesling A, Schippinger W, Stolnicheer I, Cupran I, Bitsche S, et al. IL-7, IL-18, MCP-1, MIP1-beta, and OPG as biomarkers for pain treatment response in patients with cancer. Pain Physician. 2012;15(6):499–510.
126. Minton O, Stasser F, Radbruch L, Stone P. Identification of factors associated with fatigue in advanced cancer: a subset analysis of the European palliative care research collaborative computerized symptom assessment data set. J Pain Symptom Manag. 2012;43(2):226–35.
127. Partridge M, Fallon M, Bray C, McMillan D, Brown D, Laird B. Prognostication in advanced cancer: a study examining an inflammation-based score. J Pain Symptom Manag. 2012;44(2):161–7.
128. Pond GR, Armstrong AJ, Wood BA, Lecpold L, Gehky MD, Sonpavde G. Ability of C-reactive protein to complement multiple prognostic classifiers in men with metastatic castration resistant prostate cancer receiving docetaxel-based chemotherapy. BJU Int. 2012;110:11b.
129. Wang D-s, Luo H-y, Mir Q, Wang Z-q, D-s Z, Wang F-h, et al. Comparison of the prognostic values of various inflammation based factors in patients with pancreatic cancer. Med Oncol. 2012;29(5):3092–100.
130. Aydin Y, Keplan I, Gundogdu B, Albayrak B, Turkyilmaz A, Eroglu A. Prognostic importance of serum CRP, prealbumin, and transferrin levels in patients with advanced stage esophageal cancer. Turk Gogus Kalp Damar Cerrahisi Derg. 2011;19(3):388–90.
131. Dev R, Hui D, Dalal S, Nooruddin ZI, Yennurajalingam S, Del Fabbro E, et al. Association between serum cortisol and testosterone levels, opioid therapy, and symptom distress in patients with advanced cancer. J Pain Symptom Manag. 2011;41(6):988–95.
132. Gioulbasanis I, Georgoulias P, Vlachostergios PJ, Baracos V, Ghosh S, Giannousi Z, et al. Mini nutritional assessment (MNA) and biochemical markers of cachexia in metastatic lung cancer patients: interrelations and associations with prognosis. Lung Cancer. 2011;74(3):516–20.
133. Hwang J-E, Kim H-N, Kim D-E, Choi H-J, Jung S-H, Shim H-J, et al. Prognostic significance of a systemic inflammatory response in patients receiving first-line palliative chemotherapy for recurred or metastatic gastric cancer. BMC Cancer. 2011;11(1):489.
134. Kwak SM, Choi YS, Yoon HM, Kim DG, Song SH, Lee YJ, et al. The relationship between interleukin-6, tumor necrosis factor-α, and fatigue in terminally ill cancer patients. Palliat Med. 2012;26(3):275–82.

135. Lee JS, Kwon OY, Choi HS, Hong HP, Ko YG. Serum C-reactive protein level is a predictive factor for 14-day mortality of patients with advanced cancer who present to the emergency department with acute symptoms. Acad Emerg Med. 2011;18(4):440–2.
136. Scheede-Bergdahl C, Watt HL, Trutschnigg B, Kilgour RD, Haggarty A, Lucar E, et al. Is IL-6 the best pro-inflammatory biomarker of clinical outcomes of cancer cachexia? Clin Nutr. 2012;31(1):85–8.
137. Vlachostergios P, Gioulbasanis I, Kamposioras K, Georgoulias P, Baracos V, Ghosh S, et al. Baseline insulin-like growth factor-I plasma levels, systemic inflammation, weight loss and clinical outcome in metastatic non-small cell lung cancer patients. Oncol. 2011;81(2):113–8.
138. Diakowska D, Krzystek-Korpacka M, Markocka-Maczka K, Diakowski W, Matusiewicz M, Grabowski K. Circulating leptin and inflammatory response in esophageal cancer, esophageal cancer-related cachexia-anorexia syndrome (CAS) and non-malignant CAS of the alimentary tract. Cytokine. 2010;51(2):132–7.
139. Meek CL, Wallace AM, Forrest LM, McMillan DC. The relationship between the insulin-like growth factor-1 axis, weight loss, an inflammation-based score and survival in patients with inoperable non-small cell lung cancer. Clin Nutr. 2010;29(2):206–9.
140. Ishizuka M, Nagata H, Takagi K, Kubota K. Influence of inflammation-based prognostic score on mortality of patients undergoing chemotherapy for far advanced or recurrent unresectable colorectal cancer. Ann Surg. 2009;250(2):268–72.
141. Karapanagiotou EM, Polyzos A, Dilana KD, Gratsias I, Boura P, Gkiozos I, et al. Increased serum levels of ghrelin at diagnosis mediate body weight loss in non-small cell lung cancer (NSCLC) patients. Lung Cancer. 2009;66(3):393–8.
142. Paddison JS, Temel JS, Fricchione GL, Pirl WF. Using the differential from complete blood counts as a biomarker of fatigue in advanced non-small-cell lung cancer: an exploratory analysis. Palliat Support Care. 2009;7(2):213–7.
143. Takahashi M, Terashima M, Takagane A, Oyama K, Fujiwara H, Wakabayashi G. Ghrelin and leptin levels in cachectic patients with cancer of the digestive organs. Int J Clin Oncol. 2009;14(4):315–20.
144. Inagaki M, Isono M, Okuyama T, Sugawara Y, Akechi T, Akizuki N, et al. Plasma interleukin-6 and fatigue in terminally ill cancer patients. J Pain Symptom Manag. 2008;35(2):153–61.
145. Karapanagiotou EM, Tsochatzis EA, Dilana KD, Tourkantonis I, Gratsias I, Syrigos KN. The significance of leptin, adiponectin, and resistin serum levels in non-small cell lung cancer (NSCLC). Lung Cancer. 2008;61(3):391–7.
146. Sharma R, Zucknick M, London R, Kacevska M, Liddle C, Clarke SJ. Systemic inflammatory response predicts prognosis in patients with advanced-stage colorectal cancer. Clin Colorectal Cancer. 2008;7(5):331–7.
147. Weryńska B, Kosacka M, Gołecki M, Jankowska R. Leptin serum levels in cachectic and non-cachectic lung cancer patients. Adv Respi Med. 2009;77(6):500–6.
148. Ravasco P, Monteiro-Grillo I, Camilo M. How relevant are cytokines in colorectal cancer wasting? Cancer J. 2007;13(6):392–8.
149. Richey LM, George JR, Couch ME, Kanapkey BK, Yin X, Cannon T, et al. Defining cancer cachexia in head and neck squamous cell carcinoma. Clin Cancer Res. 2007;13(22):6561–7.
150. Suh S-Y, Ahn H-Y. A prospective study on C-reactive protein as a prognostic factor for survival time of terminally ill cancer patients. Support Care Cancer. 2007;15(6):613.
151. Al Murri A, Bartlett J, Canney P, Doughty J, Wilson C, McMillan D. Evaluation of an inflammation-based prognostic score (GPS) in patients with metastatic breast cancer. Br J Cancer. 2006;94(2):227.
152. Kayacan O, Karnak D, Beder S, Güllü E, Tutkak H, Senler FC, et al. Impact of TNF-[alpha] and IL-6 levels on development of cachexia in newly diagnosed NSCLC patients. Am J Clin Oncol. 2006;29(4):328–35.
153. Ramsey S, Lamb GW, Aitchison M, Graham J, McMillan DC. Evaluation of an inflammation-based prognostic score in patients with metastatic renal cancer. Cancer. 2007;109(2):205–12.
154. Di Nisio M, Niers TM, Reitsma PH, Buller HR. Plasma cytokine and P-selectin levels in advanced malignancy: prognostic value and impact of low-molecular weight heparin administration. Cancer. 2005;104(10):2275–81.
155. Rich T, Innominato PF, Boerner J, Mormont MC, Iacobelli S, Baron B, et al. Elevated serum cytokines correlated with altered behavior, serum cortisol rhythm, and dampened 24-hour rest-activity patterns in patients with metastatic colorectal cancer. Clin Cancer Res. 2005;11(5):1757–64.
156. Bolukbas FF, Kilic H, Bolukbas C, Gumus M, Horoz M, Turhal NS, et al. Serum leptin concentration and advanced gastrointestinal cancers: a case controlled study. BMC Cancer. 2004;4(1):29.
157. De Vita F, Romano C, Orditura M, Galizia G, Martinelli E, Lieto E, et al. Interleukin-6 serum level correlates with survival in advanced gastrointestinal cancer patients but is not an independent prognostic indicator. J Interf Cytokine Res. 2001;21(1):45–52.
158. Dülger H, Alici S, Şekeroğlu M, Erkog R, Özbek H, Noyan T, et al. Serum levels of leptin and proinflammatory cytokines in patients with gastrointestinal cancer. Int J Clin Pract. 2004;58(6):545–9.
159. Elahi MM, McMillan DC, McArdle CS, Angerson WJ, Sattar N. Score based on hypoalbuminemia and elevated C-reactive protein predicts survival in patients with advanced gastrointestinal cancer. Nutr Cancer. 2004;48(2):171–3.
160. Jamieson NB, Brown DJ, Wallace AM, McMillan DC. Adiponectin and the systemic inflammatory response in weight-losing patients with non-small cell lung cancer. Cytokine. 2004;27(2-3):90–2.
161. Songur N, Kuru B, Kalkan F, Ozdilekcan C, Cakmak H, Hizel N. Serum interleukin-6 levels correlate with malnutrition and survival in patients with advanced non-small cell lung cancer. Tumori. 2004;90(2):196–200.
162. Scott HR, McMillan DC, Brown DJ, Forrest LM, McArdle CS, Milroy R. A prospective study of the impact of weight loss and the systemic inflammatory response on quality of life in patients with inoperable non-small cell lung cancer. Lung Cancer. 2003;40(3):295–9.
163. Alemán MR, Santolaria F, Batista N, Mena J, González-Reimers E, Milena A, et al. Leptin role in advanced lung cancer. A mediator of the acute phase response or a marker of the status of nutrition? Cytokine. 2002;19(1):21–6.
164. Orditura M, De Vita F, Catalano G, Infusino S, Lieto E, Martinelli E, et al. Elevated serum levels of interleukin-8 in advanced non-small cell lung cancer patients: relationship with prognosis. J Interf Cytokine Res. 2002;22(11):1129–35.
165. Scott H, McMillan D, Forrest L, Brown D, McArdle C, Milroy R. The systemic inflammatory response, weight loss, performance status and survival in patients with inoperable non-small cell lung cancer. Br J Cancer. 2002;87(3):264.
166. Jatoi A, Loprinzi CL, Sloan JA, Klee GG, Windschitl HE. Neuropeptide Y, leptin, and cholecystokinin 8 in patients with advanced cancer and anorexia - a north Central cancer treatment group exploratory investigation. Cancer. 2001;92(3):629–33.
167. Mantovani G, Macciò A, Madeddu C, Mura L, Massa E, Mudu M, et al. Serum values of proinflammatory cytokines are inversely correlated with serum leptin levels in patients with advanced stage cancer at different sites. J Mol Med. 2001;79(7):406–14.
168. Mantovani G, Macciò A, Mura L, Massa E, Mudu MC, Mulas C, et al. Serum levels of leptin and proinflammatory cytokines in patients with advanced-stage cancer at different sites. J Mol Med. 2000;78(10):554–61.
169. Nenova K, Kovatchev D. TNF-A levels in cachectic cancer patients. Arch Hellenic Med. 2000;17(6):619–22.
170. O'Gorman P, McMillan DC, McArdle CS. Longitudinal study of weight, appetite, performance status, and inflammation in advanced gastrointestinal cancer. Nutr Cancer. 1999;35(2):127–9.
171. Okada S, Okusaka T, Ishii H, Kyogoku A, Yoshimori M, Kajimura N, et al. Elevated serum interleukin-6 levels in patients with pancreatic cancer. Jpn J Clin Oncol. 1998;28(1):12–5.
172. Wallace AM, Kelly A, Sattar N, McArdle CS, McMillan DC. Circulating concentrations of "free" leptin in relation to fat mass and appetite in gastrointestinal cancer patients. Nutr Cancer. 2002;44(2):157–60.
173. Maltoni M, Manco P, Cifarna N, Mauro M, Monica I, Gramazio A, et al. Biological indices predictive of survival in 519 Italian terminally ill cancer patients. J Pain Symptom Manag. 1997;13:1.
174. Simons J, Schols A, Campfield L, Wouters E, Saris W. Plasma concentration of total leptin and human lung-cancer-associated cachexia. Clin Sci. 1997;93(3):273–7.
175. Wallace A, Sattar N, McMillan D. Effect of weight loss and the inflammatory response on leptin concentrations in gastrointestinal cancer patients. Clin Cancer Res. 1998;4(12):2977–9.
176. Marcantonio ER, Rudolph JL, Culley D, Crosby G, Alsop D, Inouye SK. Serum biomarkers for delirium. J Gerontol Series A-Med Sci. 2006;61(12):1281–6.
177. Kellum JA, Kong L, Fink MP, Weissfeld LA, Yealy DM, Pinsky MR, et al. Understanding the inflammatory cytokine response in pneumonia and sepsis: results of the genetic and inflammatory markers of sepsis (GenIMS) study. Arch Intern Med. 2007;167(15):1655–63.
178. Sarbal D, Hocaoglu-Emre F, Erdogan S, Bahtiyar N, Olur SC, Mert M. Inflammatory cytokines IL-6 and TNF-α in patients with hip fracture. Osteoporos Int. 2019;30(5):1025–31.

179. Hennessy E, Gormley S, Lopez-Rodriguez AB, Murray C, Murray C, Cunningham C. Systemic TNF-α produces acute cognitive dysfunction and exaggerated sickness behavior when superimposed upon progressive neurodegeneration. Brain Behav Immun. 2017;59:233–44.
180. Khan GH, Geluts N, Dochew N, Layfield R, Atkinson W. Overlap of proteomics biomarkers between women with pre-eclampsia and PCOS: a systematic review and biomarker database integration. Hum Reprod. 2014; 30(1):133–48.
181. Strawbridge R, Young AH, Cleare AJ. Biomarkers for depression: recent insights, current challenges and future prospects. Neuropsychiatr Dis Treat. 2017;13:1245.
182. Cho S-Y, Choi J-H. Biomarkers of sepsis. Infect Chemother. 2014;46(1):1–12.

Publisher's Note

Appendix 1.2

Study 2

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RESEARCH ARTICLE

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Toward best practice methods for delirium biomarker studies: An international modified Delphi study

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Background: Delirium is a serious and distressing neurocognitive condition common in people with advanced illness. The understanding of delirium pathophysiology is limited and largely hypothetical. To accelerate empirical understanding of delirium pathophysiology, robust scientific methods for conducting and reporting delirium biomarker studies are urgently needed. The aim of this study was to develop international consensus on the core elements of high-quality delirium biomarker studies.

Methods: A three-round modified Delphi survey was conducted from February to August 2019. Participants were international researchers experienced in conducting delirium studies from a range of settings (hospital, university, research centres). Round one commenced with open-ended questions developed from results from a prior systematic review and the REMARK (REporting recommendations for tumour MARKer prognostic studies) checklist. Responses were qualitatively analysed, and closed statements were developed. Participants then ranked the importance of these statements using a 5-point Likert scale in rounds 2 and 3. A priori consensus was defined as ≥70% participant agreement. Descriptive statistics for each item were computed including the mean Likert scores, SD and median participant scores.

Results: Twenty-eight participants completed survey round one, 16 completed round two and 19 completed the final round. Consensus was achieved for a total of 60 items.

Conclusion: The Delphi survey identified items that expert researchers agreed were important in the conduct of delirium biomarker studies. These reporting items provide a strong platform for improved methodological quality and opportunities to synthesise future delirium biomarker studies.

KEYWORDS
guidelines, methodology, consensus, pathophysiology

1 | INTRODUCTION

Delirium is a serious, acute and complex neurocognitive condition that is often precipitated by an acute medical event such as infection or surgery. Delirium is characterized by an acute change in attention, awareness and cognition and variously affects memory, language, visuospatial ability, orientation and perception.[1] Delirium is associated with multiple adverse clinical outcomes including high levels of patient and caregiver distress, increased morbidity, mortality and length of hospital stay and significant costs to the healthcare system.[2-6] A systematic review found delirium prevalence in medical in-patients at admission to hospital to range between 10% and 31%, with incidence of new delirium during admission ranging from 3% to 29%. Occurrence rates for delirium per admission ranged between 11% and 42%.[7] Despite the high prevalence and impact of delirium, knowledge of its pathophysiology is largely hypothetical.[8] Hence, biomarker

studies are crucial in this field to accelerate our understanding of delirium biology leading to potential therapies. A biomarker is a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease.[9]

Reporting guidelines currently exist that are relevant to biomarker studies. These are the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) for reporting observational studies,[10] reporting guidelines for body fluid markers in neurologic disorders,[11] the STARD (STAndards for the Reporting of Diagnostic accuracy)[12] and the REMARK (REporting recommendations for tumour MARKer prognostic studies).[13] However, no reporting guidelines currently exist for delirium biomarker studies, and it is not known how well these existing guidelines may be modified to inform optimal delirium biomarker research.

In the absence of reporting guidelines in delirium biomarker research, we applied the REMARK checklist,[13] a reporting guideline for tumour marker prognostic studies, to assess the quality of studies included in a recent systematic review of the overlap of delirium and advanced cancer biomarkers (PROSPERO CRD42017068662). The review found that most of the 151 included articles were of low quality. Unfortunately, despite the volume of studies, their overall low-quality limits the trustworthiness and impact of outcomes, comparability of results and ability to synthesise findings to inform empirical understanding of delirium pathophysiology. The absence of reporting guiddlines for delirium biomarker studies has likely contributed to this identified problem.

Therefore, this study aimed to obtain international consensus from leaders in delirium research, on the core elements for high-quality delirium biomarker studies, to improve our understanding of delirium pathophysiology.

Key Points

- Despite the prevalence and impact of delirium, knowledge of its pathophysiology is largely hypothetical. Better understanding of the pathophysiology of delirium is crucial to develop more effective ways to prevent and treat delirium.
- To understand the pathophysiology of delirium, more robust scientific methodologies for delirium biomarker research are needed.
- There are currently no guidelines for conducting and reporting delirium biomarker studies, which impacts on the individual and overall quality of this body of research. Reporting guidelines would improve the rigor of its methodology and reporting and increase the potential for future studies to be synthesised through meta-analyses.

2 | METHODS

2.1 | Study design

A three-round survey was employed in accordance with the Delphi method.[14]

2.2 | Participants

Those considered eligible were delirium researchers who had investigated delirium in humans, including but not restricted to biomarkers. Researchers with basic science and animal study backgrounds were also eligible if their research focus was on delirium. Expert panel members were required to have delirium research experience in the last 10 years (with no minimum number of years pre-specified), and computer and internet access with an email address to access the online survey. Those who met these eligibility criteria were deemed to have adequate knowledge, expertise, and opportunity to make a meaningful contribution to the topic area.

2.3 | Recruitment

A combination of purposive sampling and snowballing was used to recruit the expert panel.[15,16] Purposive recruitment approaches included (a) email invitation via membership lists of Delirium Societies' (Australasian Delirium Association, American Delirium Society and the European Delirium Association); (b) email invitations through colleagues and professional networks; and (c) researchers identified from journal articles as having experience in delirium biomarker studies. An indirect approach included a Twitter advertisement on the 2019 "World Delirium Awareness Day."[6,7] Snowball sampling was achieved by asking eligible participants and presidents of delirium societies to invite any other eligible researchers who may be interested in taking part in the study, by forwarding the invitation via email.

2.4 | Data collection

Each potential participant was sent an email invitation with a link to the online REDCap survey in three parts: a participant information sheet outlining the study procedures and their involvement in the study, a demographic section and the survey questions. Non-completion of a round did not prohibit participants from participating in the subsequent rounds. Demographic details were collected at the beginning of each round, only once per participant. A reminder email was sent around 14 days following dissemination of each survey round.

2.5 | Round 1

Round 1 aimed to generate a broad range of opinions. This round was informed by results from the quality assessment of a prior systematic

review, and predominantly used an open-ended qualitative method, as in the traditional approach to the Classic Delphi.[14] The initial draft survey of round 1 was piloted by three researchers with sufficient clinical understanding of delirium and knowledge of biomarker research. These researchers were not involved in the Delphi development and were not eligible to be study participants.

In round 1, participants were provided with both open-ended and closed questions about biomarker research in delirium based on each key domain of the REMARK checklist.[13] Participants were also invited to provide comments after each question. The answers from round 1 informed development of a list of statements for round 2 of the Delphi.

2.6 | Round 2

In round 2, 56 statements were reduced by a rating process whereby participants rated each statement on a 5-point Likert scale from 1 (*not important at all*) to 5 (*very important*). Participants were also invited to provide comments and suggest any alternate wording for each statement. Reasons for excluding comments or items suggested by participants were recorded.

2.7 | Round 3

This final round aimed to refine the final list of statements pertaining to recommendations for reporting of delirium biomarker studies. In round 3, participants were sent the survey along with the following: (a) a summary of round 2 statements that reached consensus; (b) a summary of statements that did not reach consensus (which were repeated in this round); and (c) newly suggested statements from participants' comments in round 2. Group ratings were displayed next to each statement, allowing participants to revise the collective response in a blinded way. Participants were asked to provide a new rating on the 5-point Likert scale. Only statements that did not achieve consensus from round 2 were carried into round 3. Round 2 statements that already achieved a consensus were excluded from round 3 but were still presented in the summary for participants to review.

3 | DATA ANALYSIS

3.1 | Round 1

Demographic data from each round were collated and inputted into the IBM Statistical Package for Social Science (SPSS), Version 25. Round 1 open-ended responses were compiled from Excel spreadsheets into Microsoft Word and thematically analysed by the lead author (I.A.D.), with two other reviewers (M.A. and A.M.) providing guidance and oversight of the themes and codes. Reviewers discussed any uncertainties about the coding or themes until an agreement was met. Reasons recorded for excluding or amending comments or items prior to round 2 were that the item/comment (s) were the following:

TABLE 1 Demographic characteristics of Delphi participants (n = 32)

	n (%)
Country of residence	
United States	14 (44)
Europe	11 (34)
United Kingdom	4 (13)
Australia	2 (6)
Latin America	1 (3)
Years in delirium research	
10+	15 (47)
5-10	10 (31)
0-5	7 (22)
Current role	
Clinician/researcher	21 (64)
Researcher	6 (19)
Clinician	5 (15)
Place of work	
Hospital	26
University	22
Research centre	8
Other	1
Main delirium research area	
Clinical trials	22
Epidemiology	14
Health services	9
Implementation/knowledge translation/education	9
Qualitative research	6
Other	2
Number of delirium studies conducted	
10+	15 (47)
5-10	9 (28)
0-5	8 (25)
Number of biomarker studies conducted	
10+	3 (9)
5-10	4 (13)
0-5	25 (78)
Conducted a delirium biomarker study	
Yes	22 (69)
No	10 (31)
Research higher degree (Masters or Doctorate)	
In delirium	9 (28)
In biomarkers	2 (6)
Both	6 (19)
No	15 (47)

1. too vague
2. a misunderstanding of the question
3. not relevant to the topic or study
4. repetitious in meaning or intent
5. already encompassed within another item and/or or better combined with another item

3.2 | Rounds 2 and 3

A target 70% agreement for the score of 4 or more on the 5-point Likert scale for each statement was chosen a priori. REDCap data were exported to SPSS for statistical analysis. Descriptive data for each item were obtained, including the mean Likert scores, SD and the median. Round 2 items with the greatest participant agreement in the very low and low importance categories (Likert score 1 and 2) were deemed unlikely to be included in the list of recommendations; items with the participant agreement in the moderate importance category (Likert score 3) were considered for inclusion in the recommendations, and items with the greatest participant agreement in the high to very high importance category (Likert scores ≥4) were included in the recommendations. Data analysts were blinded to participants' identities.

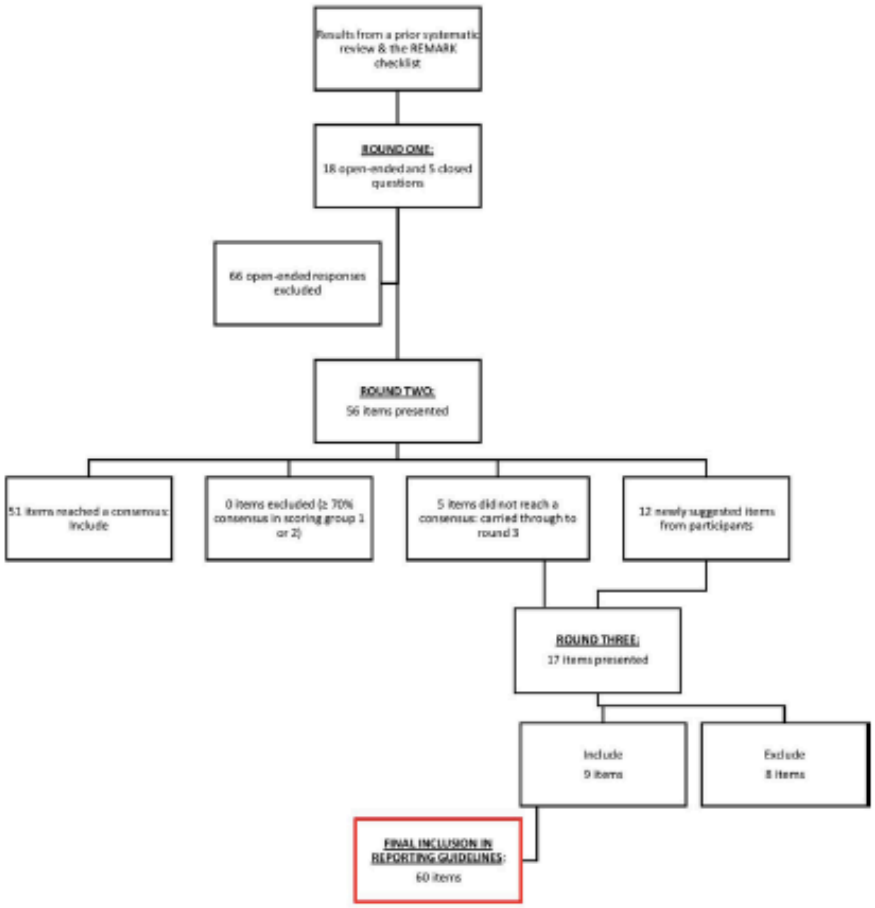

FIGURE 1 Flow chart illustrating the three-stage Delphi process, informed by a prior systematic review

TABLE 2 Summary of ratings for items that reached a ≥70% consensus after three Delphi rounds[a]

Statement	Very important (5)	Moderately important (4)	Not important or unimportant (3)	Slightly important (2)	Not important at all (1)	Mean rating/ Median rating	SD	Total % consensus achieved (category)
In delirium biomarker studies, the study objective statement should be at minimum, include the following key elements								
The biomarker under study (including source)	14 (87.5)	2 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	4.8/5	0.34	87.5% (5)
The time of collection in relation to delirium onset	11 (68.8)	3 (18.8)	2 (12.5)	0 (0.0)	0 (0.0)	4.5/5	0.72	87.6% (5,4)
The clinical endpoint(s) including their definition	13 (81.3)	2 (12.5)	1 (6.3)	0 (0.0)	0 (0.0)	4.6/5	0.79	81.3% (5)
The clinical covariates	9 (45.0)	8 (40.0)	3 (15.0)	0 (0.0)	0 (0.0)	4.3/4	0.73	85% (5,4)
The methods of biomarker collection[b]	9 (45.0)	6 (30.0)	3 (15.0)	1 (5.0)	0 (0.0)	4.2/4	0.91	75% (5,4)
Clarify which delirium pathophysiological theory the study will address	6 (30.0)	10 (50.0)	2 (10.0)	1 (5.0)	1 (5.0)	3.9/4	1.05	80% (5,4)
The biomarker in a delirium study should be:								
Chosen a priori	9 (56.3)	7 (43.8)	0 (0.0)	0 (0.0)	0 (0.0)	4.5/5	0.51	100% (5,4)
Supported by a biologically plausible rationale	12 (75.0)	3 (18.8)	1 (6.3)	0 (0.0)	0 (0.0)	4.6/5	0.60	75% (5)
Supported by a clear hypothesis	10 (62.5)	3 (18.8)	3 (18.8)	0 (0.0)	0 (0.0)	4.4/5	0.81	81.3% (5,4)
Putting practical considerations aside, the type of biological specimen chosen should:								
Be based on the capacity to measure the proposed biological process being evaluated	7 (43.8)	9 (56.3)	0 (0.0)	0 (0.0)	0 (0.0)	4.4/4	0.51	100% (5,4)
Have high specificity and sensitivity	8 (50.0)	7 (43.8)	1 (6.3)	0 (0.0)	0 (0.0)	4.4/4.5	0.62	93.8% (5,4)
In biomarker studies:								
Delirium cases should be diagnosed by a trained assessor or specialist doctor	6 (37.5)	9 (56.3)	1 (6.3)	0 (0.0)	0 (0.0)	4.2/4	0.77	93.8% (5,4)
Delirium should be assessed using a validated delirium diagnosis tool	13 (81.3)	2 (12.5)	1 (6.3)	0 (0.0)	0 (0.0)	4.6/5	1.02	81.3% (5)
Delirium should be prospectively evaluated	8 (50.0)	6 (37.5)	2 (12.5)	0 (0.0)	0 (0.0)	4.4/4.5	0.71	87.5% (5,4)
Adult and paediatric populations should be considered separately	8 (50.0)	5 (31.3)	2 (12.5)	1 (6.3)	0 (0.0)	4.2/4.5	0.93	81.3% (5,4)
In biomarker studies, confounding variables need to:								
Be decided a priori	5 (31.3)	8 (50.0)	3 (18.8)	0 (0.0)	0 (0.0)	4.1/4	0.71	81.3% (5,4)
Take into account the population being studied/the clinical condition	12 (75.0)	4 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	4.7/5	0.44	75% (5)
Be clearly defined and justified	13 (81.3)	3 (18.8)	0 (0.0)	0 (0.0)	0 (0.0)	4.8/5	0.40	81.3% (5)
Be accounted for in the analysis	15 (93.8)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	4.9/5	0.50	93.8% (5)
The minimum clinical covariates that should be taken into account in delirium biomarker studies are:								
Age, gender, concurrent medication, comorbidities, prior cognitive impairment, prior neurological conditions, frailty, delirium risk and delirium precipitants	12 (75.0)	3 (18.8)	1 (6.3)	0 (0.0)	0 (0.0)	4.7/5	0.60	75% (5)

(Continues)

TABLE 2 (Continued)

Statement	Very important (5)	Moderately important (4)	Not important or unimportant (3)	Slightly important (2)	Not important at all (1)	Mean rating/ Median rating	SD	Total % consensus achieved (category)
Illness severity	14 (70.0)	4 (25.0)	1 (5.0)	0 (0.0)	0 (0.0)	4.6/5	0.58	70% (5)
Sepsis	6 (30.0)	9 (45.0)	3 (15.0)	2 (10.0)	0 (0.0)	3.9/4	0.94	75% (5.4)
Inflammation	7 (35.0)	10 (50.0)	1 (5.0)	2 (10.0)	0 (0.0)	4.1/4	0.91	85% (5.4)
The following control groups are appropriate in a delirium biomarker study:								
Participants without delirium	10 (62.5)	5 (31.3)	1 (6.3)	0 (0.0)	0 (0.0)	4.5/5	0.81	93.8% (5.4)
As delirium is a complex clinical condition with many influencing clinical variables several control groups will strengthen the ability to interpret the findings	7 (35.0)	7 (35.0)	3 (15.0)	3 (15.0)	0 (0.0)	3.9/4	1.07	70% (5.4)
Same illness severity with and without delirium	9 (45.0)	8 (40.0)	2 (10.0)	1 (5.0)	0 (0.0)	4.2/4	1.0	85% (5.4)
Delirium superimposed on dementia	6 (30.0)	8 (40.0)	3 (15.0)	1 (5.0)	1 (5.0)	3.7/4	1.2	70% (5.4)
In studies which follow participants longitudinally, appropriate additional comparator groups are:								
Participants with delirium of a shorter duration	4 (25.0)	8 (50.0)	3 (18.8)	1 (6.3)	0 (0.0)	3.9/4	0.85	75% (5.4)
Participants who do not develop delirium	10 (62.5)	4 (25.0)	1 (6.3)	1 (6.3)	0 (0.0)	4.4/5	0.89	87.5% (5.4)
Delirium biomarker studies should support the person with delirium and their proxy decision maker by:								
Clear participant information that explains the study to the person with delirium and/or their proxy decision maker	11 (68.8)	4 (25.0)	1 (6.3)	0 (0.0)	0 (0.0)	4.6/5	0.81	93.8% (5.4)
Clear procedures to assist staff in interacting and supporting the patient during biomarker collection and other data collection	12 (75.0)	2 (12.5)	2 (12.5)	0 (0.0)	0 (0.0)	4.6/5	0.71	75% (5)
The value of the research in lay terms and how it can contribute to the understanding of delirium	12 (75.0)	3 (18.8)	1 (6.3)	0 (0.0)	0 (0.0)	4.6/5	0.80	75% (5)
Having clear processes for informed consent	12 (75.0)	3 (18.8)	1 (6.3)	0 (0.0)	0 (0.0)	4.6/5	0.80	75% (5)
Description of the assay procedure should include the following as a minimum:								
A detailed assay protocol that includes the reagents/ kits used	11 (68.8)	2 (12.5)	2 (12.5)	1 (6.3)	0 (0.0)	4.4/5	0.96	81.3% (5.4)
An assay validation for assay repeatability and robustness	6 (37.5)	6 (37.5)	3 (18.8)	1 (6.3)	0 (0.0)	4.0/4	0.92	75% (5.4)
The inter- and intra-assay coefficients of variation	7 (43.8)	5 (31.3)	2 (12.5)	2 (12.5)	0 (0.0)	4.0/4	1.06	75.0% (5.4)
Methods of preservation, storage and processing of the biological sample	11 (68.8)	3 (18.8)	1 (6.3)	1 (6.3)	0 (0.0)	4.5/5	0.89	87.5% (5.4)
The assay validity	8 (50.0)	7 (43.8)	1 (6.3)	0 (0.0)	0 (0.0)	4.4/4.5	0.62	93.8% (5.4)
The sensitivity limits of the assay	9 (56.3)	6 (37.5)	1 (6.3)	0 (0.0)	0 (0.0)	4.4/5	0.81	93.8% (5.4)
A scoring and reporting protocol	8 (50.0)	6 (37.5)	2 (12.5)	0 (0.0)	0 (0.0)	4.4/4.5	0.71	87.5% (5.4)

(Continues)

TABLE 2 (Continued)

Statement	Very important (5)	Moderately important (4)	Not important or unimportant (3)	Slightly important (2)	Not important at all (1)	Mean rating/ Median rating	SD	Total % consensus achieved (category)
In biomarker studies:								
Blinding of the assay is essential if the clinical outcome is subjective	12 (75.0)	2 (12.5)	1 (6.3)	1 (6.3)	0 (0.0)	4.6/5	0.89	75% (5)
Method of blinding should be explicit	9 (56.3)	4 (25.0)	2 (12.5)	1 (6.3)	0 (0.0)	4.3/5	0.94	81.3% (5.4)
Please indicate your level of agreement with the following statements								
Timing of the sample collection should be determined based on the clinical scenario	6 (37.5)	8 (50.0)	2 (12.5)	0 (0.0)	0 (0.0)	4.2/4	0.68	87.5% (5.4)
Timing of the sample collection should be determined based on the hypothesis being tested	12 (75.0)	3 (18.8)	1 (6.3)	0 (0.0)	0 (0.0)	4.7/5	0.60	75% (5)
In longitudinal sampling of populations AT RISK OF DELIRIUM, it is recommended that samples are collected prior to delirium onset, during delirium episode, and after delirium resolution	9 (56.3)	7 (43.8)	0 (0.0)	0 (0.0)	0 (0.0)	4.6/5	0.51	100% (5.4)
In longitudinal sampling of populations WITH DELIRIUM, it is recommended that samples are collected at delirium onset and again after delirium resolution	6 (37.5)	8 (50.0)	1 (6.3)	1 (6.3)	0 (0.0)	4.2/4	0.83	87.5% (5.4)
Please indicate your level of agreement with the following statements on sample size in a delirium biomarker study.								
Sample size should be decided a priori based on previous studies/pilot data	6 (37.5)	7 (43.8)	2 (12.5)	1 (6.3)	0 (0.0)	4.1/4	0.88	81.3% (5.4)
Sample size should be determined based on the estimated effect size of the biomarker in predicting the outcome	8 (50.0)	6 (37.5)	2 (12.5)	0 (0.0)	0 (0.0)	4.4/4.5	0.71	87.5% (5.4)
The analysis plan should plan for clinical and biomarker missing data due to:								
Clinical issues such as overall deterioration, worsening cognition, and death	11 (68.8)	5 (31.3)	0 (0.0)	0 (0.0)	0 (0.0)	4.7/5	0.47	100% (5.4)
Practical challenges of biomarker collection in people with delirium	12 (75.0)	4 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	4.8/5	0.44	75% (5)
Univariate analyses of biomarker and clinical endpoints of interest should report the following:								
Estimated effect size	6 (37.5)	7 (43.8)	1 (6.3)	0 (0.0)	2 (12.5)	3.9/4	1.2	81.3% (5.4)
Whether biomarker result was dichotomised using a cut-point and/or threshold	11 (68.8)	3 (18.8)	1 (6.3)	0 (0.0)	1 (6.3)	4.4/5	1.09	87.5% (5.4)
How missing data were handled	12 (75.0)	2 (12.5)	1 (6.3)	0 (0.0)	1 (6.3)	4.5/5	1.09	75% (5)
Number of included participants	14 (87.5)	1 (6.3)	0 (0.0)	0 (0.0)	1 (6.3)	4.7/5	1.01	87.5% (5)
Multivariate analyses of biomarker and clinical endpoints of interest should report the following:								
Estimated effect size	8 (50.0)	8 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	4.5/4.5	0.51	100% (5.4)

(Continues)

TABLE 2 (Continued)

Statement	Very important (5)	Moderately important (4)	Not important or unimportant (3)	Slightly important (2)	Not important at all (1)	Mean rating/ Median rating	SD	Total % consensus achieved (category)
Whether biomarker result was dichotomised using a cut-point and/or threshold	11 (68.8)	5 (31.3)	0 (0.0)	0 (0.0)	0 (0.0)	4.7/5	0.47	100% (6.4)
How model assumptions were verified	10 (62.5)	5 (31.3)	1 (6.3)	0 (0.0)	0 (0.0)	5.6/5	0.62	93.8% (6.4)
How missing data were handled	12 (75.0)	3 (18.8)	1 (6.3)	0 (0.0)	0 (0.0)	4.7/5	0.60	75% (6)
Number of included participants	15 (93.8)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	4.9/5	0.25	93.8% (6)
Covariates (including how they were defined)	14 (87.5)	2 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	4.9/5	0.34	87.5% (6)

[a]Italics indicate those that arose from participant suggestions/comments.
[b]One participant did not respond to this statement.

3.3 | Ethical considerations

Ethical approval was obtained from the University of Technology Sydney Human Research Ethics Committee (approval no. ETH18-2673).

4 | RESULTS

4.1 | Participants

Surveys were delivered over three rounds from February to August 2019 via email. Twenty-nine participants completed round 1; however, one participant's data were removed, as it was clear to the authors that the questions had not been understood, and therefore the responses were not able to be coded. Nineteen participants completed round 2, and 20 completed round 3, with a total of 32 participants completing at least one round and 10 completing all three rounds. Participants were from 12 countries (Argentina, Australia, Belgium, Germany, Italy, Norway, Portugal, Sweden, Switzerland, The Netherlands, United Kingdom, and United States). Overall, the expert panel were predominantly clinician researchers (n = 21; 64%), with 47% of participants having over 10 years' experience in delirium research and 47% having conducted more than 10 delirium studies. Twenty-five (78%) of participants had conducted between 0 and 5 biomarker studies, 13% between 5 and 10, and 3 participants (9%) had conducted over 10 biomarker studies. Twenty-two (69%) had conducted a delirium biomarker study, and nine (28%) of participants had a research higher degree in delirium and two (6%) in biomarkers (Table 1).

4.2 | Consensus

The 18 open-ended questions and 5 closed questions of round 1 were grouped and reduced to 56 statements for round 2, with statements adjusted or removed if unclear, repetitive or already encompassed in another statement, not relevant to topic, or better combined with another item. An outline of the process of including items in the final delirium biomarker recommendations is shown in Figure 1. Following round 2, 51 statements reached consensus for inclusion, and 5 statements did not. Twelve newly suggested statements arising from round 2 were carried into round 3, along with the 5 statements that did not reach a consensus (n = 17 items in total). Following round 3, 60 statements reached a consensus, and 8 did not.

The 60 statements that achieved a priori level of consensus for inclusion in the delirium biomarker study reporting guidelines (ie, ≥70% agreement with scores 4 or 5) are shown in Table 2. Table 3 lists the 8 items that did not achieve consensus after 3 rounds of the Delphi. No item received a score of ≤2 and hence was not excluded based on this criteria.

The final list of recommendations is presented in Table 4.

TABLE 3 Summary of ratings for items that did NOT reach a consensus after three rounds of Delphi[a]

Statement	Very important	Moderately important	Not important or unimportant	Slightly important	Not important at all	Mean rating/ Median rating	SD
The following control groups are appropriate in a delirium biomarker study:							
Healthy participants matched by baseline characteristics such as age and gender	3 (15.0)	8 (40.0)	3 (15.0)	5 (25.0)	1 (5.0)	3.3/4.0	1.18
Participants with dementia, without delirium	4 (20.0)	9 (45.0)	5 (25.0)	1 (5.0)	1 (5.0)	3.7/4.0	1.03
In studies which follow participants longitudinally, an appropriate additional comparator group is:							
Participants with less severe delirium	3 (15.0)	6 (30.0)	8 (40.0)	3 (15.0)	0 (0.0)	3.4/3.0	.94
Description of the assay procedure should include:							
Information about where the kit was purchased and whether it was commercially available	4 (20.0)	9 (45.0)	4 (20.0)	3 (15.0)	0 (0.0)	3.7/4.0	.97
The minimum clinical covariates that should be taken into account in delirium biomarker studies are:							
Ethnicity/race	3 (15.0)	6 (30.0)	6 (30.0)	3 (15.0)	2 (10.0)	3.2/3.0	1.20
Education[b]	4 (20.0)	9 (45.0)	3 (15.0)	1 (10.0)	1 (5.0)	3.6/4.0	1.10
Psychiatric history	4 (20.0)	8 (40.0)	4 (20.0)	2 (10.0)	2 (10.0)	3.5/4.0	1.23
Injuries	3 (15.0)	10 (50.0)	6 (30.0)	1 (5.0)	0 (0.0)	3.7/4.0	.78

Note: Italics indicate those that arose from participant suggestions/comments.
[a]Round 3 results shown in this table.
[b]One participant did not respond to this statement.

5 | DISCUSSION

This study presents the first set of delirium-specific recommendations to aid in the conduct and reporting of future delirium biomarker research. Consensus was achieved in 60 items, with a total of 8 items that did not reach a consensus. Based on open-ended findings from round 1 and 2, consensus was not achieved on the more complex methodological aspects of delirium biomarker research, for example, accounting for underlying diseases in patients with delirium.

Despite a large number of emerging delirium biomarker studies, the pathophysiology of delirium is still poorly understood. A concerted effort is required to standardise the methodology used in delirium biomarker studies, in order to progress this fundamental field of research. Inadequate and/or unclear reporting of methodological processes can lead to discrepancies in results, which may be misleading and potentially detrimental.[18] Reporting guidelines are necessary to promote studies that are standardised and reported in a transparent manner to facilitate reliable and consistent interpretation, application and synthesis of study results. A systematic review examining the extent to which journals encourage reporting guidelines found that nearly half of the online instructions to authors mentioned reporting guidelines (19/41 (46%)).[19] Other studies have found that reporting guidelines such as the CONSORT (Consolidated Standards of Reporting Trials) Statement[20] has led to improvements in the reporting rigor, particularly in the method of sequence generation and the allocation concealment, compared to studies that did not adopt the CONSORT.[21]

Current guidelines that focus on different aspects of biomarkers include the REMARK, STARD and CONSORT statements, which are used when the focus is on prognostic biomarkers, diagnostic testing or when conducting randomised controlled trials. However, none of these guidelines are specific to delirium. We therefore utilised the REMARK checklist as a framework to guide in the development of these preliminary recommendations for guidelines. The final items illustrate areas where specific guidance was deemed useful by international delirium experts, to specifically address methodological issues in delirium. Three domains overlap with the REMARK checklist (assay procedures, sample size calculation and univariate and multivariate results), and the remainder are unique to delirium biomarker studies.

5.1 | Limitations and strengths

Several limitations of this study are worth noting. First, some participants in round 1 did not understand the questions which relied on some background knowledge in the biomarker field. This resulted in 66 comments (66/224; 29.4%) that were excluded from round 1. Second, there was noteworthy attrition between rounds, with only 10 participants completing all three rounds. Third, since delirium is a condition which often occurs in the context of other conditions with similar pathophysiological processes, such as cancer, complex questions with multiple competing issues that need to be considered in methodological design are not suited to be reduced down to simple statements within a Delphi method. This requires a more in-depth qualitative approach to identify the nuanced methodological considerations needed. Hence, the guidelines presented in this study may not be universal, and researchers will still need to consider whether there are additional special considerations to be considered when applying them to specific scenarios and settings. Lastly, there is no universally agreed definition of "consensus" for a Delphi. Some argue that 51% agreement on an item is acceptable,[22] while others maintain anywhere from 75%[23] to 100% agreement amongst respondents.[24] It should also be noted that although the Delphi concludes when a consensus has been achieved, the end results are not

TABLE 4 The final list of recommendations for delirium biomarker studies

The study objective should include the following:
The biomarker under study (including source)
The time of collection in relation to delirium onset
The clinical endpoint(s) including their definition
The clinical covariates
The methods of biomarker collection
A description of which delirium pathophysiological theory the study will address
In defining the population:
Delirium cases should be diagnosed by a trained assessor or specialist doctor
Delirium should be assessed using a validated delirium diagnosis tool
Delirium should be prospectively evaluated
Adult and paediatric populations should be considered separately
Delirium biomarker studies should support the person with delirium and their proxy decision maker by:
Providing a clear participant information that explains the study to the person with delirium and/or their proxy decision maker
Providing clear procedures to assist staff in interacting and supporting the patient during biomarker collection and other data collection
Explaining the value of the research in lay terms and how it can contribute to the understanding of delirium
Clear processes for informed consent
When selecting control(s) group: study:
1. As delirium is a complex clinical condition with many influencing clinical variables several control groups will strengthen the ability to interpret the findings
2. The following control groups would be appropriate to consider
a. Participants without delirium
b. Participants with the same illness severity, with and without delirium
c. Participants with delirium superimposed onto dementia
d. In studies which follow participants longitudinally, the following are appropriate additional comparator groups:
a. Participants with delirium of a shorter duration
b. Participants who do not develop delirium
The biomarker in a delirium study should be:
Chosen a priori
Supported by a biologically plausible rationale
Supported by a clear hypothesis
The type of biological specimen chosen should:
Be based on the capacity to measure the proposed biological process being evaluated
Have high specificity and sensitivity
Description of the assay procedure should include the following as a minimum:
A detailed assay protocol that includes the reagents/kits used
An assay validation for assay repeatability and robustness
The inter- and intra-assay coefficients of variation
Methods of preservation, storage and processing of the biological sample
The assay validity
The sensitivity limits of the assay
A scoring and reporting protocol
Blinding of the assay is essential if the clinical outcome is subjective
Method of blinding should be explicit
In biomarker studies, confounding variables need to:
Be decided a priori
Take into account the population being studied/the clinical condition
Be clearly defined and justified
Be accounted for in the analysis

(Continues)

TABLE 4 (Continued)

The minimum clinical covariates that should be taken into account are:
Age, gender, concurrent medication, comorbidities, prior cognitive impairment, illness severity, sepsis, prior neurological conditions, frailty, inflammation, delirium risk and delirium precipitants
Timing of collection
Timing of the sample collection should be determined based on the clinical scenario and/or the hypothesis being tested
In longitudinal sampling of populations AT RISK OF DELIRIUM, it is recommended that samples are collected prior to delirium onset, during delirium episode, and after delirium resolution
In longitudinal sampling of populations WITH DELIRIUM, it is recommended that samples are collected at delirium onset and again after delirium resolution
Sample size
Sample size should be decided a priori based on previous studies/pilot data
Sample size should be determined based on the estimated effect size of the biomarker in predicting the outcome
The analysis plan should plan for clinical and biomarker missing data due to:
Clinical issues such as overall deterioration, worsening cognition, and death
Practical challenges of biomarker collection in people with delirium
Univariate analyses of biomarker and clinical endpoints of interest should report the following:
Estimated effect size
Whether biomarker result was dichotomised using a cut-point and/or threshold
How missing data were handled
Number of included participants
Multivariate analyses of biomarker and clinical endpoints of interest should report the following:
Estimated effect size
Whether biomarker result was dichotomised using a cut-point and/or threshold
How model assumptions were verified
How missing data were handled
Number of included participants
Covariates (including how they were defined)

necessarily the most reliable or appropriate end-product[25] but rather, a majority opinion.[26]

Key strengths include the following: the systematic approach to generate the final items, drawing on both the existing literature from a prior systematic review and expert opinion. Another key strength of this study was the breadth of expertise within the international expert panel, though we acknowledge that we may have not encompassed all possible perspectives. Lastly, although there is no universal agreement of the ideal sample size for Delphi studies, most Delphi's have included between 15 and 20 participants, and the expertise of the panel is considered more important that the size of the sample itself.[14,27,28] Considering the small cohort of expert delirium researchers worldwide, we believe 32 participants was a sufficient sample.[16]

5.2 | Implications for future research and practice

This Delphi study proposes the first set of recommendations to inform development of reporting guidelines for delirium biomarker studies, which can be refined after experience of their utility in practice. The systematic review undertaken by the same authors demonstrated a number of poor quality studies that were likely affected by a lack of guidelines for delirium biomarker research. Developing reporting guidelines was therefore an essential step to improving methodological and reporting rigor, which will increase the potential for future studies to be synthesised through meta-analyses. This Delphi study proposes a preliminary list of 60 items to be considered in these reporting guidelines. To supplement these recommendations, the authors have conducted interviews with experts in the field discussing the key methodological issues that were more complex for which a Delphi approach was not suited. Namely, how to account for other co-existing conditions (eg, cancer or sepsis) that plausibly impact on the pathophysiological and/or biological findings. Likewise, the practicalities of obtaining biomarkers from people with delirium for research were another issue that arose from this study which was explored in depth in a follow-up interview study. Ongoing international collaboration will be needed to achieve a tighter consensus.

6 | CONCLUSION

This study presents the first step towards development of reporting guidelines for delirium biomarker studies through a rigorously

conducted Delphi survey of international experts in delirium research. Results will support the development of greater methodological rigor in future delirium biomarker research, which will ultimately contribute to better understanding of the pathophysiology of delirium.

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CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

All data generated or analysed in this study are included within this manuscript.

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REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM-5)*. Arlington, VA: American Psychiatric Publisher; 2013.
2. Brajtman S. The impact on the family of terminal restlessness and its management. *Palliat Med*. 2003;17(5):454-460.
3. Bruera E, Bush SH, Willey J, et al. Impact of delirium and recall on the level of distress in patients with advanced cancer and their family caregivers. *Cancer*. 2009;115(9):2004-2012.
4. Salluh JI, Wang H, Schneider EB, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. *Br Med J*. 2015; 350:h2538.
5. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, Van Gool WA. Delirium in elderly patients and the risk of post-discharge mortality, institutionalization, and dementia: a meta-analysis. *JAMA*. 2010;304(4):443-451.
6. Pezzullo L, Streatfeild J, Hickson J, Teodorczuk A, Agar MR, Caplan GA. Economic impact of delirium in Australia: a cost of illness study. *BMJ Open*. 2019;9(9):e027514.
7. Siddiqi N, House A, Holmes J. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. *Age Ageing*. 2006; 35(4):350-364.
8. Maldonado JR. Delirium pathophysiology: an updated hypothesis of the etiology of acute brain failure. *Int J Geriatr Psychiatr*. 2017;33(11): 1428-1457.
9. National Cancer Institute. NCI Dictionary of Cancer Terms. https://www.cancer.gov/publications/dictionaries/cancer-terms/?CdrID=45618. Accessed November 28, 2017.
10. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Int J Surg*. 2014; 12(12):1495-1499.
11. Gnanapavan S, Hegen H, Khalil M, et al. Guidelines for uniform reporting of body fluid biomarker studies in neurologic disorders. *Neurology*. 2014;83(13):1210-1216.
12. Bossuyt PM, Reitsma JB, Bruns DE, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *Radiology*. 2015;277(3):826-832.
13. Altman DG, McShane LM, Sauerbrei W, Taube SE. Reporting recommendations for tumor marker prognostic studies (REMARK): explanation and elaboration. *BMC Med*. 2012;10(1):51.
14. Hsu C-C, Sandford BA. The Delphi technique: making sense of consensus. *Pract Assess Res Eval*. 2007;12(10):1-8.
15. Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. *J Adv Nurs*. 2000;32(4):1008-1015.
16. Keeney S, McKenna H, Hasson F. *The Delphi Technique in Nursing and Health Research*. Oxford: John Wiley & Sons; 2011.
17. iDelirium. The International Federation of Delirium Societies. 2019. http://www.idelirium.org/. Accessed October 2, 2019.
18. Simera I, Moher D, Hirst A, Hoey J, Schulz KF, Altman DG. Transparent and accurate reporting increases reliability, utility, and impact of your research: reporting guidelines and the EQUATOR Network. *BMC Med*. 2010;8(1):24.
19. Hirst A, Altman DG. Are peer reviewers encouraged to use reporting guidelines? A survey of 116 health research journals. *PLoS One*. 2012; 7(4):e35621.
20. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMC Med*. 2010;8(1):18.
21. Plint AC, Moher D, Morrison A, et al. Does the CONSORT checklist improve the quality of reports of randomised controlled trials? A systematic review. *Med J Aust*. 2006;185(5):263-267.
22. Loughlin KG, Moore LF. Using Delphi to achieve congruent objectives and activities in a pediatrics department. *J Med Educ*. 1979;54(2): 101-106.
23. Keeney S, Hasson F, McKenna H. Consulting the oracle: ten lessons from using the Delphi technique in nursing research. *J Adv Nurs*. 2006;53(2):205-212.
24. Williams PL, Webb C. The Delphi technique: a methodological discussion. *J Adv Nurs*. 1994;19(1):180-186.
25. Keeney S, Hasson F, McKenna HP. A critical review of the Delphi technique as a research methodology for nursing. *Int J Nurs Stud*. 2001;38(2):195-200.
26. Rauch W. The decision delphi. *Technol Forecast Soc Change*. 1979;15 (3):159-169.
27. Murphy M, Black N, Lamping D, et al. Consensus development methods, and their use in clinical guideline development. *Health Technol Assess*. 1998;2(3):i-88.
28. Okoli C, Pawlowski SD. The Delphi method as a research tool: an example, design considerations and applications. *Inform Manag*. 2004; 42(1):15-29.

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Appendix 1.3

Study 3

Amgarth-Duff, I., Hosie, AM., Caplan, G., Agar, M. Delirium researchers' perspectives of the challenges in delirium biomarker research: A qualitative study. *PLoS ONE*. 2021; 16(4):e0243254.

PLOS ONE

RESEARCH ARTICLE

Delirium researchers' perspectives of the challenges in delirium biomarker research: A qualitative study

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Data Availability Statement: The data for this study consists of transcripts of 15 participants that contain identifying information. The data cannot be shared publicly due concerns of participant confidentiality and ethics requirements. Interviews were confidential to enable freedom of expression by participants, and participants consented to the study with the understanding that only de-identified quotations would be made public, not the entirety of the transcripts. Therefore, only illustrative quotes from the transcripts have been included in this paper. Data access requests may be made to

Abstract

Background

Despite the prevalence and impact of delirium, its pathophysiology remains unclear. In order to advance this field of research, robust scientific methodology is required, yet quality of reporting in this field of research has been highly inconsistent. Delirium biomarker research poses several challenges, none of which have been documented in the literature before. The aim of this study was to explore the perspectives of delirium researchers about key methodological issues in delirium biomarker research.

Methods

Following a Delphi study with delirium experts resulting in 60 recommendations for reporting delirium biomarker studies, semi-structured interviews with international delirium researchers were conducted. Interviews were audio-taped and transcribed verbatim, followed by thematic analysis of the qualitative data.

Results

Fifteen participants were interviewed between August and November 2019. Most were male (n = 12; 75%), clinician researchers (n = 13; 86%), and had more than ten years' experience in conducting delirium research (n = 9; 60%). Analysis revealed two major themes and ten sub-themes, outlining key considerations to advance the field of delirium biomarker research. The major themes were: 1) Practical and scientific challenges of delirium biomarker research: stagnation versus driving improved methods and reporting; and 2) Valuing delirium research through investment and collaboration.

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Conclusion

Findings identified a range of factors that contribute to the practical and ethical challenges of conducting delirium biomarker research, which have not previously been explicitly acknowledged or reported. A clear vision for collaborative efforts to enhance research quality for improved impact was also presented by the delirium researchers. This work complements the preceding Delphi and together these studies provide an in-depth understanding of what is needed in the field to inform and improve methods and reporting of delirium biomarker research.

Introduction

Delirium is a common, serious and complex neurocognitive condition which is often precipitated by medical illness and hospitalisation [1]. The hallmark features of delirium include changes in attention, awareness and cognition, which variously affect memory, language and visuospatial ability, orientation and perception [2]. Delirium is associated with multiple adverse clinical outcomes including high levels of patient and caregiver distress, significant morbidity and mortality, impairment in activities of daily living, and significant costs to the healthcare system [3–6].

Delirium prevalence in medical in-patients at admission to hospital has been shown to range between 10 and 31%, with incidence of new delirium during admission ranging from 3 to 29% [7]. Occurrence rates for delirium per admission ranged between 11 and 42% [7]. Despite the high prevalence and impact of delirium, knowledge of its pathophysiology is unclear. Current hypotheses include: neuronal ageing, neuroinflammation, oxidative stress, neuroendocrine dysregulation, and disruption to the circadian rhythm [8]. To date, there has been remarkably high heterogeneity of delirium biomarker findings addressing these hypotheses. Other challenges to understanding include unsettled questions about whether delirium represents a single, unified physiological condition or whether there are physiologically discrete subtypes [9]; and ongoing terminological confusion (e.g., delirium vs acute encephalopathy) that drives specialty-specific silos [10]. These high-level issues in the conceptualization of delirium mean that high quality methodological approaches to biomarker research are critical to accelerate understanding of delirium pathophysiology in order to lead to potential therapies.

However, a systematic review of biomarkers in delirium by Amgarth-Duff et al. (2020) [11] highlighted many quality issues in the reporting of delirium biomarker studies. The overall low quality of studies has limited the reliability of outcomes, comparability of results, and ability to synthesise results to develop empirical understanding of delirium pathophysiology. This poor quality reporting has likely contributed to heterogeneity of findings and biological and conceptual uncertainty [12]. In response to the need to improve the field of delirium pathophysiology, a Delphi study was conducted [13] to gather opinions of international experts on delirium research methodology that resulted in a list of reporting guidelines for future delirium biomarker studies. To supplement these recommendations, interviews with Delphi participants and other delirium researchers were then undertaken for an in-depth exploration into the more complex aspects of biomarker study methods and those with a range of methodological options. The consensus and primarily quantitative approach of the Delphi method was not suited to fully explore these aspects; and, furthermore our present goal was not to obtain recommendations but rather to understand the key considerations and the reasons underpinning

them. Therefore, the aim of this study was to explore the perspectives of delirium researchers about key methodological issues in delirium biomarker research.

Methods

Design

A qualitative study using semi-structured interviews reported in accordance with the Consolidated Criteria for Reporting Qualitative Research (COREQ) [14].

Participants

Eligible participants were researchers, clinicians and basic scientists with experience in delirium research in either humans or animals, including but not restricted to biomarker research. There was no pre-specified minimum number of years of clinical or research experience; however, experience in delirium research was required to have been in the last ten years to ensure recent knowledge of the study topic.

Recruitment

Purposive sampling was employed whereby potential participants were actively selected to take part [15]. This was achieved by emailing the international delirium researchers who completed the final round of the Delphi study [13] and other delirium researchers who were not involved in the Delphi process (n = 27) and asking them to participate in a semi-structured interview. Delirium researchers were identified by authorship of relevant papers in the field of delirium, as well as through the lead researchers' supervisory networks. Snowball sampling [16] was also employed by asking invitees whether they knew any other relevant persons who may be interested in participation. Those who indicated willingness to participate were emailed a participant information sheet and a consent form by the researcher (IAD), which was required to be signed and sent back prior to the interviews taking place. The participant information sheet explained the aim of the study: general content to be discussed, anticipated length of the interview, measures for privacy and confidentiality, and use of data for academic and research purposes.

Data collection

The interview guide was aligned with the key findings from the earlier Delphi study, while also allowing other topics to arise [13] (Box 1). The interviews were conducted individually, limiting the influence of group bias. The three key areas explored were: 1) the practical challenges of conducting delirium biomarker research, and how they can be overcome; 2) how to account for underlying conditions that are present in many patients with delirium; and 3) the key gaps

Box 1. Interview guide.
1. Delirium is a condition that often occurs in the context of other conditions with similar pathophysiological processes. What are your thoughts on accounting for co-existing conditions such as cancer in delirium biomarker studies?
2. Delirium biomarker research poses many practical challenges. In your experience, what some of the key challenges and some ways to overcome these challenges?
3. Where do you think current biomarker studies are falling short?
4. Do you have any comments on the Delphi statements? (for Delphi participants only)
5. Is there anything else you would like to add before we finish up?

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and methodological shortcomings in current delirium biomarker studies. Questions were open-ended and designed to gain an in-depth understanding of the challenges and nuances of delirium biomarker methodology. The interview guide was piloted with two clinicians who did not formally take part in an interview. The first had extensive experience in delirium research, and the other had clinical experience of caring for patients with delirium. The final interview guide is presented in Box 1.

All interviews were conducted by the lead author (IAD), a female research assistant and PhD candidate who holds undergraduate and honours qualifications in biomedical science. IAD has prior interviewing and qualitative analysis experience and an in-depth knowledge of existing deficiencies in the quality of reporting of delirium biomarker research [11], but no prior experience of conducting biomarker research. There were no pre-existing relationships between IAD and participants, although the remaining authors knew some of the participants through delirium research collaborations, conferences and advocacy networks. IAD had minimal contact with participants from the time of the Delphi through to the interviews, with the exception of scheduling interviews over email. During telephone interviews, IAD was located in a private office. Data collection continued until no new information emerged (i.e. data saturation). All interviews were audio recorded and transcribed verbatim in a de-identified format.

Data analysis

A combination of inductive and deductive thematic data analysis [12] was used, as follows:

Deductive thematic analysis. Firstly, key areas identified in Round 1 qualitative analysis of the modified Delphi study [13] that were too complex to be resolved through a consensus process (and therefore required a more in-depth analysis) formed the framework for the interview guide. The lead author (IAD) familiarised herself with the data through the transcription process and rereading of the final transcripts. Line-by-line coding of the transcripts was conducted, and a coding tree was developed to elucidate categories. Categories were then collapsed into themes. To ensure rigour, preliminary themes were independently identified by two researches (IAD and AH) and refined collaboratively until the final themes and sub-themes were established.

Inductive thematic analysis. Initial data coding was guided by the semi-structured interview questions, with codes and collated data examined for potential sub-themes. Codes were considered important if they were mentioned more than once. IAD identified preliminary sub-themes, that were then refined through an iterative process until the final sub-themes were confirmed by a second researcher (AH).

Data were managed using NVIVO QSR International Pty Ltd. Version 12 software package.

Trustworthiness of the data

The procedures used in this study were guided by the four general types of trustworthiness in qualitative research, namely: credibility, transferability, dependability and confirmability. Trustworthiness of the data was achieved by using purposive sampling, targeting delirium researchers from a broad range of contexts and countries. The voices of the participants were widely represented in the quotes which supported the themes and achieved transparently in the data interpretation. Discussion among co-authors were also used to enhance the trustworthiness of the data analysis.

Ethical considerations

Ethical approval for the interviews was obtained from the University of Technology Human Research Ethics Committee on 25/01/2019 (HREC ETH18-2673).

Participant lists were stored on a password protected computer and all participant names were removed from the data transcripts. Participant confidentiality, privacy and anonymity were ensured through the allocation of participant ID codes in the transcripts and manuscript. Data were only accessible to the lead author (IAD) and de-identified data were only shared with the other authors (MA, AH and GC) for their input into analysis and interpretation.

Findings

Fifteen delirium researchers participated in semi-structured interviews between August and November 2019. Most participants were male (n = 12;75%), clinician/researchers (n = 13;86%), had conducted five or more delirium studies (n = 12;80%) and had more than 10 years' experience in delirium research (n = 9;60%). Participants were from Europe (n = 7), USA (n = 3), Australia (n = 2), the United Kingdom (UK) (n = 2) and South America (n = 1). Demographic characteristics of participants are outlined in Table 1. Although participants had the option of attending a face-to-face or a telephone interview, all participants opted for a telephone interview. Interview duration ranged from 18–80 minutes (mean 37 (±16)).

Thematic analysis resulted in two major themes and ten sub-themes.

1. Practical and scientific challenges of delirium biomarker research: stagnation versus driving improved methods and reporting
   a. Accuracy of diagnostic assessment of delirium

Table 1. Participant demographics (n = 15).

	n (%)
Gender	
Male	12 (80)
Female	3 (20)
Continent	
Europe	6 (40)
USA	4 (27)
Australia	2 (13)
UK	2 (13)
South America	1 (7)
Years in delirium research	
10+	9 (60)
5–10	3 (20)
1–5	3 (20)
Current role	
Clinician/researcher	13 (87)
Researcher	2 (13)
Number of delirium studies conducted	
10+	7 (47)
5–10	5 (33)
1–5	3 (20)
Number of biomarker studies conducted	
10+	3 (20)
5–10	2 (13)
1–5	5 (33)
0	5 (33)

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b. Delirium superimposed on dementia (DSD)

c. Hypothesis driven

d. Limited infrastructure and resource investment

e. Fluctuating nature of delirium means time point of biomarker collection is a crucial consideration

f. Collecting CSF and imaging in people with delirium

g. Accounting for the complexity/biology of the whole person

h. Standardise delirium biomarker research

2. Valuing delirium research through investment and collaboration:

a. Ethics committee barriers

b. Transdisciplinary collaboration

Practical and scientific challenges of delirium biomarker research: Stagnation versus driving improved methods and reporting

Participants generally asserted that delirium biomarker research is an extremely difficult and complex field:

"Yes well the hard thing with this is it is such a complex area and no one actually knows. People know what you have to do but they don't know how to get there. It's very difficult. It's a very grey area." (P09)

Some expressed a sense of frustration, stagnation and pessimism in the field, due to the complexities, challenges and overall uncertainty:

"It's a difficult field. There is quite a lot of frustration. There are no quick wins. There is no money coming into the research. I'm not frustrated but I am seeing more difficulties and I am not sure how to get around them in the long run because ethics committees get more difficult, money gets scarce, the pressure of clinical work [. . .] I'm such a pessimist! But that's the way I see the course of delirium research going in our institution." (P03)

The need to branch out from siloed investigations and from biomarkers already shown to be associated with delirium was noted:

"In the 1940's they found similar things to us now. And it's like. . . ok let's move forward! [. . .] I think there is some element of reconfirming. But I also think there are some elements of splitting it into medical delirium, or ICU delirium–it's important but we have kind of just got so into that that we have delirium in the cardiac population, delirium in the vascular population, and delirium in. . .you know. We have so many of these little pocket categories. We are reconfirming results because we are interested to see if it's the same in those populations which is good but I also think it's kind of not leading to a huge mass of knowledge [. . .] I think it's time we either need to branch out, or use a different method." (P07)

Delirium biomarker research was perceived to have been a "*hype*" that has since been dulled as there have been no "*quick wins*" (*P03*), which ironically had become a short-term enterprise:

"Delirium is something like a hype. Everyone was very excited when the first paper came out–the one from the States, but it's gone a bit quiet since then because I think we all realise it's not going to be a quick win. So we try to focus on something that is easy to sell." (P03)

1a. Accuracy of diagnostic assessment of delirium. Participants perceived clinical recognition of delirium to be generally poor, adding to the difficulties of timely diagnosis:

"The downside is that I'm seeing a very small percentage of people that need to be seen. Because they're not recognized. People think 'oh they're old' or 'they have dementia' without even knowing if they have dementia. Or 'oh they have been in intensive care, of course they are going to be confused.' So outside of the geriatric medicine it's quite challenging." (P13)

It appeared that there were conflicting processes for delirium assessment and that most identification of delirium for research purposes relied on clinicians' identification of delirium, rather than researcher assessment. This was seen as problematic because participants felt they could not rely on the accuracy of clinicians' recognition and assessment of delirium:

"The first is how to classify patients having delirium or not. Because we have to define whether the patient has delirium and sometimes when we are assessing the patient, he has no delirium, but we have previous reports from the nursing staff or from clinical records that the day before he was on delirium. So it's difficult to classify this type of patient." (P10)

Participants readily acknowledged the difficulty of precisely defining delirium, noting that it is a syndrome that varies from person to person:

"Because delirium is a set of signs and symptoms and it's not necessarily a diagnosis that you make with histopathology or with very specific lab tests. So you may not detect delirium until a certain time point but that doesn't mean the brain wasn't injured prior to that time point, so there is a lot of uncertainty about when delirium started and when it's resolved–these make it very challenging." (P12)

Others highlighted uncertainties with the classification of sub-syndromal delirium, noting that these individuals are often placed in the 'control group' (i.e. no delirium) in delirium biomarker studies:

"I think when you use the binary of delirium–the yes/no it is because there can be symptoms present- like sub-syndromal delirium–and they're not going to sell it by the full-blown delirium. [. . .] I think understanding the symptom burden at the time of the biomarker being drawn is really important [. . .] maybe they are fluctuating and have some disorganised thinking but they don't have inattention—so technically they can't qualify as having delirium but some can certainly argue that there definitely is some brain dysfunction going on. Therefore, if they do not have a proper diagnosis of delirium at the time of blood draw then they would be categorised as non-delirious. So it's introducing a lot of noise into the data." (P07)

1b. Delirium superimposed on dementia (DSD). DSD was a significant challenge mentioned by several participants, and the importance of adjusting for dementia in all delirium biomarker studies was highlighted:

"If you are doing biomarker studies in delirium you really need to have a picture of the dementia status of the patient both because dementia is the strongest risk factor for delirium

and because dementia also impacts on the biomarkers that you want to measure and sometimes the relation is in the opposite direction [. . .] So if you don't adjust for dementia in your analysis then they will level one another out." (P11)

The need to have multiple control groups in delirium biomarker studies to understand which biomarkers are affected by dementia was identified:

"Well that's why we are doing this study. . .to distinguish. We are classifying patients into four groups. So we have patients who are totally normal, with no delirium and no dementia. And then we have patients with dementia and delirium, then dementia without delirium and also patients with no dementia and [with] delirium. So we can compare the effects of delirium superimposed on dementia." (P10)

1c. Hypothesis driven. The importance of taking into consideration the underlying biology of delirium by testing for a hypothesis was discussed. It was noted that *"there isn't any thought going into it" (P15)* including about which biomarkers were being studied and why:

"People are doing these studies with no eye on the biology. I mean I find it really frustrating [. . .] Everyone is going–'Ok we will just get this kit, put the 27 chemokines or cytokines on there, bang them on', but there isn't any thought going into it. For me, it's a huge problem because no one is actually testing a hypothesis. I think that not enough biomarker studies have a real clear guiding principle, and that is a hypothesis that they are testing. Because if you are testing a hypothesis then you have to think about what it would take to provide support to the hypothesis, or to refute the hypothesis. I just feel that no one states a clear hypothesis, no one is studying a hypothesis so we just have very weak associations." (P15)

One participant noted that authors often concluded that there was a 'dysregulation' in inflammatory markers, without taking into account any *priori* hypothesis. The need to clearly state and define a hypothesis was perceived as one reason for weak associations in delirium biomarker studies:

"And it means that if they do a panel of 27 markers and only 2 of them change, then they can just say 'this provides evidence for inflammatory dysregulation in delirium'–and that's of no value whatsoever, because if you look at 27 things then statistically at least one of them will change by chance. And therefore you are going to find something and if it goes up or down and you don't really care which, because you can say 'dysregulation' either way and that means you're going into a paper with zero hypothesis, you're just saying throw it at the wall [. . .] I find it very infuriating- those studies are not contributing to the knowledge of delirium." (P15)

1d. Limited infrastructure and resource investment. The difficulties of conducting biomarker research without appropriate infrastructure was perceived as a potential barrier to rigorous delirium biomarker research:

"I guess it's difficult to do collection of samples for biomarker research or any kind when you don't have the infrastructure. We have only just got a minus 80 freezer so basically if you were in a place that is not an academic centre and they haven't given you a shelf for research samples that can be tricky [. . .] It's not impossible but it's obviously useful to do research outside of academic." (P6)

Whereas another participant believed that there are fundamental principles of conducting and reporting delirium biomarker studies that should be adhered to if the results are to inform the field, regardless of funding.

"I guess it's a resource argument. But I disagree, because if we aren't following some sort of guidelines then we are really doing our patients a disservice because we are not going to make any progress [. . .] Whenever you draw a biomarker you should follow the same steps regardless of whether you have funding or not. You're not saying what assay they should use, you're saying when you write up your findings you need to share which assay and how they did it. I don't see how you need money for that." (P07)

1e. Fluctuating nature of delirium means time point of biomarker collection is a crucial consideration. Several participants acknowledged the great challenge with ensuring the right timing of biomarker collection due to the fluctuating nature of delirium:

"They're difficult. Essentially because delirium is normally fixed pretty quickly around the hospital environment, especially around geriatrics. There is a small window of finding those patients." (P01)

Some highlighted the need for longitudinal samples to track delirium over time:

"And then you need to follow the patient, ideally several times a day to be safe. Because delirium episodes can be for maybe some hours, and it can develop during the weekend or during the night and if you don't have a plan for how you are going to assess this information then you will lose it and falsely classify the patient as non-delirious." (P11)

However, other participants thought that longitudinal sampling was not always feasible:

"You need to make a system where you still are able to pick up the CSF the day it comes and that is very hard unless you want to employ a person to be at the hospital 24/7—it will be extremely expensive." (P11)

1f. Collecting CSF and imaging in people with delirium. CSF was considered the 'gold standard' in delirium biomarker research, due to the proximity to the brain, providing an advantage over blood. Despite most participants believing that CSF collection posed too many practical challenges, others emphasised the need for more CSF sampling, noting that it was more likely to directly reflect brain processes during delirium:

"So the first problem is, in my opinion, you really need CSF. You cannot do delirium biomarker studies in blood. Well you can, but there are not so many good candidates for biomarkers in blood that give you good information about the brain." (P11)

Yet most participants spoke about the difficulties of CSF collection via lumbar puncture, namely its invasiveness and burden on patients:

"CSF is not easy to get hold of because you need to do a lumbar puncture which is considered invasive." (P11)

Similarly, despite the great opportunity that neuroimaging has to offer, several participants focused on the practical challenges of imaging studies and the difficulties associated with undertaking a PET scan when a patient is agitated:

"Yes well you can't do a PET during the delirium, you would have to wait for the delirium to be resolved so that you can coach him through a PET session." (P03)

For this reason, there was a perceived bias towards hypoactive subtypes in PET studies, resulting in unrepresentative samples:

"Yes that's part of the other problems. We tend to have much more of a bias for the hypoactive delirium [in imaging studies]." (P01)

1g. Accounting for the complexity/biology of the person as a whole. Majority of participants commented on the need to create a homogenous and "*clean*" cohort, acknowledging that people with delirium, particularly in the ICU, often had several underlying conditions affecting the results:

"I think you want to have a really clean cohort and not too many comorbidities so if you want to come up with a biomarker that you want to associate with the disease process [. . .] we need cleaner cohorts so we can isolate a biomarker that is specific to delirium." (P09)

In contrast, other participants concurred that the next step to broaden delirium biomarker studies is to biomarkers across several settings:

"Well repeating it in more ICU patients might not be that helpful. For instance, it's a lot easier for me to do it in the ICU because that's where a lot of my research lies. If we really find something that hits then you—start looking at that biomarker in other populations. And if it's hitting across multiple [populations] then that gives you a lot more confidence that it's actually specific to delirium, right?" (P02)

One participant argued that *"existing brain state is going to be the key determinant of whether those acute changes are enough to trigger delirium" (P15)*, therefore emphasising the need to obtain true baseline measurements. Not having a precise baseline was considered a major shortcoming in delirium biomarker studies:

"I think a key practical challenge with delirium is that we don't have baselines [. . .] that's particularly important for somebody with my mindset because I think your brain state before delirium is the major predictor of who will get delirium and how badly they will be affected. So the severity of the acute insult is obviously a major determinant, but who is vulnerable to having delirium in those situations—we learn about that by having a baseline." (P15)

The surgical space was considered the best setting for conducting delirium biomarker research with respect to having true baseline measurements:

"I would say the best cohort is probably peri-operative and post-operative because you know exactly what kind of injury is happening and when it is happening and you can have a biomarker before the injury and then you can have the biomarker after the insult." (P09)

Some participants asserted that patients in this setting generally had less co-existing conditions that can influence the results and therefore can provide a more accurate depiction of the specific biomarkers for delirium:

"You should need to take patients perhaps in surgery. So the hip fracture patient group is a possible patient group because they break their hips and you can distinguish these biomarkers that come from the hip fracture and those that come from the delirium so this is a very interesting population. Normally you don't have sepsis. Normally you don't have cancer or something like that." (P08)

On the other hand, others emphasised that the prevalence of delirium in this group was much lower, which subsequently introduces a selection bias:

"If you do cognitive studies in elective surgery patients you will always have a selection bias. So if we look at the patients who participate in our studies they are cognitive at baseline, pre operatively, they are much better. . .three points lower . . .than if you take a random sample of the patients we treat here and that puts you in an awkward position. So there is a methodological flaw right from the start." (P03)

The heterogeneity of delirium causation was considered a major challenge which varied from person to person. The common approach of relying on clinical identification of delirium left people uncertain:

"Delirium is so multifactorial so if you take an ICU patient, you have so many possible pathophysiological mechanisms that will lead to delirium [. . .] That's why it's so heterogeneous and why it will never have a magic bullet or an overall approach to the problem. It's different in every patient. In every patient, it's his personal mix of mechanisms to go into delirium. That makes therapy so difficult because there are so many underlying causes [. . .] so there are several mechanisms that lead to delirium that makes standardisation in studies nearly impossible." (P03)

When asked about accounting for underlying conditions present in people with delirium, participants acknowledged that, as a whole, delirium researchers have thus far inadequately tackled this issue:

"Nobody is doing it (accounting for underlying conditions) and nobody knows what to do about it so it's really good you are writing this. It will give some ideas to people." (P09)

1h. Standardisation of delirium biomarker research. Participants reflected on the quality of current delirium biomarker research and highlighted the issue of poorly reported and/or conducted delirium biomarker studies:

"We don't do a very good job on the side of reporting and reporting that precision so it's rather messy and a lot of the time unable to tell whether the person doing the biomarkers whether they were drawn before or during the delirium." (P07)

Participants asserted the need for reporting guidelines, highlighting that often researchers merely replicated procedures of others in the field without considering best practice methods:

"I think our field is missing a metric or a standard to follow. So you just end up doing what your institution or other studies typically do and that's how you report it." (P07)

Using the same protocols for assay procedures was considered important for standardisation, as well as for the potential to combine samples for larger delirium biomarker studies:

"We should try to use similar protocols at different centres so it's possible to combine samples [. . .] You can also standardise the way you handle your samples after you collect them–just basic things like using the same tubes because some biomarkers that you want to analyse they can adhere. . . if you don't use the correct material to collect the CSF then the proteins can adhere to the surface then you can't trust your results." (P11)

Valuing delirium research through investment and collaboration

2a. Ethics committee barriers. Many participants shared a frustration towards ethics committees' restrictions in relation to delirium biomarker studies, highlighting it as a notable barrier to progressing the field:

"We are very restrictive for supporting this kind of research. For example, you won't get patients with a very severe dementia and delirium because most of the ethical committees won't let family members give proxy consent.' (P08)

A reason for the strict restrictions was the perception of ethics committees that patients did not directly profit from being involved in a delirium biomarker study:

"We have a general problem with perception of doing research on patients. They think we use them like guinea pigs. Particularly with delirium research where you don't have a personal profit. It is different if you are in the oncology and you are coming up with a treatment regimen—there you have a potential profit for yourself. In delirium research you don't and they are very reluctant to say yes and go along with that." (P03)

There was a perception that ethics committees considered people with delirium too vulnerable to be included in research; hence, introducing a selection bias whereby cohorts in these studies often consisted of people with lower risk of delirium:

"Essentially our ethics committees are getting more difficult. Many patients who have a high risk of delirium are a cognitively impaired at baseline so they fall into the category of vulnerable group of patients which makes it difficult to approach them. Then we have the problem that the . . . if you approach, you will get the good ones with too low rates of delirium." (P03)

A pragmatic solution to this barrier was to append the biomarker study onto an already existing trial, alleviating the hurdles of obtaining ethical approval for delirium biomarker studies:

"Linking to some sort of ongoing trial that is enrolling people for another reason [. . .] So I think linking on to randomised controlled trials or big observational cohorts, whatever they're doing, getting funding and adding it on something that is co-existing is a lot easier." (R02)

In contrast, one participant took a long-term approach, and disagreed with tagging the biomarker component onto an existing study. They argued that in order to conduct robust delirium biomarker research, the studies must be "*bespoke*" and original:

"If you want to do a really good biomarker study, or really good pathophysiology work then sometimes you just can't build that on the back of routine clinical care. They have to be

bespoke studies where you have to go the extra mile [. . .] You have to write up a protocol that's more involved, that asks more of the patient and carers [. . .] It's one of those things, that if you really want to advance the research, then you need to do a real research study. And by real, I mean bespoke. That's not being critical of the opportunistic studies, but sometimes if you want to answer the hard questions, you have to do the hard studies." (P15)

2b. Transdisciplinary collaboration. Participants described a number of areas where current delirium biomarker studies were falling short. They acknowledged that current studies were predominantly conducted by clinicians:

"I think delirium is a relatively young field and it's been driven primarily by clinicians which is great because they're really invested or embedded in the health system next to the patient so you have that really rich clinical representation. But the down side is that they just aren't necessarily trained very strong methodologically." (P07)

The importance of collaboration between clinicians and scientists to improve the science of delirium biomarker studies was highlighted by most:

"I am not sure whether the basic scientists work on this topic. It's more that delirium clinicians work on this type of research [. . .] I think it's about integrating these people into the study." (P08)

Discussion

This study of delirium researchers' perspectives about the key methodological challenges in the conduct and reporting of delirium biomarker research sheds light on the current state of the scientific field. Findings identified a range of factors that contribute to the challenges of conducting delirium biomarker research and the risk of the field not accelerating efforts, which have not previously been explicitly acknowledged or reported. It provides the most in-depth exploration of these challenges to date, and some important insights into how to address the many practical, scientific and quality issues in research into delirium pathophysiology.

Practical and scientific challenges of delirium biomarker research: Stagnation versus driving improved methods and reporting

Overall, researchers in this study concurred that delirium biomarker research is in practical terms an extremely difficult and complex field. A minority took a long-term view, whereas many reported taking short-term approaches, even as they acknowledged that the latter was unlikely to advance scientific knowledge of delirium. Although the practical difficulties and complexities of delirium biomarker research was a common finding, some participants also provided clues and suggestions as to how some issues may be addressed.

The issue of delirium under-recognition and misdiagnosis by clinicians, which has been extensively studied and reported as occurring in 21% - 79% of cases across settings [18–20]. It appears from the present study that reliance on clinical identification of delirium, as opposed to researcher assessment, has contributed to much uncertainty about whether delirium was indeed present, or not, at the time of biomarker collection. This finding flags the urgent need for more systematic and reliable processes for delirium identification in research into its biomarkers, which will require greater involvement of researchers and reporting of diagnostic quality. Furthermore, there are conflicting methods in how the features of delirium are

assessed for research purposes. The difficulties with classifying delirium sub-types was also highlighted. The ability to distinguish between the different etiologic subtypes will be critical to elucidate delirium pathophysiology and to develop effective treatments.

There was congruence in the researchers' views that accounting for co-existing conditions in delirium was important but extremely challenging, and divergent views about how to resolve the question. Most were uncertain about how to tackle this topic, and yet addressing this uncertainty in a united way is crucial to advancing the field of research. Delirium superimposed on dementia (DSD) was considered a key challenge by researchers, who noted the importance of adjusting for dementia in delirium biomarker studies. Delirium is a risk factor for dementia, and is associated with worsening severity in individuals with existing dementia [21]. The prevalence of DSD in community and hospitalised settings is well documented and ranges between 22% and 89% in people aged 65 and older [22]. When dementia and delirium co-exist, it is difficult to ascertain whether the observed changes in a particular biomarker were related to the delirium, or confounded by the underlying dementia [23]. Animal models of delirium during dementia have been developed, which suggest that prior synaptic loss and microglial priming are predisposing factors for acute cognitive impairment induced by systemic inflammation [24]. Although this model is highly promising, further validation in more studies is required. There is also an urgent need to characterise these two conditions biologically and clinically in human studies. Including multiple control/comparator groups would help to elucidate the distinctions.

A challenge identified in this study was the acuity, fluctuating course and often brief duration of delirium. These factors make precise determination of its onset and resolution extremely difficult, and yet research recruitment and precision in the timing of biomarker collection is crucial in delirium biomarker studies to accurately capture the delirium episode [25]. Furthermore, pathophysiological processes may differ in active delirium compared to those individuals who are not yet delirious. A standardised way of determining delirium resolution is also required, as there is currently no consensus on the definition of delirium resolution [26].

The proximity of CSF to the brain makes it a good target for studying the pathophysiology of central nervous system conditions. Obtaining CSF for research purposes however has numerous practical challenges. Most delirium researchers discussed the burden of CSF collection by lumbar puncture (LP), and referred to the procedure as "invasive". Although there is no literature on the experience of adults undergoing LP, there has been much research in children and adolescents. One study demonstrated that 75% of parents/caregivers of children who were scheduled to undergo an LP did not consent because of the fear of complications [27]. One proposed solution to this barrier is to improve the quality and person-centeredness of information given to potential participants, to increase their understanding of the proposed research. A recent scoping review reported that many older people were willing to participate in research in the event of reduced decision-making capacity from a desire to contribute to scientific knowledge, although less so in studies with higher risks or burdens for them [28]. Reducing study risks and burdens, as well as improved communication processes with potential participants and proxies, are therefore crucial. For example, simplified information and consent forms using lay language that avoids medical jargon as well as extended discussions can lead to improvements in participant understanding and appreciation of study information [29, 30].

Neuroimaging is another method that has sparked interest in attempts to understand the neural correlates of delirium. Neuroimaging is routinely used in clinical practice, however, there are still very few studies on neuroimaging in delirium, which likely reflects the practical and ethical challenges involved in imaging patients with hyperactive delirium. Delirium

researchers in this study expressed concerns about the practical challenges of getting a person who is agitated to lie still in a PET scanner. One solution is to ensure patients are accompanied by a relative or carer to reassure them prior to and during the scans, as was effectively enacted in another study [31]. Although imaging studies are deemed to be extremely difficult, large samples which adjust for confounding factors (for example, pre-existing cognitive impairment) are needed, as well as long-term vision and planning of research programs to facilitate the advancement of adequately powered studies [32].

The need to account for and understand the complexity and biology of the whole person was highlighted as a gap in current delirium biomarker studies. A key limitation of many previous studies in acutely admitted patients was the lack of objective cognitive testing at baseline, therefore making it difficult to know if any observed changes in biomarkers were related to the delirium, or were confounded by underlying conditions. Many researchers suggested that future delirium biomarker studies focus on the surgical setting, where patients have a true preoperative baseline. The limitation of this approach is that delirium is a multifactorial condition, which almost always occurs in the context of other physiological processes that need to be accounted for in study participants.

This study confirmed that standardised methods in the form of reporting guidelines for delirium biomarker research are urgently required, as was initially identified in a previous systematic review [11]. Inadequate and/or unclear reporting of methodological processes can lead to discrepancies in results, which may be misleading and potentially detrimental to the research [33]. Overall, reporting guidelines are deemed necessary to promote studies that are standardised and reliable. This statement is consistent with other studies that reported improvements in reporting rigor when reporting guidelines such as the CONSORT (Consolidated Standards of Reporting Trials) [34] were adopted. Many journals have taken steps to improve the quality of the research articles that they publish by requiring the use of reporting guidelines, although research shows there is still room for improvement [35]. Having global standardised guidelines to conduct delirium biomarker research with similar reference standards will help to improve the quality of reporting within studies and thereby increase opportunities for syntheses across studies.

Valuing delirium research through investment and collaboration

There are several ethical challenges to conducting research in patient populations at higher risk of harm, such as delirious patients who are often considered too vulnerable for research participation [36]. There is an ethical tension in delirium research; balancing the need to protect this more vulnerable population with upholding their rights to be included in research and the need to improve medical care [25]. This study confirmed that ethics committee interpretation of current research regulations when applied to delirium research are perhaps exceedingly stringent. This is driven by several factors: patients are unlikely to directly profit from participating in a delirium biomarker study, concerns about potential harms to a vulnerable population, perceived burden of specimen collection and the quality of informed consent. Those with impaired capacity are often either excluded from research or less frequently recruited, to circumvent the challenges of tailoring methods and study measures [28]. However, this evasion leads to unrepresentative study populations and thereby limits external validity of the research [25, 37].

Common motivations of older people to participate in research in the context of impaired decision-making include altruism, potential personal benefits, and a desire to contribute to scientific knowledge [28]. Greater consumer (e.g. people who have previously experienced delirium or their caregivers) input into delirium biomarker study development would help to

ensure improved value proposition and communication by researchers to ethics committees and potential participants/proxies so they can better weigh the rewards/risks of delirium studies might help to overcome some of the barriers identified in this study.

The common approach of relying on the clinical identification of delirium within biomarker research should be replaced with a more rigorous process. Such a process could be elucidated by clinicians, scientists and researchers working in a more united way to improve methods in delirium biomarker research. This issue was identified in this study by the frequent acknowledgement that currently delirium biomarker research is predominantly conducted by clinicians with minimal background in basic science. To address these gaps, multi-institutional collaborative efforts are needed to generate valid, reproducible and generalisable findings in delirium biomarker research. The Successful Aging after Elective Surgery (SAGES) [32] program is one example of a collaborative project aiming to achieve research rigour and results that would likely be unattainable by investigators working independently.

Implications for research

Delirium is a major clinical and public health concern, and robust scientific research on pathophysiological mechanisms are urgently needed. Developing reporting guidelines is an essential step to improving methodological and reporting quality in delirium biomarker research. Increased international, multisite and transdisciplinary collaboration, along with concept development workshops focused on methodology of conducing delirium biomarker research at international delirium society meetings, would enable improvements in the field. Furthermore, better explanation of study rationales to ethics committees, and involvement of consumers, could help in alleviating some of the challenges identified in this study. Despite many studies seeking to better understand the pathophysiology of delirium, these barriers continue to impede high-quality delirium biomarker research. Raising awareness and changing practice and culture offer the multidimensional effort that is needed to progress this fundamental field of delirium research. Details regarding our recommendations for future research are given in Table 2.

Strengths and limitations

A key strength of this study was the inclusion of participants from multiple disciplines and countries who were actively involved in delirium research, allowing data saturation to be reached. Secondly, the qualitative method allowed for an in-depth exploration into the reasons underpinning the participant views, giving clearer guidance of the specific areas for advancement in the field.

Participants were purposefully sampled in order to facilitate in-depth exploration delirium researchers' perspectives, and so these findings are likely to be specific to the challenges of delirium biomarker research, rather than be transferable to biomarker research more generally. We are unsure if the predominance of male and clinician researcher participants is representative of the field, or had any particular influence on the findings of the study; however, this is worth noting as a potential limitation. Another limitation was that almost all participants in the study were from high-income countries.

Conclusion

Findings of this qualitative study identified a range of factors that contribute to the challenges of conducting delirium biomarker research, which have not previously been explicitly acknowledged or reported. These factors all contribute to the overall quality of research in this field. Findings complemented the preceding systematic review and Delphi survey, and

Table 2. Recommendations for future research.

Interview theme	Recommendation
Practical and scientific challenges of delirium biomarker research: stagnation versus driving improved methods and reporting	
Accuracy of diagnostic assessment of delirium	Development of a reference standard for the diagnosis of delirium is needed.
Delirium superimposed on dementia (DSD)	In acutely admitted patients, assessments on cognitive decline should be used to assess dementia status. The use of multiple control/comparator groups could help elucidate the distinctions.
Hypothesis driven	Pre-defined hypotheses need to be supported by a strong biological underpinning.
Limited infrastructure and resource investment	Standardising protocols to allow for future collaborations between laboratories is essential.
Fluctuating nature of delirium means time point of biomarker collection is a crucial consideration	A standardised way of determining delirium resolution is required.
Collecting CSF and imaging in people with delirium	Person-centeredness is essential to increase participants understanding of the proposed research.
Accounting for the complexity/biology of the whole person	In elective studies, patients should undergo objective cognitive testing to obtain a true baseline before biomarker sampling.
Standardise delirium biomarker research	Reporting guidelines specific to delirium biomarker studies are needed.
Valuing delirium research through investment and collaboration	
Ethics committee barriers	Greater consumer input into delirium biomarker study development would help to ensure improved value proposition and communication by researchers to ethical committees and potential participants.
Transdisciplinary collaboration	Ongoing international, multisite and transdisciplinary collaboration, including concept development workshops on delirium biomarker research is essential.

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together these studies will inform strategies to improve the methods and reporting of delirium biomarker research. A concerted effort is now required to standardise and strengthen several aspects of the conduct and reporting of delirium biomarker studies, in order to advance this highly promising but yet to deliver scientific field of research.

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References

1. National Institute for Health and Clinical Excellence. Delirium: diagnosis, prevention and management 2010 [Available from: https://www.nice.org.uk/guidance/cg103.
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Arlington, VA: American Psychiatric Publisher; 2013.
3. Bruera E, Bush SH, Willey J, Paraskevopoulos T, Li Z, Palmer JL, et al. Impact of delirium and recall on the level of distress in patients with advanced cancer and their family caregivers. Cancer. 2009; 115 (9):2004–12. https://doi.org/10.1002/cncr.24215 PMID: 19241430
4. Salluh JI, Wang H, Schneider EB, Nagaraja N, Yenokyan G, Damluji A, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. Bmj. 2015; 350:h2538. https://doi.org/10.1136/bmj.h2538 PMID: 26041151
5. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, Van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. JAMA: Journal of the American Medical Association. 2010; 304(4):443–51. https://doi.org/10.1001/jama.2010.1013 PMID: 20664045
6. Pezzullo L, Streatfeild J, Hickson J, Teodorczuk A, Agar MR, Caplan GA. Economic impact of delirium in Australia: a cost of illness study. Bmj. 2019; 9(9):e027514. https://doi.org/10.1136/bmjopen-2018-027514 PMID: 31530588
7. Siddiqi N, House A, Holmes J. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. Age and Ageing. 2006; 35(4):350–64. https://doi.org/10.1093/ageing/afl005 PMID: 16648149
8. Maldonado JR. Delirium pathophysiology: An updated hypothesis of the etiology of acute brain failure. International Journal of Geriatric Psychiatry. 2017; 33(11):1428–57. https://doi.org/10.1002/gps.4823 PMID: 29278283
9. Khachaturian AS, Hayden KM, Devlin JW, Fleisher LA, Lock SL, Cunningham C, et al. International drive to illuminate delirium: A developing public health blueprint for action. Alzheimer's & Dementia. 2020; 16(5):711–25.
10. Slooter AJ, Otte WM, Devlin JW, Arora RC, Bleck TP, Claassen J, et al. Updated nomenclature of delirium and acute encephalopathy: statement of ten Societies. Intensive Care Medicine. 2020:1–3. https://doi.org/10.1007/s00134-019-05907-4 PMID: 32055887
11. Amgarth-Duff I, Hosie A, Caplan G, Agar M. A systematic review of the overlap of fluid biomarkers in delirium and advanced cancer-related syndromes. BMC psychiatry. 2020; 20(1):1–32. https://doi.org/10.1186/s12888-019-2374-2 PMID: 31898506
12. Oh ES, Akeju O, Avidan MS, Cunningham C, Hayden KM, Jones RN, et al. A roadmap to advance delirium research: Recommendations from the NIDUS Scientific Think Tank. Alzheimer's & Dementia. 2020; 16(5):726–33. https://doi.org/10.1002/alz.12076 PMID: 32291901
13. Amgarth-Duff I, Hosie A, Caplan G, Agar M. Toward Best Practice Methods for Delirium Biomarker Studies: An International Modified Delphi Study. International Journal of Geriatric Psychiatry. 2020. https://doi.org/10.1002/gps.5292 PMID: 32150303
14. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Journal for Quality in Health care. 2007; 19(6):349–57. https://doi.org/10.1093/intqhc/mzm042 PMID: 17872937
15. Patton MQ. Qualitative research & evaluation tools. 4th ed. ed. Los Angeles, California: SAGE 2015.
16. Marshall MN. Sampling for qualitative research. Family Practice. 1996; 13(6):522–6. https://doi.org/10.1093/fampra/13.6.522 PMID: 9023528
17. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology. 2006; 3 (2):77–101.
18. Lange PW, Lamanna M, Watson R, Maier AB. Undiagnosed delirium is frequent and difficult to predict: Results from a prevalence survey of a tertiary hospital. Journal of Clinical Nursing. 2019; 28(13–14):2537–42. https://doi.org/10.1111/jocn.14833 PMID: 30786081
19. de la Cruz M, Fan J, Yennu S, Tanco K, Shin S, Wu J, et al. The frequency of missed delirium in patients referred to palliative care in a comprehensive cancer center. Supportive Care in Cancer. 2015; 23 (8):2427–33. https://doi.org/10.1007/s00520-015-2610-3 PMID: 25617070

20. Mayoral R, Madrigal F, Perez S, Aviles E. Delirium in terminal cancer inpatients: short-term survival and missed diagnosis. Salud Mental. 2018; 41(1).

21. Fong T, Jones R, Shi P, Marcantonio E, Yap L, Rudolph J, et al. Delirium accelerates cognitive decline in Alzheimer disease. Neurology. 2009; 72(18):1570–5. https://doi.org/10.1212/WNL.0b013e3181a4129a PMID: 19414723

22. Fick DM, Agostini JV, Inouye SK. Delirium superimposed on dementia: a systematic review. Journal of the American Geriatrics Society. 2002; 50(10):1723–32. https://doi.org/10.1046/j.1532-5415.2002.50468.x PMID: 12366629

23. Inouye SK, Ferrucci L. Introduction: Elucidating the pathophysiology of delirium and the interrelationship of delirium and dementia. The Journals of Gerontology Series A: Biological Sciences Medical Sciences. 2006; 61(12):1277–80.

24. Murray C, Sanderson DJ, Barkus C, Deacon RM, Rawlins JNP, Bannerman DM, et al. Systemic inflammation induces acute working memory deficits in the primed brain: relevance for delirium. Neurobiol Aging. 2012; 33(3):603–16. e3. https://doi.org/10.1016/j.neurobiolaging.2010.04.002 PMID: 20471138

25. Holt R, Siddiqi N, Young J. The ethics of consent in delirium studies. Journal of Psychosomatic Research. 2008; 65(3):283–7. https://doi.org/10.1016/j.jpsychores.2008.05.023 PMID: 18707952

26. Adamis D, Devaney A, Shanahan E, McCarthy G, Meagher D. Defining 'recovery'for delirium research: a systematic review. Age and Ageing. 2015; 44(2):318–21. https://doi.org/10.1093/ageing/afu152 PMID: 25476590

27. Narchi H, Ghatasheh G, Al Hassani N, Al Reyami L, Khan Q. Why do some parents refuse consent for lumbar puncture on their child? A qualitative study. Hospital Pediatrics. 2012; 2(2):93–8. https://doi.org/10.1542/hpeds.2011-0034 PMID: 24510955

28. Hosie A, Kochovska S, Ries N, Gilmore I, Parker D, SinclairC, et al. Older persons' and their caregivers' perspectives and experiences of research participation with impaired decision-making capacity: a scoping review. The Gerontologist. 2020. https://doi.org/10.1093/geront/gnaa118 PMID: 32866239

29. Kim EJ, Kim SH. Simplification improves understanding of informed consent information in clinical trials regardless of health literacy level. Clin Trials. 2015; 12(3):232–6. https://doi.org/10.1177/1740774515571139 PMID: 25701156

30. Nishimura A, Carey J, Erwin PJ, Tilburt JC, Murad MH, McCormick JB. Improving understanding in the research informed consent process: a systematic review of 54 interventions tested in randomized control trials. BMC Medical Ethics. 2013; 14(1):28. https://doi.org/10.1186/1472-6939-14-28 PMID: 23879694

31. Haggstrom L, Nelson J, Wegner E, Caplan G. 2-18F-fluoro-2-deoxyglucose positron emission tomography in delirium. Journal of Cerebral Blood Flow & Metabolism. 2017; 37(11):3556–67. https://doi.org/10.1177/0271678X17701764 PMID: 28350285

32. Schmitt EM, Marcantonio ER, Alsop DC, Jones RN, Rogers SO Jr, Fong TG, et al. Novel risk markers and long-term outcomes of delirium: the successful aging after elective surgery (SAGES) study design and methods. J Am Med Dir Assoc. 2012; 13(9):818. e1–. e10. https://doi.org/10.1016/j.jamda.2012.08.004 PMID: 22999782

33. Simera I, Moher D, Hirst A, Hoey J, Schulz KF, Altman DG. Transparent and accurate reporting increases reliability, utility, and impact of your research: reporting guidelines and the EQUATOR Network. BMC Medicine. 2010; 8(1):24.

34. Plint AC, Moher D, Morrison A, Schulz K, Altman DG, Hill C, et al. Does the CONSORT checklist improve the quality of reports of randomised controlled trials? A systematic review. Medical Journal of Australia. 2006; 185(5):263–7.

35. Levine D, Kressel HY. 2016: Reviewing for Radiology—Reporting Guidelines and Why We Use Them. Radiology 2016;280. https://doi.org/10.1148/radiol.2016152641 PMID: 27797679

36. Bracken-Roche D, Bell E, Macdonald ME, Racine E. The concept of 'vulnerability'in research ethics: an in-depth analysis of policies and guidelines. Health Research Policy and Systems. 2017; 15(1):8. https://doi.org/10.1186/s12961-016-0164-6 PMID: 28173859

37. Prusaczyk B, Cherney SM, Carpenter CR, DuBois JM. Informed consent to research with cognitively impaired adults: transdisciplinary challenges and opportunities. Clinical Gerontologist. 2017; 40(1):63–73. https://doi.org/10.1080/07317115.2016.1201714 PMID: 28452628

Appendix 2: MEDLINE search strategy

MEDLINE- Delirium		
	Searches	**Results**
1	delirium.m_titl.	6535
2	"delir*".m_titl.	6847
3	"acute confusion".m_titl.	122
4	"acute organic psychosyndrome".m_titl.	4
5	"acute brain syndrome".m_titl.	23
6	"metabolic encephalopathy".m_titl.	76
7	"acute psycho-organic syndrome".m_titl.	3
8	"clouded state".m_titl.	2
9	"clouding of consciousness".m_titl.	18
10	"exogenous psychosis".m_titl.	15
11	"toxic psychosis".m_titl.	106
12	"toxic confusion".m_titl.	2
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	7207
14	Biomarkers/ or biomarker*.mp.	423459
15	Cytokines/ or cytokine*.mp.	340463
16	tryptophan.mp. or Tryptophan/	54367
17	melatonin.mp. or Melatonin/	22624
18	serotonin.mp. or Serotonin/	138213
19	chemokine*.mp.	78017
20	interleukin.mp. or Interleukins/	302129
21	S100 Proteins/ or S100b.mp. or S100 Calcium Binding Protein beta Subunit/	12404
22	cortisol.mp.	54671
23	"S100 beta".mp.	251
24	"TNF alpha".mp. or Tumor Necrosis Factor-alpha/	159040
25	IGF-1.mp. or Insulin-Like Growth Factor I/	37447
26	"apolioprotein E4".mp. or Apolipoproteins E/	16307
27	"C reactive protein".mp. or C-Reactive Protein/	64777
28	C-Reactive Protein/ or CRP.mp.	57755
29	Dopamine/ or dopamine.mp.	146886
30	neurotransmitter*.mp.	86313
31	14 or 15 or 16 or 17 or 18 or 29 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30	86313

32	13 and 31	998
33	limit 32 to (yr="1980 -Current" and English and humans)	703

MEDLINE- cancer prognosis		
#	**Searches**	**Results**
1	(cancer adj5 prognosis).m_titl	6670
2	prognostication.mp.	5636
3	1 or 2	12260
4	cancer.mp. or Neoplasms/	2831489
5	Advanced.mp.	381443
6	metastasis.mp. or Neoplasm Metastasis/	325957
7	end stage".mp.	63359
8	"late stage".mp.	19595
9	"stage 4".mp.	5379
10	"stage four".mp.	258
11	5 or 6 or 7 or 8 or 9 or 10	853407
12	Biomarkers/ or biomarker*.mp.	330208
13	Cytokines/ or cytokine*.mp.	533139
14	tryptophan.mp. or Tryptophan/	68521
15	melatonin.mp. or Melatonin/	32995
16	serotonin.mp. or Serotonin/	203499
17	chemokine*.mp.	117568
18	interleukin.mp. or Interleukins/	555852
19	S100 Proteins/ or S100b.mp. or S100 Calcium Binding Protein beta Subunit/	24409
20	cortisol.mp.	67889
21	"S100 beta".mp.	175
22	"TNF alpha".mp. or Tumor Necrosis Factor-alpha/	233733
23	IGF-1.mp. or Insulin-Like Growth Factor I/	52614
24	"apolipoprotein E".mp. or Apolipoproteins E/	23229
25	"C reactive protein".mp. or C-Reactive Protein/	137997
26	C-Reactive Protein/ or CRP.mp.	156134
27	Dopamine/ or dopamine.mp.	203307
28	neurotransmitter*.mp.	100938

29	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28	1743254
30	3 and 4 and 11 and 29	328
31	limit 30 to (yr="1980 -Current" and English and humans)	251
MEDLINE- Anorexia cachexia		
#	**Searches**	**Results**
1	Cachexia/ or "anorexia cachexia".mp.	4814
2	cachexic.mp.	83
3	wasting syndrome/	1106
4	(anorexia adj5 cachexia).mp.	875
5	1 or 2 or 3 or 4	6046
6	Biomarkers/ or biomarker*.mp.	344307
7	Cytokines/ or cytokine*.mp.	533139
8	tryptophan.mp. or Tryptophan/	68521
9	melatonin.mp. or Melatonin/	32995
10	serotonin.mp. or Serotonin/	203499
11	chemokine*.mp.	117568
12	interleukin.mp. or Interleukins/	555852
12	IL.mp. or Interleukins/	423394
13	S100 Proteins/ or S100b.mp. or S100 Calcium Binding Protein beta Subunit/	24409
14	cortisol.mp.	67889
15	"S100 beta".mp.	175
16	"TNF alpha".mp. or Tumor Necrosis Factor-alpha/	233733
17	IGF-1.mp. or Insulin-Like Growth Factor I/	52614
18	Apolipoproteins E/ or "apolipoprotein E".mp.	28815
19	"C reactive protein".mp. or C-Reactive Protein/	137997
20	“CRP”.mp.	70815
21	Dopamine/ or dopamine.mp.	203307
22	neurotransmitter*.mp.	100938
23	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	2041019
24	cancer.mp. or Neoplasms/	2831489
25	Advanced.mp.	347554
26	metastasis.mp. or Neoplasm Metastasis/	301151
27	"end stage".mp.	57570
28	"late stage".mp.	17564

29	"stage 4".mp.	4931
30	"stage four".mp.	237
31	25 or 26 or 27 or 28 or 29 or 30	694442
32	5 and 23 and 24 and 31	1409
34	limit 32 to (yr="1980 -Current" and English and humans)	468
MEDLINE- cognitive impairment		
#	**Searches**	**Results**
1	“chemo brain”	47
2	“chemo fog”	23
3	"cognitive impairment".mp. or Cognitive Dysfunction/	42832
4	1 or 2 or 3	42874
5	cancer.mp. or Neoplasms/	1574769
6	Advanced.mp.	381443
7	metastasis.mp. or Neoplasm Metastasis/	325957
8	"end stage".mp.	63359
9	"late stage".mp.	19595
10	"stage 4".mp.	5379
11	"stage four".mp.	258
12	6 or 7 or 8 or 9 or 10 or 11	757866
13	Biomarkers/ or biomarker*.mp.	426688
14	Cytokines/ or cytokine*.mp.	340463
15	tryptophan.mp. or Tryptophan/	54367
16	melatonin.mp. or Melatonin/	22624
17	serotonin.mp. or Serotonin/	138213
18	chemokine*.mp.	78017
19	interleukin.mp. or Interleukins/	302129
20	S100 Proteins/ or S100b.mp. or S100 Calcium Binding Protein beta Subunit/	12404
21	cortisol.mp.	54671
22	"S100 beta".mp.	251
23	"TNF alpha".mp. or Tumor Necrosis Factor-alpha/	159040
24	IGF-1.mp. or Insulin-Like Growth Factor I/	37447
25	"apolioprotein E4".mp. or Apolipoproteins E/	16307
26	"C reactive protein".mp. or C-Reactive Protein/	64777
27	C-Reactive Protein/ or CRP.mp.	57755
28	Dopamine/ or dopamine.mp.	146886

29	neurotransmitter*.mp.	86313
30	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	1146997
31	4 and 5 and 12 and 30	120
32	limit 31 to (yr="1980 -Current" and English and humans)	82
MEDLINE: Cancer pain		
#	**Searches**	**Results**
1	“cancer pain”.mp. or Cancer Pain/	6674
2	(cancer adj5 pain).mp.	11491
3	1 or 2	11491
4	cancer.mp. or Neoplasms/	2831489
5	Advanced.mp.	381443
6	metastasis.mp. or Neoplasm Metastasis/	325957
7	"end stage".mp.	63359
8	"late stage".mp.	19595
9	"stage 4".mp.	5379
10	"stage four".mp.	258
11	6 or 7 or 8 or 9 or 10 or 11	853407
12	Biomarkers/ or biomarker*.mp.	330208
13	Cytokines/ or cytokine*.mp.	533139
14	tryptophan.mp. or Tryptophan/	68521
15	melatonin.mp. or Melatonin/	32995
16	serotonin.mp. or Serotonin/	203499
17	chemokine*.mp.	117568
18	interleukin.mp. or Interleukins/	555852
19	S100 Proteins/ or S100b.mp. or S100 Calcium Binding Protein beta Subunit/	24409
20	cortisol.mp.	67889
21	"S100 beta".mp.	175
22	"TNF alpha".mp. or Tumor Necrosis Factor-alpha/	233733
23	IGF-1.mp. or Insulin-Like Growth Factor I/	52614
24	"apolioprotein E4".mp. or Apolipoproteins E/	23229
25	"C reactive protein".mp. or C-Reactive Protein/	137997
26	C-Reactive Protein/ or CRP.mp.	156134
27	Dopamine/ or dopamine.mp.	203307
28	neurotransmitter*.mp.	100938

29	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	1743254
30	3 and 4 and 11 and 29	409
31	limit 30 to (yr="1980 -Current" and English and humans)	196
MEDLINE- Fatigue		
#	**Searches**	**Results**
1	"cancer fatigue".mp. or cancer fatigue/	147
2	(cancer adj5 fatigue).mp.	2262
3	1 or 2	2262
4	cancer.mp. or Neoplasms/	2831489
5	Advanced.mp.	381443
6	metastasis.mp. or Neoplasm Metastasis/	325957
7	"end stage".mp.	63359
8	"late stage".mp.	19595
9	"stage 4".mp.	5379
10	"stage four".mp.	258
11	5 or 6 or 7 or 8 or 9 or 10	853407
12	Biomarkers/ or biomarker*.mp.	330208
13	Cytokines/ or cytokine*.mp.	533139
14	tryptophan.mp. or Tryptophan/	68521
15	melatonin.mp. or Melatonin/	32995
16	serotonin.mp. or Serotonin/	203499
17	chemokine*.mp.	117568
18	interleukin.mp. or Interleukins/	555852
19	S100 Proteins/ or S100b.mp. or S100 Calcium Binding Protein beta Subunit/	24409
20	cortisol.mp.	67889
21	"S100 beta".mp.	175
22	"TNF alpha".mp. or Tumor Necrosis Factor-alpha/	233733
23	IGF-1.mp. or Insulin-Like Growth Factor I/	52614
24	"apolioprotein E4".mp. or Apolipoproteins E/	23229
25	"C reactive protein".mp. or C-Reactive Protein/	137997
26	C-Reactive Protein/ or CRP.mp.	156134
27	Dopamine/ or dopamine.mp.	203307
28	neurotransmitter*.mp.	100938
29	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	1572684

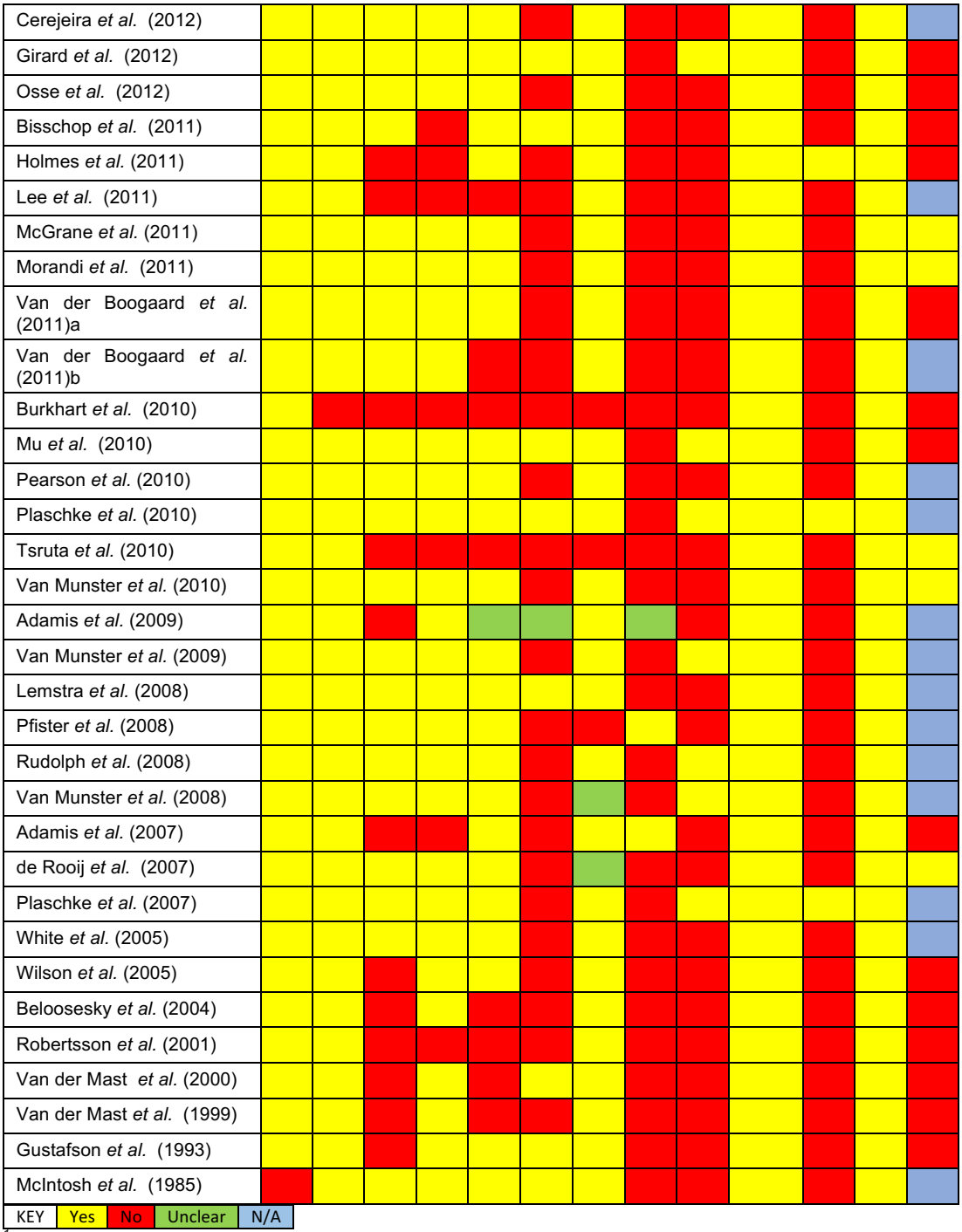
30	3 and 4 and 11 and 29	267
31	limit 37 to (yr="1980 -Current" and English and humans)	207
MEDLINE- Sickness behaviour		
#	**Searches**	**Results**
1	"sickness behavior".mp.	571
2	"sickness behaviour".mp.	179
3	1 or 2	748
4	cancer.mp. or Neoplasms/	2831489
5	Biomarkers/ or biomarker*.mp.	330208
6	Advanced.mp.	381443
7	metastasis.mp. or Neoplasm Metastasis/	325957
8	"end stage".mp.	63359
9	"late stage".mp.	19595
10	"stage 4".mp.	5379
11	"stage four".mp.	258
12	6 or 7 or 8 or 9 or 10 or 11	853407
13	Cytokines/ or cytokine*.mp.	533139
14	tryptophan.mp. or Tryptophan/	68521
15	melatonin.mp. or Melatonin/	32995
16	serotonin.mp. or Serotonin/	203499
17	chemokine*.mp.	117568
18	interleukin.mp. or Interleukins/	555852
19	S100 Proteins/ or S100b.mp. or S100 Calcium Binding Protein beta Subunit/	24409
20	cortisol.mp.	67889
21	"S100 beta".mp.	175
22	"TNF alpha".mp. or Tumor Necrosis Factor-alpha/	233733
23	IGF-1.mp. or Insulin-Like Growth Factor I/	52614
24	"apolioprotein E4".mp. or Apolipoproteins E/	23229
25	"C reactive protein".mp. or C-Reactive Protein/	137997
26	C-Reactive Protein/ or CRP.mp.	156134
27	Dopamine/ or dopamine.mp.	203307
28	neurotransmitter*.mp.	100938
29	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	1572684
30	3 and 4 and 12 and 29	267

31	limit 27 to (yr="1980 -Current" and English and humans)	207

Appendix 3: Quality assessment of included systematic review studies

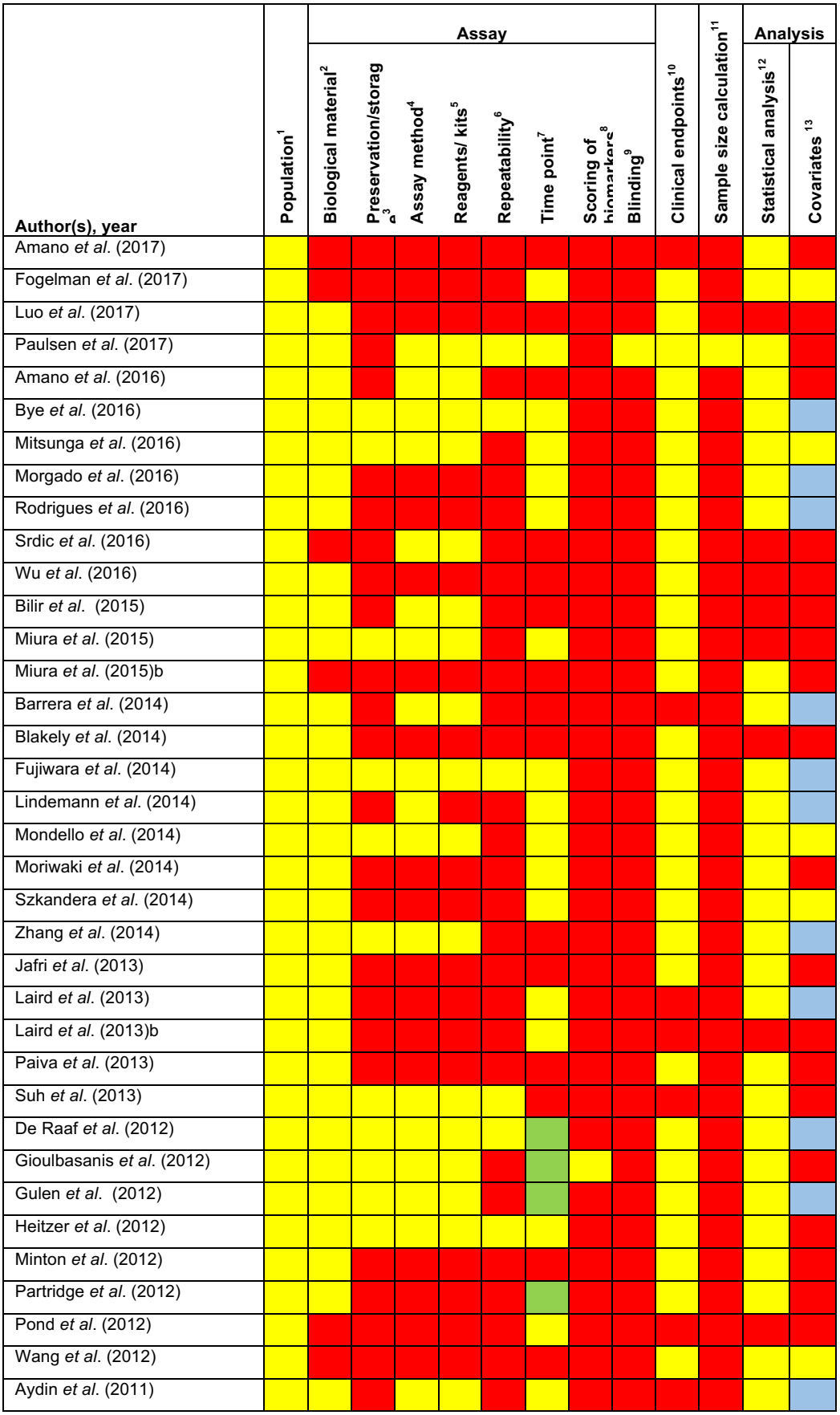
Appendix 3.1: Delirium studies

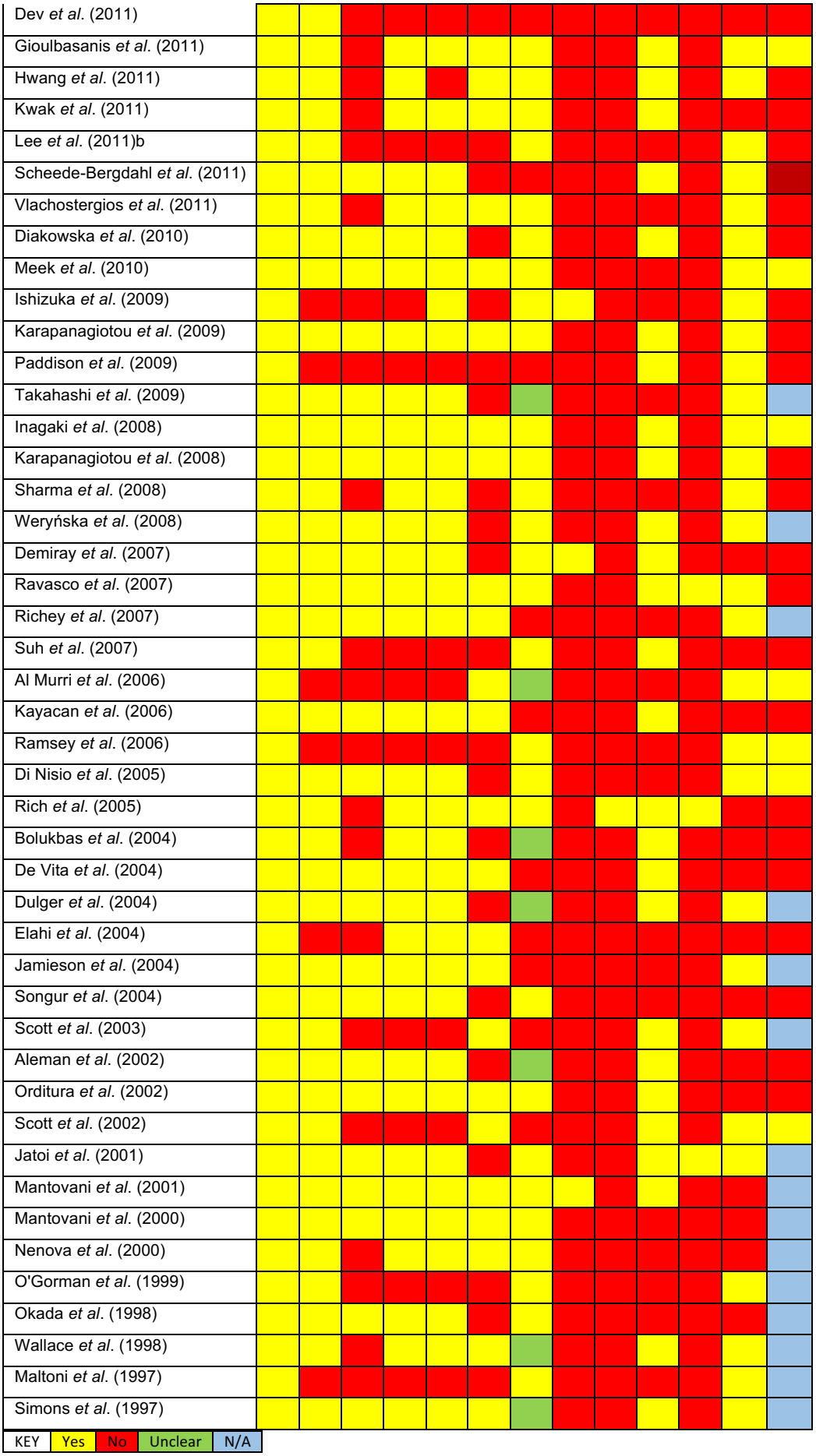
Author(s), year	Population[1]	Assay								Clinical endpoints[10]	Sample size calculation[11]	Analysis	
		Biological material[2]	Preservation/storage[3]	Assay method[4]	Reagents/kits[5]	Repeatability[6]	Time point[7]	Scoring of biomarker[8]	Blinding[9]			Statistical analysis[12]	Covariates[13]
Egberts *et al.* (2017)													
Kozak *et al.* (2017)													
Tomasi *et al.* (2017)													
Vasunilashorn *et al.* (2017)													
Chu *et al.* (2016)													
Dillon *et al.* (2016)													
Guo *et al.* (2016)													
Karlicic *et al.* (2016)													
Neerland *et al.* (2016)													
Shen *et al.* (2016)													
Sun *et al.* (2016)													
Yen *et al.* (2016)													
Avila-Funes *et al.* (2015)													
Brum *et al.* (2015)													
Egberts *et al.* (2015)													
Foroughan *et al.* (2015)													
Skrede *et al.* (2015)													
Vasunilashorn *et al.* (2015)													
Alexander *et al.* (2014)													
Baranyi *et al.* (2014)													
Cape *et al.* (2014)													
Capri *et al.* (2014)													
Chen *et al.* (2014)													
Hatta *et al.* (2014)													
Kazmierski *et al.* (2014)													
Ritchie *et al.* (2014)													
Ritter *et al.* (2014)													
Zhang *et al.* (2014)													
Cerejeira *et al.* (2013)													
Colkesen *et al.* (2013)													
Kazmierski *et al.* (2013)													
Kazmierski *et al.* (2013)b													
Liu *et al.* (2013)													
Plaschke *et al.* (2013)													
Skrobik *et al.* (2013)													
Westhoff *et al.* (2013)													
Bakker *et al.* (2012)													
Baranyi *et al.* (2012)													



[1] *Describe the characteristics (for example, disease stage or co-morbidities) of the study patients, including their source and inclusion and exclusion criteria.*
[2] *Describes the type of biological material used (including control samples)*
[3] *Describes the methods of preservation and storage*
[4] *Specifies the assay method used and provides (or references) a detailed protocol*
[5] *Specifies the specific reagents or kits used*
[6] *Reports any reproducibility assessments*
[7] *The time point of the assay in relation to delirium*
[8] *Provides a scoring and reporting protocol*
[9] *Specifies whether and how assays were performed blinded to the study endpoint.*
[10] *Precisely define all clinical endpoints examined.*
[11] *Gives a rationale for sample size; if the study was designed to detect a specified effect size, the study gives the target power and effect size.*
[12] *Describes univariate or multivariate analysis in detail including which model was used and what was compared*
[13] *For multivariate analysis only: justifies the covariates used in the multivariate model*

Appendix 3.2: Cancer syndrome studies




Dev et al. (2011)
Gioulbasanis et al. (2011)
Hwang et al. (2011)
Kwak et al. (2011)
Lee et al. (2011)b
Scheede-Bergdahl et al. (2011)
Vlachostergios et al. (2011)
Diakowska et al. (2010)
Meek et al. (2010)
Ishizuka et al. (2009)
Karapanagiotou et al. (2009)
Paddison et al. (2009)
Takahashi et al. (2009)
Inagaki et al. (2008)
Karapanagiotou et al. (2008)
Sharma et al. (2008)
Weryńska et al. (2008)
Demiray et al. (2007)
Ravasco et al. (2007)
Richey et al. (2007)
Suh et al. (2007)
Al Murri et al. (2006)
Kayacan et al. (2006)
Ramsey et al. (2006)
Di Nisio et al. (2005)
Rich et al. (2005)
Bolukbas et al. (2004)
De Vita et al. (2004)
Dulger et al. (2004)
Elahi et al. (2004)
Jamieson et al. (2004)
Songur et al. (2004)
Scott et al. (2003)
Aleman et al. (2002)
Orditura et al. (2002)
Scott et al. (2002)
Jatoi et al. (2001)
Mantovani et al. (2001)
Mantovani et al. (2000)
Nenova et al. (2000)
O'Gorman et al. (1999)
Okada et al. (1998)
Wallace et al. (1998)
Maltoni et al. (1997)
Simons et al. (1997)
KEY
Yes
No
Unclear
N/A

[1] *Describe the characteristics (for example, disease stage or co-morbidities) of the study patients, including their source and inclusion and exclusion criteria.*
[2] *Describes the type of biological material used (including control samples)*
[3] *Describes the methods of preservation and storage*
[4] *Specifies the assay method used and provides (or references) a detailed protocol*
[5] *Specifies the specific reagents or kits used*
[6] *Reports any reproducibility assessments*
[7] *The time point of the assay in relation to the patients clinical course*
[8] *Provides a scoring and reporting protocol*
[9] *Specifies whether and how assays were performed blinded to the study endpoint*
[10] *Precisely define all clinical endpoints examined.*
[11] *Gives a rationale for sample size; if the study was designed to detect a specified effect size, the study gives the target power and effect size.*
[12] *Describes univariate or multivariate analysis in detail including which model was used and what was compared*
[13] *For multivariate analysis only: justifies the covariates used in the multivariate model*

Appendix 4: HREC Approval for Study 2 and 3

Your ethics application has been approved as low risk - ETH18-2673

research.ethics@uts.edu.au

Fri 25/01/2019 11:08 AM

To: Ingrid Amgarth-Duff <Ingrid.Amgarth-Duff@uts.edu.au>; Meera Agar <Meera.Agar@uts.edu.au>;

Cc: Chris Fernandes <ChristopherFernandes@uts.edu.au>; Karen Gomez <Karen.Gomez@uts.edu.au>; Priya Nair <Priya.Nair@uts.edu.au>; Rebekah Tatian <Rebekah.Tatian@uts.edu.au>;

Dear Applicant

Your local research office has reviewed your application titled, "Defining Best Practice Methods for Studies of Biological and Clinical Correlates of Delirium: An International Modified Delphi Study", and agreed that this application now meets the requirements of the National Statement on Ethical Conduct in Human Research (2007) and has been approved on that basis. You are therefore authorised to commence activities as outlined in your application, subject to any conditions detailed in this document.

You are reminded that this letter constitutes ethics approval only. This research project must also be undertaken in accordance with all UTS policies and guidelines including the Research Management Policy (http://www.gsu.uts.edu.au/policies/research-management-policy.html).

Your approval number is UTS HREC REF NO. ETH18-2673.

Approval will be for a period of five (5) years from the date of this correspondence subject to the submission of annual progress reports.

The following standard conditions apply to your approval:

- Your approval number must be included in all participant material and advertisements. Any advertisements on Staff Connect without an approval number will be removed.

- The Principal Investigator will immediately report anything that might warrant review of ethical approval of the project to the Ethics Secretariat (Research.Ethics@uts.edu.au).

- The Principal Investigator will notify the UTS HREC of any event that requires a modification to the protocol or other project documents, and submit any required amendments prior to implementation. Instructions can be found at https://staff.uts.edu.au/topichub/Pages/Researching/Research%20Ethics%20and%20Integrity/Human%20research%20ethics/Post-approval/post-approval.aspx#tab2.

- The Principal Investigator will promptly report adverse events to the Ethics Secretariat

Appendix 5: Participant information sheets (PIS) and consent forms

Appendix 5.1: Study 2a (Delphi)

UTS UNIVERSITY OF TECHNOLOGY SYDNEY

Participant information sheet: Online Delphi study

PARTICIPANT INFORMATION SHEET

Study Title: Defining Methodological and Best Practice for Studies of Biological and Clinical Correlates of Delirium in Advanced Cancer - A Delphi Study

As an expert in the field of delirium research, we would like to invite you to take part in a Delphi Study. Before you decide whether or not you would like to take part, it is important to consider why the research is being done and what it will involve. Please read this information sheet carefully.

WHAT IS THE PURPOSE OF THIS STUDY?

There currently are no recommended guidelines for conducting delirium biomarker studies. The aim of this Delphi study is to obtain expert consensus on the most robust ways to undertake and report delirium biomarker research.

WHO IS DOING THE RESEARCH?

This research will be conducted by Ms Ingrid Arngarth-Duff, a doctoral student at the University of Technology Sydney under the supervision of Professor Meera Agar, Dr Annmarie Hosie and Associate Professor Gideon Caplan.

This research is part of a larger doctoral study by Ingrid Arngarth-Duff investigating the biological and clinical correlates of delirium in people with advanced cancer.

WHAT IS A DELPHI STUDY?

The Delphi technique seeks to obtain consensus on the opinions of experts (panel members) through a series of structured surveys. As part of the process, the responses from each round are aggregated and fed back in summarised form to the participants, who are then given an opportunity to respond and reflect again in response to the emerging data.

WHY HAVE I BEEN ASKED?

As an established expert in this field, you have important insights into the conduct, reporting, appraisal and synthesis of delirium biomarker research.

IF I SAY YES, WHAT WILL IT INVOLVE?

If you decide to participate, I will invite you to complete three online surveys delivered via email with a link to RedCap.

In the first round, you will be provided with open-ended questions about biomarker research in delirium. In the second round, you will be provided with a list of statements based on the previous rounds from all Delphi participants. You will be asked to rank them in terms of their importance in biomarker research. Detailed instructions for completion will be included on the survey to guide you. This process will continue until a group consensus has been achieved (we expect this will take three rounds). To allow a timely conclusion of the study we would respectfully request a response time of 2 weeks for completion of each round.

You will also be asked to give some background information about yourself including your area of specialty, how many years you have worked in that area, your involvement in delirium research, your country of residence, and a few more.

At completion of the survey, you will be asked to provide your email address in order to facilitate an invitation to be sent to you to complete Round 2. The email address you provide will not be used for any other purpose and will not be linked to your response data in any way.

No video or audio recording is involved.

It is greatly appreciated if you could complete each round. It is estimated that each round will take approximately 20 minutes to complete.

Study findings may be published, but you will not be identified in these publications.

ARE THERE ANY RISKS INVOLVED?

We expect minimal risks associated with participation in this study and all care will be taken to maintain participant privacy and confidentiality.

ARE THERE ANY BENEFITS INVOLVED?

You will not directly benefit from participation. The knowledge gained from the study may help researches in the future to better understand the pathophysiology of delirium, therefore benefiting people experiencing delirium.

DO I HAVE TO SAY YES?

Participation in this study is voluntary. It is entirely up to you whether or not you decide to take part. Your consent is implied when you complete the survey.

WHAT WILL HAPPEN IF I SAY NO?

If you decide not to participate, it will not affect your relationship with the researchers or the University of Technology Sydney. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage. If you wish to withdraw from the study once it has started, you can do so at any time without having to give a reason, by contacting Ingrid Amgarth-Duff at Ingrid.Amgarth-Duff@uts.edu.au

If you decide to leave the research project, the researchers will not collect additional personal information from you/ However, personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected up to the time you withdraw will form part of the research project results. If you do not want your data to be included, you must tell the researchers when you withdraw from the research project.

CONFIDENTIALITY

By completing the online survey, you consent to the research team collecting and using background information about you for the research project. All this information will be treated confidentially and all identifying data will be de-identified. All responses received in the study will be strictly confidential, and your identity will not be divulged. Your information will only be used for the purpose of this research project.

All electronic and hardcopy data will be securely locked and safely stored on a secure server. The data will be stored for five years following completion of the study and then will be destroyed. Only study staff will have access to the data and participant information.

We plan to publish the results in a peer reviewed journal. In any publication, information will be provided in such a way that you or your place of work cannot be identified.

STUDY CONTACT

If you have any questions, concerns about the research, or you would like to speak to the study team for any reason, please contact Ingrid Amgarth-Duff on +61401250706 or at Ingrid.Amgarth-Duff@uts.edu.au

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Appendix 5.2: Study 2b (Consensus meeting)

Participant information sheet: Consensus meeting

PARTICIPANT INFORMATION SHEET

Study Title: Toward Best Practice Methods for Delirium Biomarker Studies: Stage 2- Consensus Meeting

As an expert in the field of delirium research and/or reporting guideline development, we would like to invite you to take part in an online consensus meeting for development of reporting guidelines for delirium biomarker research. Before you decide whether or not you would like to take part, it is important to consider why the research is being done and what it will involve. Please read this information sheet carefully.

WHAT IS THE PURPOSE OF THIS STUDY?

There currently are no recommended reporting guidelines for delirium biomarker studies. The aim of the former Delphi study conducted in 2019 by our research team was to obtain expert consensus on the most robust ways to undertake and report delirium biomarker research. This consensus meeting follows on from the Delphi and aims to gather feedback on the preliminary reporting items generated in the Delphi.

WHO IS DOING THE RESEARCH?

This research will be conducted by Ms Ingrid Amgarth-Duff, a doctoral student at the University of Technology Sydney under the supervision of Professor Meera Agar, Associate Professor Annmarie Hosie and Associate Professor Gideon Caplan.

This research is part of a larger doctoral study by Ingrid Amgarth-Duff.

WHY HAVE I BEEN ASKED?

As an established expert in this field, you have important insights into the conduct, reporting, appraisal and synthesis of delirium biomarker research, or you have expertise in developing reporting guidelines.

IF I SAY YES, WHAT WILL IT INVOLVE?

If you decide to participate, you will be invited to take part in an online consensus meeting with Ingrid Amgarth-Duff (PhD candidate) and her three supervisors (Prof. Meera Agar, A/Prof Annmarie Hosie and A/Prof Gideon Caplan).

The consensus meeting is aimed at discussing the items that should be included in the final reporting guidelines. Furthermore, specifics on the wording and layout of items in the reporting guidelines will be discussed.

You will also be asked to give some background information about yourself including your area of specialty, how many years you have worked in that area, your involvement in delirium research and/or guideline development, and your country of residence.

We ask that each participant has access to a computer during the meeting to facilitate live voting of Delphi items. The meeting will be audio recorded then transcribed verbatim. No video recording is involved.

ARE THERE ANY RISKS INVOLVED?

We expect minimal risks associated with participation in this study and all care will be taken to maintain participant privacy and confidentiality.

ARE THERE ANY BENEFITS INVOLVED?

You will not directly benefit from participation. The knowledge gained from the study may help researches in the future to better understand the pathophysiology of delirium, therefore benefiting people experiencing delirium.

DO I HAVE TO SAY YES?

Participation in this study is voluntary. It is entirely up to you whether or not you decide to take part.

WHAT WILL HAPPEN IF I SAY NO?

If you decide not to participate, it will not affect your relationship with the researchers or the University of Technology Sydney. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage. If you wish to withdraw from the study once it has started, you can do so at any time without having to give a reason, by contacting Ingrid Amgarth-Duff at Ingrid.Amgarth-Duff@uts.edu.au.

If you decide to leave the research project, the researchers will not collect additional personal information from you.

CONFIDENTIALITY

All data collected will be treated confidentially and all identifying data will be de-identified. Your information will only be used for the purpose of this research project.

All electronic and hardcopy data will be securely locked and safely stored on a secure server. The data will be stored for five years following completion of the study and then will be destroyed. Only study staff will have access to the data and participant information.

We plan to publish the results in a peer reviewed journal. In any publication, information will be provided in such a way that you or your place of work cannot be identified.

STUDY CONTACT

If you have any questions, concerns about the research, or you would like to speak to the study team for any reason, please contact Ingrid Amgarth-Duff on +61 [redacted] or at Ingrid.Amgarth-Duff@uts.edu.au

NOTE:

This study has been approved by the University of Technology Sydney Human Research Ethics Committee [UTS HREC]. If you have any concerns or complaints about any aspect of the conduct of this research, please contact the Ethics Secretariat on ph.: +61 2 9514 2478 or email: Research.Ethics@uts.edu.au], and quote the UTS HREC reference number. Any matter raised will be treated confidentially, investigated and you will be informed of the outcome.

CONSENT FORM

Toward Best Practice Methods for Delirium Biomarker Studies: Stage 2- Consensus Meeting

(UTS HREC ETH20-4993)

I have read this form and have had the opportunity to consider and ask questions about the information regarding my involvement in this research project.

I agree to participate in this study. I understand that I am agreeing to take part in an online consensus meeting that will be audio recorded and transcribed verbatim.

By signing this form, I do not waive any legal rights. I may withdraw at any time after signing this form, without consequence and may ask for my data to be removed from the study. I understand that all information given will be strictly confidential and that my identity will not be divulged. I am aware that any given information will only be used for the purposes of this research project.

If you have any further questions or concerns about this research project, please contact Ingrid Amgarth-Duff on [redacted] or email Ingrid.Amgarth-Duff@uts.edu.au.

_____ ____/____/____

Name and Signature [participant] Date

_____ ____/____/____

Name and Signature [researcher] Date

Appendix 5.3: Study 3 (Qualitative study)

PARTICIPANT INFORMATION SHEET

Study Title: Defining Methodological and Best Practice for Studies of Biological and Clinical Correlates of Delirium in Advanced Cancer - A sub-study of the Delphi Study

UTS HREC APPROVAL NUMBER: ETH18-2673

As an expert in the field of delirium research, we would like to invite you to take part in an interview. Before you decide whether or not you would like to take part, it is important to consider why the research is being done and what it will involve. Please read this information sheet carefully.

WHAT IS THE PURPOSE OF THIS STUDY?

There currently are no recommended guidelines for conducting delirium biomarker studies which impacts on the quality of delirium studies. The aim of the Delphi study was to obtain expert opinion in delirium biomarker research methodology in order to develop reporting recommendations for future delirium biomarker studies. 60 statements reached consensus and remained 'in'.

There were however some key areas that were not able to be resolved through the Delphi process, which is why we are gathering your views about some of the complexities and nuances around conducting an ideal delirium biomarker study.

WHO IS DOING THE RESEARCH?

This research is conducted by Ms Ingrid Amgarth-Duff, a doctoral student at the University of Technology Sydney under the supervision of Professor Meera Agar, Dr Annmarie Hosie and Associate Professor Gideon Caplan.

This research is part of a larger doctoral study by Ingrid Amgarth-Duff investigating the biological and clinical correlates of delirium in people with advanced cancer.

WHY HAVE I BEEN ASKED?

As an established expert in this field, we would like your opinion about the methodological challengers of delirium biomarker studies, and the tailoring of delirium biomarker studies in the presence of underlying conditions.

IF I SAY YES, WHAT WILL IT INVOLVE?

Participation in this study includes an interview about your opinions on the best ways to conduct a robust biomarker study in delirium. We will conduct the interview at a time that is convenient to you. Depending on your location, the interview will be conducted either face-to-face or over the telephone or audio conferencing over the computer. All interviews will be audio recorded and transcribed verbatim. We anticipate the interview will take no longer than 60 minutes.

ARE THERE ANY RISKS INVOLVED?

We expect minimal risks associated with participation in this study. Completion of the interview may be tiring. We will make every effort to accommodate your schedule and you may take breaks if you need them.

ARE THERE ANY BENEFITS INVOLVED?

You will not directly benefit from participation in this study, although you might gain some satisfaction from the opportunity to discuss your experiences in delirium or cancer research. The knowledge gained from the study will help researchers in the future to better understand the pathophysiology of delirium, therefore potentially benefiting people at risk of or with delirium.

DO I HAVE TO SAY YES?

Participation in this study is voluntary. It is completely up to you whether or not you decide to take part.

WHAT WILL HAPPEN IF I SAY NO?

If you decide not to participate, it will not affect your relationship with the researchers or the University of Technology Sydney. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage. If you wish to withdraw from the study once it has started, you can do

so at any time without having to give a reason, by contacting Ingrid Amgarth-Duff on Ingrid.Amgarth-Duff@uts.edu.au.

If you decide to leave the research project, the researchers will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected up to the time you withdraw will form part of the research project results. If you do not want your data to be included, you must tell the researchers when you withdraw from the research project.

CONFIDENTIALITY

Your privacy and confidentiality will be respected. No information that reveals your identity will be released or published without consent unless required by law. All information and responses will be strictly confidential, and your identity will not be divulged. Your information will only be used for the purpose of this research project.

All electronic and hardcopy data will be securely locked and safely stored on a secure server. The data will be stored for five years following completion of the study and then will be destroyed. Only study staff will have access to the study data and participant information.

We plan to publish the results in a peer reviewed journal. In any publication, information will be provided in such a way that you or your place of work cannot be identified.

STUDY CONTACT

If you have any questions, concerns about the research, or you would like to speak to the study team for any reason, please feel free to contact Ingrid Amgarth-Duff on +61 [redacted] or at Ingrid.Amgarth-Duff@uts.edu.au

CONSENT FORM

Defining Best Practice Methods for Studies of Biological and Clinical Correlates of Delirium: A Delphi Study (HREC ETH18-2673)

I have read the participant information sheet and agree to participate in this study. I understand that I am agreeing to take part in an interview that will be audio recorded and transcribed verbatim.

By signing this form, I do not waive any legal rights. I may withdraw at any time after signing this form, without consequence and may ask for my data to be removed from the study. I understand that all information given will be strictly confidential and that my identity will not be divulged. I am aware that any given information will only be used for the purposes of this research project.

If you have any further questions or concerns about this research project, please contact Ingrid Amgarth-Duff by email Ingrid.Amgarth-Duff@uts.edu.au.

_____ ____/____/____

Name and Signature [participant] Date

_____ ____/____/____

Name and Signature [researcher] Date

Appendix 6: Delphi survey Round 1

Confidential

Delphi Round one (R1)

STUDY TITLE: Defining Methodological and Best Practice for Studies of Biological and Clinical Correlates of Delirium in Advanced Cancer - A Delphi Study.

Thank you for taking the time to complete this survey.

As an expert in the field of delirium, we would like to invite you to take part in this three-round Delphi Study. You are able to take part if you have had any experience in delirium research (including, but not restricted to delirium biomarker research).

Before you decide whether or not you would like to take part, it is important to consider why the research is being done and what it will involve. For more information please see attached the participant information sheet below.

WHAT IS THE PURPOSE OF THIS STUDY?

There currently are no recommended guidelines for conducting delirium biomarker studies. The aim of this Delphi study is to obtain expert consensus on the most robust ways to undertake and report delirium biomarker research.

As an established expert in this field, you have important insights into the conduct, reporting, appraisal and synthesis of delirium biomarker research.

WHAT WILL IT INVOLVE?

If you decide to participate, I will invite you to complete three online surveys. This is round one of the survey and it consists of a combination of open-ended questions and multiple choice. After completion of this survey, two other surveys will be sent to you via email some weeks apart. Round two and three will consist of closed-ended statements, whereby you will rank the importance of each statement.

It is greatly appreciated if you could complete all three rounds. Each round will take approximately 20 minutes to complete. To allow a timely conclusion of the study we respectfully request a response time of 2 weeks for completion of each round.

Please click 'next page' to start round one survey.

Participant information

Link to participant information sheet

[Attachment: "Participant information sheet_delphi_redcap.pdf"]

1. BACKGROUND

The first section of this survey will ask you some background questions about yourself and about your involvement in delirium research.

Have you been involved in any delirium research in the past 10 years?	○ Yes ○ No
How many years have you worked in delirium research?	○ 0-5 years ○ 5-10 years ○ 10+ years
How many delirium studies have you been involved in?	_____
What is your main delirium research area(s)? (choose as many as applicable)	☐ Basic science/animal research ☐ Epidemiology ☐ Implementation/knowledge translation/education ☐ Health services ☐ Clinical trials ☐ Qualitative research ☐ Other
Please specify.	_____
Have you conducted a biomarker study in delirium and/or another clinical area? (Choose as many as applicable)	☐ Yes- in delirium ☐ Yes- in another clinical area ☐ No
How many biomarker studies have you conducted?	_____
What is your current role?	○ Clinician ○ Researcher ○ Clinician/researcher ○ Laboratory researcher/scientist ○ Other
Please specify.	_____

What is your country of residence?	○ Afghanistan ○ Albania ○ Algeria ○ Andorra ○ Angola ○ Anguilla ○ Antigua & Barbuda ○ Argentina ○ Armenia ○ Australia ○ Austria ○ Azerbaijan ○ Bahamas ○ Bahrain ○ Bangladesh ○ Barbados ○ Belarus ○ Belgium ○ Belize ○ Benin ○ Bermuda ○ Bhutan ○ Bolivia ○ Bosnia & Herzegovina ○ Botswana ○ Brazil ○ Brunei Darussalam ○ Bulgaria ○ Burkina Faso ○ Burundi ○ Cambodia ○ Cameroon ○ Canada ○ Cape Verde ○ Cayman Islands ○ Central African Republic ○ Chad ○ Chile ○ China ○ China - Hong Kong / Macau ○ Colombia ○ Comoros ○ Congo ○ Democratic Republic of (DRC) ○ Costa Rica ○ Croatia ○ Cuba ○ Cyprus ○ Czech Republic ○ Denmark ○ Djibouti ○ Dominica ○ Dominican Republic ○ Ecuador ○ Egypt ○ El Salvador ○ Equatorial Guinea ○ Eritrea ○ Estonia ○ Ethiopia ○ Fiji ○ Finland ○ France ○ French Guiana ○ Gabon ○ Gambia ○ Georgia ○ Germany

- ○ Philippines
- ○ Poland
- ○ Portugal
- ○ Puerto Rico
- ○ Qatar
- ○ Reunion
- ○ Romania
- ○ Russian Federation
- ○ Rwanda
- ○ Saint Kitts and Nevis
- ○ Saint Lucia
- ○ Saint Vincent and the Grenadines
- ○ Samoa
- ○ Sao Tome and Principe
- ○ Saudi Arabia
- ○ Senegal
- ○ Serbia
- ○ Seychelles
- ○ Sierra Leone
- ○ Singapore
- ○ Slovak Republic (Slovakia)
- ○ Slovenia
- ○ Solomon Islands
- ○ Somalia
- ○ South Africa
- ○ South Sudan
- ○ Spain
- ○ Sri Lanka
- ○ Sudan
- ○ Suriname
- ○ Swaziland
- ○ Sweden
- ○ Switzerland
- ○ Syria
- ○ Tajikistan
- ○ Tanzania
- ○ Thailand
- ○ The Netherlands
- ○ Timor Leste
- ○ Togo
- ○ Trinidad & Tobago
- ○ Tunisia
- ○ Turkey
- ○ Turkmenistan
- ○ Turks & Caicos Islands
- ○ Uganda
- ○ Ukraine
- ○ United Arab Emirates
- ○ United Kingdom
- ○ United States of America (USA)
- ○ Uruguay
- ○ Uzbekistan
- ○ Venezuela
- ○ Vietnam
- ○ Virgin Islands (UK)
- ○ Virgin Islands (US)
- ○ Yemen
- ○ Zambia
- ○ Zimbabwe

What is your place of work?

(choose all that apply)

- ☐ Hospital
- ☐ University
- ☐ Research Centre
- ☐ Other

Please specify	_____
Do you have a research higher degree? (eg PhD or masters degree)	◯ Yes ◯ No
Was the topic in delirium or biomarkers?	◯ Yes - delirium ◯ Yes - biomarkers ◯ Yes - both ◯ No
Completion bar (%)	

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2. STUDY SAMPLE AND BIOMARKER **Section 2 questions focus on the study participants and the biomarker used in a study of delirium. Please respond in point form and/or written text.**	
What are the key elements to consider when choosing a biomarker to study?	_____
What are the key characteristics of the study sample that should be included/reported? (ie. inclusion/exclusion criteria)	_____
What do you consider are appropriate control groups?	_____
What are some key reasons for attrition in a delirium biomarker study?	_____
If you have any additional comments relating to study participants or biomarker selection, please comment here.	_____
Completion bar (%)	

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3. ASSAY PROCEDURES

Section 3 focuses on specimen characteristics and the assay procedures in delirium biomarker studies.

What are the most important elements of the assay procedure to consider and report?

_____

What are the most optimal biological materials for use in a delirium biomarker study? (rank each material on a scale from most optimal to least optimal)

	Most optimal	Sub-optimal (still provides useful information but has limitations)	Least optimal
Blood (plasma/serum)	○	○	○
Urine	○	○	○
Saliva	○	○	○
Cerebrospinal fluid	○	○	○
Other	○	○	○

Please specify and provide a reason for your choice.

_____

For the markers rated 'sub-optimal' above, please give a reason as to why these are less optimal.

_____

Do you believe blinding of the biomarker results to the clinical endpoint is essential?

○ Yes
○ No

Please explain.

_____

In what scenario(s) would blinding the biomarker to the clinical endpoints be essential? Please explain.

_____

What are the ideal time points that biomarkers should be collected in relation to delirium occurrence?

(choose all that apply)

☐ Prior to delirium episode
☐ During the first 24 hours of delirium episode
☐ At any stage during delirium episode
☐ Delirium resolution

Of the following variables, which are needed to ascertain the critical time points for biomarker collection?

☐ Time of delirium onset
☐ Time of specimen collection
☐ Other

Please specify.

_____

Do you think a delirium biomarker study can be embedded within an interventional study?	○ Yes ○ No ○ In some circumstances
Please explain.	_____
What are the key methodological considerations for the biomarker sub-study?	_____
If you have any additional comments relating to specimen characteristics or assay procedures please comment here.	_____
Completion bar (%)	

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4. CLINICAL VARIABLES

Section three focuses on the study design specific to delirium biomarker studies.

What core clinical covariates should be considered in delirium biomarker research?

(List all that apply)

- ☐ Age
- ☐ Gender
- ☐ Concurrent medication
- ☐ Comorbidities
- ☐ Other

Please specify.

_____

What are the important considerations when deciding which covariates to include in multivariate analysis?

_____

If you have any additional comments relating to clinical variables please comment here.

_____

Completion bar (%)

5. ANALYSIS AND RESULTS

Section four focuses on data analysis and reporting of the results of delirium biomarker studies. It is the final section of the survey.

What are the key elements to consider when deciding on a sample size for a delirium biomarker study?

_____

Which the following elements should be reported in univariate and multivariate analysis?

(Please tick only the ones that should be reported)

	Univariate	Multivariate
Estimated effect (hazard ratio, confidence intervals for the marker)	☐	☐
Use of cut-point and/or threshold	☐	☐
How model assumptions were verified	☐	☐
How missing data were handled	☐	☐
Sensitivity analyses	☐	☐
Internal validation	☐	☐
Number of included participants	☐	☐

What important confounding factors should be considered in delirium biomarker studies?

_____

If you have any additional comments relating to analysis and results please comment here.

_____

Completion bar (%)

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Thank you for completing round one of the survey.

Please note that when you click submit, you will be redirected to a page to provide your email address so round two can be sent out in some weeks.

Your email address will not be linked to your data responses in this survey.

Appendix 7: The REDEEMS checklist: Examples from published delirium biomarker studies

Item number	REDEEMS items	Vasunilashorn, 2017	Foroughan, 2015
1	**Study rationale**		
a	State the biomarker under study (including nature of the specimen)	Y	N
b	Describe the biological hypothesis(/es) tested*	Y	N
2	**Ascertainment of delirium**		
a	Describe the training and/or credentials of personnel who ascertained delirium cases	Y	Y
b	Specify the delirium tool and/or diagnostic process that was used to ascertain cases	Y	Y
c	Describe frequency, timing and duration of delirium assessment	Y	N
3	**Outcome measures**		
a	Define and justify all clinical endpoint(s) and their measures (including relationship to delirium where relevant)	Y	N
4	**Assay procedure**		
a	Specify the assay method used with a detailed protocol that includes reagents/kits	Y	N
b	Describe the methods of preservation, storage and processing of the biological sample	Y	N
c	Describe the assay validation method for repeatability and robustness including the sensitivity limits of the assay	Y	N
d	Specify the inter- and intra- assay coefficients of variation	Y	N
e	Specify the method of blinding biomarker results	N	N
5	**Timing of collection of the biological sample**		
a	Precisely describe the time of collection of the biological sample in relation to delirium (onset, presence, resolution)	Y	N
b	Provide a rationale for the timing of the sample collection based on the clinical scenario, the hypothesis being tested, and/or the study design	Y	N
6	**Confounding variables**		
a	State the confounding variables assessed and whether or not they were specified *a priori*	Y	N
b	Clearly define and provide justification for the confounding variables (including the relationship to delirium where relevant)	N	N
7	**Sample size**		
a	Describe how sample size was determined and provide a rationale	N	N
8	**Statistical analysis**		
a	Account for clinical and biomarker missing data in the analysis plan based on the design of the study	Y	N
b	State how confounding variables were accounted for in the analysis	Y	N
9	**Univariate and multivariable analysis**		

a	Report the estimated effect size or the p values with their Confidence Intervals (CI)	Y	Y
b	Specify whether the biomarker was dichotomised using a cut-point and/or threshold	Y	N
c	Specify the number of included participants and reasons for attrition or missing data	Y	N
d	Describe how model assumptions were verified (multivariable)	Y	N