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A scoping review to map empirical evidence regarding key domains and questions in the clinical pathway of delirium in palliative care.

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Abstract**Context**

Based on the clinical care pathway of delirium in palliative care (PC), a published analytic framework (AF) formulated research questions in key domains and recommended a scoping review to identify evidence gaps.

Objectives

To produce a literature map for key domains of the published AF: screening; prognosis and diagnosis; management and the health-related outcomes.

Methods

A standard scoping review framework was used by an interdisciplinary study team of nurse and physician delirium researchers, an information specialist and review methodologists to conduct the review. Knowledge user engagement provided context in refining nineteen AF questions. A peer reviewed search strategy identified citations in Medline, PsycINFO, Embase & CINAHL databases between 1980 and 2018. Two reviewers independently screened records for inclusion using explicit study eligibility criteria for the population, design, delirium diagnosis, and investigational intent.

Results

Of 104 studies reporting empirical data and meeting eligibility criteria, most were conducted in patients with cancer (73.1%) and in inpatient PC units (52%). The most frequent study design was a one or more group nonrandomized trial or cohort (67.3%). Evidence gaps were identified: delirium risk prediction; comparative effectiveness and harms of prevention, variability in delirium management across PC settings, advanced directive and substitute decision-maker input, and transition of care location; and estimating delirium reversibility. Future rigorous primary studies are required to address these gaps and preliminary concerns regarding the quality of extant literature.

Conclusion

Substantial evidence gaps exist, providing opportunities for future research regarding the assessment, prognosis and management of delirium in PC settings.

Key words: delirium, palliative care, assessment, prognosis, management, analytic framework.

Running Title: Scoping review of delirium in palliative care

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Introduction

Delirium is a complex neurocognitive and behavioral manifestation of an underlying medical abnormality. Its frequent occurrence is therefore not unexpected in the context of patients with advanced life-threatening illness in palliative care (PC) settings. Although the terms PC and hospice care are often used interchangeably, PC is considered applicable anywhere in a person's life-threatening illness trajectory, whereas hospice care has a more traditional association with the terminal phase of end-of-life care.¹ Both specialists and generalists deliver PC across a variety of settings: inpatient PC units in acute care settings and stand-alone inpatient hospices; hospital PC consult teams; and community PC services.¹ Although delirium is acknowledged as a frequent clinical problem in the context of PC,² its poor recognition and documentation in clinical practice is a substantive concern.^{3,4} Across all healthcare settings, delirium is associated with high levels of mortality and morbidity, and poorer outcomes in general;^{5,6} it is thus a major contributor to healthcare costs.⁷

Standardized clinical criteria, such as those of the International Classification of Diseases, tenth and recently released eleventh edition (ICD-10 and ICD-11), and the Diagnostic Statistical Manual of Mental Disorders, fifth edition (DSM-5) exist to aid clinicians in diagnosing delirium.⁸⁻¹⁰ The Confusion Assessment Method (CAM) is a briefly administered assessment tool that is widely used to screen for delirium.¹¹ Although it was validated in relation to the earlier DSM-III-R criteria,¹² it broadly operationalizes the current DSM-5 delirium criteria.¹³ The DSM-5 delirium features include the following: a disturbance of attention and awareness; short onset (hours to days) and fluctuation over the course of the day; an additional cognitive disturbance, such as disorientation, memory or language deficits, or perceptual abnormalities; the disturbances are not better explained by an evolving or existing dementia, or that they occur in a coma; and there is clinical evidence through history, examination or investigations that the disturbance is related to another general medical condition, substance intoxication (for example, a medication) or withdrawal, or multiple etiologic factors.¹³ On the basis of the type of psychomotor disturbance observed, delirium is classified as no motor subtype (normal psychomotor activity), hypo- or hyperactive, or a mixed subtype with both hypo- and hyperactive features.^{14,15} The hypoactive subtype is common in PC settings and is the most prone to go undetected.¹⁶ Misdiagnosis of delirium most commonly occurs as dementia and depression.¹⁷⁻¹⁹ Regular screening for delirium in PC settings has been advocated,^{20,21} particularly in

view of its characteristic fluctuations, the frequency of the hypoactive subtype, and the risk of misdiagnosis, but there has been very limited evaluation of the effectiveness of screening in this context.²²

Although advanced age, pre-existing or evolving dementia, and frailty may confer a baseline vulnerability or risk toward delirium in older persons in general,² delirium occurring in the PC context is particularly precipitated by one or more acute medical events, such as organ failure, infection, and medication or metabolic effects.²³ Although baseline and precipitant risk factors for delirium have been identified in other care settings, there has been relatively limited evaluation of these in PC settings. Furthermore, findings from studies that evaluate either delirium risk or therapeutic interventions in settings such as postoperative or critical care may have limited generalizability to PC settings. Delirium generates high levels of distress for patients, their families and their professional caregivers in PC settings by impeding potentially precious communication and generating behavioral disturbances.²⁴ The standard PC approach to delirium management involves symptomatic management, treatment of reversible precipitating factors (if consistent with the goals of care) in addition to patient and family support.^{22 23} Symptomatic management may involve varying degrees of non-pharmacological and pharmacological intervention.^{22 26}

Most patients in PC settings experience an irreversible delirium in the last hours or days of life.²⁷ Part or full reversal of delirium may occur prior to the terminal phase, but depends on the presence of modifiable etiologic factors, their investigation, and treatment. The patient's goals of care are typically more focused on comfort in many PC settings, particularly in hospice care. This may limit the investigation and treatment of delirium precipitants, thus perhaps increasing the use of antipsychotic and other sedating medications to symptomatically treat delirium. If the goals of care are unclear and clinical uncertainty exists regarding the reversibility of an episode of delirium, there is a potential risk of adopting the extremes of either undue fatalism (missing potentially reversible delirium precipitants and premature use of deep pharmacological sedation to control the symptoms of delirium) or alternatively, taking an overly medicalized (inappropriately burdensome and non-cost-effective intervention) approach to delirium management.²³

The association of delirium with older age, dementia and comorbidity burden,^{2 28} and the projected population increase in the proportion of elderly person,²⁹ together signal a pressing need for knowledge synthesis

to guide all practitioners in palliative and end-of-life care to conduct effective, evidence-based interventions at all points along the clinical care pathway of delirium. Recognizing this need, our group organized an international interdisciplinary research planning meeting with a broad spectrum of leading delirium researchers and knowledge-users in 2012 as part of an overarching program of research, entitled Studies to UNderstand Delirium In Palliative Care Settings (SUNDIPS).³⁰ We identified key areas of potential uncertainty, controversy or clinical equipoise in the clinical care pathway of delirium in PC: the benefit/burden ratio for therapeutic decisions; the outcomes and impact of delirium; the goals of care; the use of deep pharmacological sedation to control the symptoms of delirium; cost-effectiveness issues; patient-reported outcomes, experiential impact of delirium and its treatment on family and caregivers; and limited access to certain therapeutic interventions and the potential need to transition to a new place of care, such as home to hospice or hospice to acute care. We subsequently constructed and published an analytic framework (AF) with pivotal research questions, based on the delirium care pathway in PC.³¹

As a preliminary step, a comprehensive map of the scope and nature of the knowledge in the scientific literature and its gaps is a prerequisite to proceeding with systematic reviews and further clinical research studies.³¹ We conducted a scoping review of delirium in PC settings with specific aims: (1) to map the literature for the key domains and pivotal questions in the clinical care pathway of delirium in PC settings, as previously identified in our AF: screening, prognosis and diagnosis; management (including pharmacological and non-pharmacological therapeutic interventions) in the context of the goals of care; and outcomes and impact, including clinical, experiential (patient, family and professional caregivers) and economic; (2) to identify the knowledge gaps and research priorities regarding delirium in PC settings, thus providing the potential to refine the existing research questions in our AF, and determine where systematic reviews are feasible and warranted prior to planning future clinical research studies; and (3) to consolidate our integrated knowledge user, consultative and collaborative process, as initiated in our SUNDIPS meeting, so as to address the specific contextual decision-making issues regarding delirium in PC and establish research priorities.

Methods

Study team composition

The core study team consisted of two PC physicians based in an inpatient care setting, a critical care physician, two post-doctoral PC nursing delirium researchers, a critical care pharmaco-epidemiologist, an information specialist, a systematic review methodologist, an epidemiologist and two research assistants. Collaborative author input was received from a psychiatrist that conducted many delirium studies in a hospice setting and PC physicians from across a variety of settings, including a community consult service, a hospital consult service and a university academic department.

Scoping review framework

A scoping review has been defined as “a form of knowledge synthesis that addresses an exploratory research question aimed at mapping key concepts, types of evidence, and gaps in research related to a defined area or field by systematically searching, selecting, and synthesizing existing knowledge.”³² Scoping reviews thus represent a novel approach to mapping the landscape of published literature. Following previous recommendations regarding scoping review methodology,^{32,33} we adopted a standard six-phase framework approach to the conduct of the review: (1) developing a rationale and identifying the research questions; (2) identifying relevant studies; (3) study selection; (4) charting the data; (5) collating, summarizing, and reporting the results; and (6) collaborative consultation, which partly preceded but was also an integral part of phase one and phase five of this framework.

Developing a rationale and identifying the research questions

The background and rationale for this scoping review have been described in relation to the inaugural SUNDIPS meeting.^{30,31} Many of the knowledge users, methods experts and independent researchers who attended this meeting collaborated on many of its related publications.^{21,27,31,34-36} Although a broader consultative meeting is not a formal requirement in scoping reviews,³³ we considered the initial and sustained engagement of knowledge users (administrators, senior nursing personnel and policy developers) as an important aspect of the review. We therefore scheduled an initial 2-hour meeting of knowledge users and core study team members to review the research questions from the AF. Through this meeting and both subsequent consultation and iterative input, the 18 initially identified AF questions were refined and a question in relation to transition of care was added. An

updated version of the AF is depicted in **Figure 1** and the refined research questions, now totalling 19 are outlined in **Table 1**. We did not publish or register the protocol due to the absence of such formal arrangements for scoping reviews, but signalled the basis of the scoping review in our published AF paper.³¹

Consistent with standard recommendations that the primary research question of a scoping review be broad, we asked the question: *what is the scope and nature of the scientific literature addressing the assessment, management, outcomes and impact of delirium in PC settings?* This broad question encompasses the specific AF research questions, as initially identified in the SUNDIPS meeting and further refined through subsequent consultation.

Identifying relevant studies

A search strategy was developed by an experienced information specialist (LS), and externally peer reviewed by another information specialist. The search was conducted across Medline (via Ovid), Embase (via Ovid), CINAHL (via EBSCOHost) and PsycINFO (via Ovid) databases. Pilot screening of a sample of retrieved records was employed to further refine the search concept and strategy and help finalize key data extraction items. The search strategy included a combination of various terms in relation to 'palliative care' and 'delirium'. (**Appendix 1, Supplementary Table 1**) The strategy was modified as appropriate in accordance with the specific database searched. Secondary searching of the included studies was also used to identify and map studies in relation to the pivotal areas in the AF. The literature search was initially limited to the time period of 1980 to July 2nd 2015; further updated searches were conducted to December 31st 2016 and May 16th 2018. The rationale for the 1980 limit was based on the absence of DSM diagnostic criteria for delirium prior to 1980.

Study selection

The titles and abstracts of those studies identified in the literature search were uploaded into DistillerSR,³⁷ a software program designed to support the conduct of systematic reviews. Explicit *a priori* eligibility criteria (**Table 2**) were applied at Level 1 (title and abstract) and Level 2 (full text) screening. The principal inclusion criterion was for the study (including systematic reviews) to address one or more of the 19 questions in the AF. Furthermore,

from a feasibility perspective, we reserved the option of modifying the scoping review and limiting it to a subset of questions if either the volume of retrieved records or included studies became unmanageable.

In addition to including relevant studies that were clearly documented as having been conducted in palliative settings and involving participants with a clearly defined principal palliative indicator diagnosis, we also included relevant studies whose study populations had cancer or Adult Immune Deficiency Syndrome (AIDS) as a progressive life-threatening illness and were unequivocally eligible for PC referral but had study assessments conducted by oncology, psychiatry, psycho-oncology or a designated supportive care service. We excluded publications such as editorials, commentaries, narrative reviews and letters that did not report primary empirical data. Studies were excluded if the diagnosis of delirium was not clearly defined according to standard criteria such as DSM or ICD diagnostic criteria, or a diagnostic cut-off score on a validated assessment (diagnostic or screening) tool such as the Confusion Assessment Method (CAM), or standard psychiatric assessment. The scoping methodology supported an inclusive approach, which involved the inclusion of conference abstracts and systematic reviews, based on their meeting eligibility criteria and their potential to address at least one of the 19 AF questions.

Full texts of included studies were examined to confirm inclusion, extract relevant data and map them to specific research questions. In the absence of a full text publication, an abstract-only article was included if it otherwise met the eligibility criteria. Dual screening at Levels 1 and 2 was conducted independently by two senior researchers (PGL and SHB) and all conflicting selections were discussed and resolved, if necessary through the input of a third reviewer (MTA). The single best reason for exclusion at Level 2 was also recorded. The data extraction process was undertaken by a single reviewer (PGL) with a two-reviewer (PGL and SHB) consensus reserved for unclear records. As a quality check to verify the accuracy of data extraction, a random 10% of the data were independently verified by a third reviewer (NAR).

Charting the data

Data extraction included the following items: study design; country of origin; study population; sample size; delirium diagnostic criteria used or validated tool used for diagnosis; and key outcome domains. Study records

were tagged by the research question(s) that they addressed. In keeping with the standards for scoping reviews, included studies were not formally appraised for risk of bias.^{33,38} We adopted an inclusive approach to comparative effectiveness and harms evaluation: in addition to therapeutic interventions, we also included screening, diagnostic and prognostic tool evaluations if they reported some comparative effectiveness or harms outcomes.

Collating, summarizing, and reporting the results

Cognizant of the potential overlap between some primary studies and included systematic reviews, relevant findings were reported separately or discretely (for example, using the term 'multiple' in relation to systematic review characteristics) where possible to avoid exaggerating the available evidence in relation to our research questions. We used the broad qualitative characteristics and the numerical distribution of mapped evidence addressing each of the *a priori* research questions to formulate our recommendations for future research: a subsequent systematic review, a survey of patient experience or experience of those who care for patients at risk of or in delirium in a PC setting, or a primary experimental/observational study to fill the knowledge gaps identified.

Towards the end of the project, once the data were summarized, the knowledge users were again consulted and their opinions noted in relation to future research priorities from among the research questions, the identified knowledge gaps and the potential for knowledge synthesis, as generated through the scoping review. The main outcome of our scoping review was to answer the broad primary research question and thus advance the SUNDIPS program of research by setting the foundation for future studies.

Results

Study screening and inclusion

The literature search, including updates, identified 6800 citation records. The flow of information in identifying, screening and selecting studies is summarized in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)³⁹ flow diagram in **Figure 2**. Screening at title and abstract level identified 390 citation records as eligible to proceed to full text review level. Of the 287 references reviewed and excluded at full text review level,

the three most frequent single reasons for exclusion were the investigational intent of the study (n=90), the study design (n=63) and the lack of valid diagnostic criteria used for delirium diagnosis (n=56), together accounting for 209 (73%) of the single reasons for exclusion. A total of 104 studies therefore met the eligibility criteria for final inclusion.⁴⁰⁻¹⁴³ These included a published PhD thesis⁵⁰ and also a prospective study with 19 patients¹⁰⁶ that despite the arbitrary eligibility cut-off of 20 for sample size, was deemed by consensus to warrant inclusion because of the very few studies that prospectively evaluated terminal delirium. Eleven of the included studies were conference abstracts with no available full text but were included because their abstracts met the review's eligibility criteria.^{40,58,74,79,89,99,104,114,115,116,143}

General study characteristics

The general study characteristics of the included studies are summarized individually in **Appendix 2**, **Supplementary Table 2**, and an aggregate summary of their characteristics with citations is presented in **Table 3**. Thirty-seven studies (35.6%) originated from the USA, 14 (13.5%) from Japan, 10 (9.6%) from Canada, 6 (5.8%) from ≥ 2 countries, 6 (5.8%) from Australia, 5 (4.8%) from UK, 4 (3.8%) from each of Ireland, Spain and Portugal, 2 (1.9%) from each of Netherlands, Germany, Italy and Taiwan, and 1 (1%) from each of Hong Kong, South Korea, Belgium, Norway, Turkey and Mexico.

Seventy-six (73.1%) of study samples were individually comprised mostly ($\geq 79\%$) of subjects with a cancer diagnosis. Eight (7.7%) studies had sample subjects with a heterogeneous mix of life-threatening diagnoses. In 3 (2.9%) studies,^{54,75,141} all or $\geq 90\%$ of the sample had a diagnosis of AIDS. One (1%) study was conducted exclusively in patients with hepatic failure¹³⁹ and 1 (1%) exclusively in patients with dementia.¹²¹ In 12 (11.5%) studies, the palliative indicator diagnosis was unclear or not reported. The baseline dementia status was unclear or unreported in 55 (52.9%) of the included studies. Patients with dementia were excluded in 15 (14.4%) studies and 33 (31.7%) studies included or reported a mix of patients with and without dementia. In 1 (1%) study,¹²¹ all patients had dementia. Three studies reported a subgroup analysis on the basis of dementia status.^{47,56,111} One included study (1%) reported the baseline Parkinson's disease status of the study sample.⁹⁴

Forty-eight (46.2%) studies were conducted exclusively in single centre inpatient PC units. The other PC specific settings of study samples consisted of a mix across hospital and community settings. Seventeen (16.3%) studies were conducted through a psychiatry service in an eligible population for study inclusion in our review. A further 15 (14.4%) studies were conducted in hospitalized oncology patients who met our population eligibility criteria but PC service involvement was not reported, and similarly, 1 (1%) study of patients with cancer attending a cancer centre emergency department was also included.

Of the included studies, 60 (57.7%) were uncontrolled, nonrandomized trials or single group cohort studies, 10 (9.6%) involved two or multiple groups in a nonrandomized trial or cohort study (comparative studies of ≥ 2 interventions, tests, risk factors or other exposures). Forty-two (40.4%) of the included studies had either a prospective cohort design or a prospective cohort component, and a further 12 (11.5%) were reported as secondary analyses of prospectively collected data; the remainder ($n=15$) of the cohort studies were retrospective. The second most frequent design was cross-sectional, occurring in 18 (17.3%) studies. There were both 5 (4.8%) formal systematic reviews and randomized controlled trials among the included studies. Based on reviewer consensus, two additional reviews were included:^{124,131} both involved systematic literature searches and addressed some of the AF questions but lacked a quality appraisal of their included studies, and by definition were not formal systematic reviews. Apart from these reviews, the remaining 97 included primary studies were conducted in a total of 25,690 subjects. Most (79.8%, $n=83$) of the study samples had a mix of adult age groups and were not age selected. Similarly, most (71.2%, $n=74$) of the study samples were comprised of a heterogeneous mix of male and female subjects. Age and sex status were either unclear or unreported in 15 (14.4%) and 25 (24%) studies, respectively.

The diagnostic criteria and/or validated assessment tools used to make the diagnosis of delirium are summarized in **Appendix 3, Supplementary Table 3.**^{8 9 12 55 67 82 144-156} The most common criteria used among the included studies were those of the DSM: the DSM-IV¹⁴⁶ or DSM-IV-TR¹⁴⁷ was used in 45 (43.3%) studies and the DSM-III-R¹⁴⁵ in 9 (8.7%). Of validated tools, the CAM,¹² Delirium Rating Scale (DRS) or its revised form (DRS-98-R),¹⁴⁸¹⁴⁹ and MDAS⁵⁵ were used in 32 (30.8%), 17 (16.3%) and 27 (26%) studies, respectively. A classification of delirium

based on psychomotor status was reported in 36 (35%) studies; one of these also reported a syndromal and subsyndromal classification.¹²⁷

Studies of epidemiological burden, prediction and prevention of delirium

Studies investigating the epidemiological burden (prevalence or incidence), prediction of and prevention of delirium are summarized in **Table 4** in relation to related questions (**Q1-Q5**) from the AF. A total of 48 (46.2%) and 31 (29.8%) studies investigated prevalence and incidence, respectively. Thirty-eight studies (36.5%) investigated risk factors for the onset of delirium; these included 9 (8.7%) that reported some form of risk prediction model. There were 2 (1.9%) studies that reported the comparative effectiveness/harms of delirium prevention strategies,^{57,77} one involved hydration as a preventive intervention,⁵⁷ and no study examined delirium preventative management strategies guided by risk prediction.

Studies of screening, diagnosis and classification of delirium

Studies investigating the screening, diagnosis and classification of delirium are summarized in **Table 5** in relation to related questions (**Q6-Q9**) from the AF. A total of 18 (17.3%) studies investigated delirium screening; these included 7 (6.7%) and 5 (4.8%) studies that investigated the diagnostic performance of a screening test against a reference standard, and the diagnostic performance of two or more screening tests against a reference standard, respectively. Nine (8.7%) studies reported the comparative effectiveness or harms of screening tests.

A total of 9 (8.7%) studies investigated the diagnosis of delirium; these included 6 (5.8%) and 2 (1.9%) studies that evaluated the test performance of a diagnostic test against a reference standard, and the test performance of two or more diagnostic tests against a reference standard, respectively. Three (2.9%) studies reported on the comparative effectiveness or harms of diagnostic tests.

A total of 3 (2.9%) studies investigated the psychomotor classification of delirium; these included 2 (1.9%) and 1 (1%) studies that investigated the diagnostic performance of a psychomotor classification test against a reference standard, and the diagnostic performance of two or more psychomotor classification tests against a reference standard, respectively. None of these studies reported on the comparative effectiveness or harms of psychomotor classification tests.

Studies of the management of delirium and prediction of response

Studies investigating the management of delirium and the prediction of response to management are summarized in **Table 6** in relation to related questions (**Q10-Q19**) from the AF. A total 24 (23.1%) studies investigated the comparative effectiveness or harms of one or more pharmacological management approach (Q13), whereas 2 (1.9%) studies, including a systematic review, investigated the comparative effectiveness or harms of non-pharmacological management approaches (Q14). A total of 13 (12.5%) studies investigated risk factors for the prediction of response (reversibility) to the management of delirium (Q16); these included 4 (3.8%) studies of predictive models for reversibility (Q17). None of the included studies investigated variability in delirium management across PC settings (Q10, Q11), delirium management strategies incorporating advanced directives (Q12), or the impact of transition of care setting for delirium management (Q15).

Reported comparative effectiveness or harms outcomes

A total of 37 (35.9%) of the included studies reported comparative effectiveness or harms outcomes; three of these studies involved the use of additional assessment tools that were not previously referenced in the review: the Richmond Agitation-Sedation Scale (RASS),¹⁵⁷ the Chinese version of the DRS (DRS-Chinese),¹⁵⁸ and Mini-mental State Examination (MMSE).¹⁵⁹ (**Appendix 4, Supplementary Table 4**) Thirteen (12.5%) of these studies involved a direct comparison of 2 or more active study interventions.^{46-48,54,59,62,74,80,86,94,95,103,124} Among these there were 2 formal systematic reviews, one of screening tools,^{62,95,119} and one of pharmacological intervention⁹⁵ that overlapped with a primary study⁵⁴; one systematic literature review study of pharmacological interventions,¹²⁴ overlapping with two primary studies;^{47,54} one study of screening;⁸⁰ the remaining 10 studies involved pharmacological comparisons with most having delirium severity change and adverse events related to therapy as study outcomes. A further 13 (12.5%) studies included two formal systematic reviews, one of screening tools⁶² and one of assisted hydration and delirium severity;⁹⁵ a systematic literature review study that reported on effectiveness and harms of pharmacological interventions and exercise,¹³¹ overlapping with one primary study in relation to exercise;¹³⁸ primary studies comparing one or more active study interventions against placebo^{41,57} or no active intervention^{122,138} or current standard management,^{72,77,113,121,127} or reference standard in the context of an assessment tool.¹⁰¹ A total of 14 (13.5%) studies reported comparative effectiveness or harms using a before and

after analysis; these included one systematic literature review study,¹²⁴ overlapping with a primary study on olanzapine,⁵⁶ four studies of assessment tools,^{44,89,126,128} and the remaining nine studies involved pharmacological intervention.^{45,53,56,69,75,85,107,117,133} Although a wide variety of outcomes were reported in association with comparative effectiveness and harms analyses, neither falls nor economic cost were among these outcomes. Objective outcomes were most commonly reported, for example, delirium severity measure changes and adverse events related to treatment were reported in 21 (20.3%) and 18 (17.3%) of studies, respectively, whereas experiential outcomes were infrequently reported.

Evidence gaps and potential opportunities for further studies

Based on identified gaps, the study group's recommendations regarding future primary studies and related outcomes, endorsed by knowledge user consultation, are summarized along with systematic review opportunities in **Table 7**. Among the studies investigating the epidemiological burden (prevalence or incidence), prediction of and prevention of delirium (Q1-5 in AF), there were substantive study numbers to address Q1-3, with most of the risk factor studies reporting crude, unadjusted risk association. However, none of the studies with risk prediction models reported external validation (Q4) and there were only 2 studies addressing Q5, the prevention of delirium in PC settings. Overall, these data suggest that there are enough studies to consider systematic reviews for Q1-3 and that further primary studies are needed for Q4-5. Among the studies investigating delirium screening (Q6-7), diagnosis (Q8-9), psychomotor classification (Q8 only), and management (Q13-14 and Q16-17 only) there appears to be sufficient numbers of studies to support the conduct of a systematic review in relation to each of these questions. Remarkably, none of the primary studies that were included in this scoping review addressed the questions regarding variability of practice across different PC settings (Q10-12), nor did any address the comparative effectiveness or harms of care location transition in relation to delirium (Q15), the external validation of any of the predictive models for delirium reversibility (Q18) or their comparative effectiveness or harms (Q19), indicating the need for primary studies in relation to Q10-12, Q15 and Q18-19

Discussion

Using recommended scoping review methods, 104 published studies with empirical data were mapped onto research domains and key questions from a prespecified AF. In addition to the contribution of recognized delirium researchers, the generation of key questions and their subsequent refinement and expansion was based on the initial and ongoing engagement of a broad spectrum of decision makers and knowledge users from clinical, administrative and policy sectors in palliative and hospice care. These collective perspectives informed commentary on core aspects of the review: general appraisal of the literature; the strengths, challenges and limitations of the review; methodological and other considerations regarding future research. The emerging methodological concerns, as identified in the scoping review, along with related recommendations are summarized in **Table 8**.

General appraisal of the literature

Of the 278 excluded studies at full text level review, 56 (19.5%) were excluded because of failure to report clear or valid delirium diagnostic criteria, which highlights the importance of using standardized diagnostic criteria in future studies. Most (73.1%) of the included studies in the review were conducted in patients with cancer. This raises concerns for the generalizability for some research findings to the broader current and projected PC population, which will not only include a substantive proportion of patients with cancer but increasingly is likely to be comprised of a heterogeneous mix of palliative indicator diagnoses, co-morbid chronic illness and multimorbidity, including dementia and various organ failure diagnoses.^{160 161} Moreover, dementia is one of the strongest risk factors for delirium in the elderly, yet its baseline status was either not reported or unclear in 52.9% of the studies included in the review. Similarly, the baseline Parkinson's disease status was only documented in 1 study; this is a concern, particularly in studies of antipsychotics in delirium management and the need to determine extrapyramidal effects due to these medications. Of the included studies, approximately half were conducted in inpatient PC units, whereas only 6.7% and 2% were conducted in hospital PC consult service settings and community PC settings, respectively. The generalizability of any study findings across these different study settings could be problematic. There were few systematic reviews and randomized controlled trials (RCTs); the lack of RCTs may reflect ethical, symptom burden and attritional challenges of conducting such studies in frail PC populations.³⁶

¹⁶² Taken together, the under representation of certain palliative indicator diagnoses in study samples, the low

number of hospital consultation and community-based PC service studies, the deficits in baseline documentation, the relative paucity of RCTs and systematic reviews highlight gaps and raise both generalizability and quality concerns in the current literature, with the caveat that a full quality and risk of bias appraisal is beyond the remit of a scoping review.

Strengths, challenges and limitations of the review

This review has many strengths: a rigorous peer reviewed search strategy; an updated search of the most relevant databases; engagement of knowledge-users; interprofessional study team input with high-level clinical and methodological expertise; refined and expanded key questions derived from an AF that was based on the clinical pathway of delirium in PC; independent dual screening of records; and conduct of the review in accordance with recommended standards. The restriction of studies selected to those of English language is a limitation. We also encountered many challenges in conducting the review, some of which might also be acknowledged as limitations.

One of the challenges encountered was semantic ambiguity in relation to delirium terminology. The literature on delirium is replete with multiple terms for delirium,²⁸ such as encephalopathy and acute confusional state, to name just two. We addressed this issue in part by setting clear eligibility criteria for study inclusion: for the diagnosis of delirium, included studies were required to have met DSM or ICD diagnostic criteria or have used a diagnostic score on an assessment tool that had been either directly or indirectly validated against the DSM or ICD diagnostic criteria. Despite this, there were many studies of hepatic encephalopathy, for example, in which we strongly suspect that the subjects had delirium. However, while the criteria used specifically for hepatic encephalopathy were clearly met in these studies, they were not directly congruent with DSM or ICD criteria. This mismatch in taxonomy between the disciplines of hepatology and psychiatry meant that many of the hepatic encephalopathy studies were excluded at Level 1 or 2 screening phases.

We encountered somewhat similar issues in relation to defining the PC population for the purposes of the review. The World Health Organization definition of PC is inclusive of those with “life-threatening illness.”¹⁶³ This broad definition includes many patients who are admitted to critical care units, although such units might not be conventionally viewed as “palliative care settings” per se. There has been a huge surge in studies of delirium in

critical care over the past decade, and although this has contributed greatly to our understanding of delirium, the focus and intensity of medical management may differ quite a bit between an inpatient hospice and critical care setting. Consequently, studies of patients admitted to critical or intensive care were excluded in our review: the consensus was that ultimately the inclusion of critical care studies of delirium, although desirable, might limit the generalizability of the scoping review findings. We acknowledge this as a limitation that was arguably unavoidable. We also encountered some uncertainty regarding studies of patients with cancer or AIDS as a progressive life-threatening illness and were not necessarily seen by a PC service in consultation, yet were unequivocally eligible for PC referral but assessed by oncology, psychiatry, psycho-oncology or supportive care services; such studies were included in our review if they otherwise met the eligibility criteria.

Although the AF key questions encompassed many of the pertinent decision-making questions in the clinical care pathway of delirium, we acknowledge that the review's calibration towards addressing these clinical and epidemiological questions with empirical data and the consequent exclusion of grey literature and qualitative studies could mean that important components of care such as family education and support may have fallen outside the scope of the review. Similarly, by limiting the scope of screening and diagnostic assessment tools to the palliative care context, perhaps the search did not capture studies addressing the use of delirium assessment tools in other populations or contexts that might have potential applicability in the palliative care setting. Moreover, the outcomes reported in the included studies were largely clinical and limited in relation to patient, family and professional caregiver experience. Although we adopted a standardized approach to capturing data in relation to knowledge user input through the SUNDIPS meeting, funding restrictions meant that subsequent knowledge user input was recorded in a less formal, standardized and therefore transparent manner. Furthermore, lack of a more formal engagement of knowledge users at the end of the study can be viewed as a missed opportunity in terms of knowledge translation.

Methodological and other considerations regarding future research

Based on absence of data, primary studies are required in relation to many issues in the care pathway of delirium in PC settings: external validation of delirium risk prediction models; comparative effectiveness and harms of prevention strategies and psychomotor classification of delirium; variability in delirium management and related

outcomes across the various PC settings and in relation to advanced directive and substitute decision-maker input; the experiential impact of transition of care location in relation to delirium management; and external validation of predictive models in estimating delirium reversibility. In addition to these primary study requirements, other primary studies and methodological issues warrant consideration.

Our group are currently conducting systematic reviews of delirium in the palliative care context with regard to its epidemiological burden, assessment and reversibility. Although systematic reviews appear feasible in relation to some of our research questions, our preliminary concerns, based on a broad and admittedly not an in-depth appraisal of quality and risk of bias of the selected extant literature, also indicate a need for more rigorous primary studies in relation to the domains or questions for which data already exists. This is particularly relevant to the evidence base for delirium management in PC, especially the pharmacological approach to the symptomatic management of delirium in PC settings, for which four RCTs were identified in the review.^{41,54,94,103} One of these RCTs included a placebo arm and demonstrated better symptom distress scores in the placebo treated group compared to the antipsychotic treated (haloperidol or risperidone) groups.⁴¹ This result has generated vigorous debate and calls for more studies regarding this issue.¹⁶⁴ A recent survey of medical specialists in Palliative Medicine highlighted the marked variability in pharmacological management of delirious symptoms and the perceived need for more rigorous studies.¹⁶⁵ Although RCTs contribute the highest level of evidence, depending on the intervention, pragmatic clinical trials, despite their challenges,¹⁶⁶ may provide useful data regarding effectiveness, and in the PC setting may offer a more feasible alternative.

Risk prediction models or scores for the onset and reversibility of delirium could potentially provide key information for optimal management decision-making by categorising and triaging patients into specific risk categories and accordingly tailoring patient management.^{167,168} Use of this approach has the potential to reduce unnecessary testing and treatment, thus minimizing related harms and costs. Evidence for risk prediction is ideally developed sequentially, involving development, validation and impact assessment phases.¹⁶⁹ Studies of risk factors inform the development of high performing risk prediction models, which are subsequently externally validated in various relevant population subgroups and settings. Finally, evidence of their effectiveness and impact establishes them in routine clinical practice. This scoping review highlights important gaps in evidence in this regard. No

studies exist that have established the effectiveness of an externally validated risk prediction model, while few extant risk prediction model development studies for delirium occurrence and reversibility were identified. Future research agenda filling this research gap could employ existing administrative databases to develop and validate rigorous risk prediction models; their clinical effectiveness could be established in subsequent studies. The degree to which existing databases can be examined might be compromised due to uncertainty regarding the validity of the coding for the diagnosis of delirium; validating the relevant diagnostic codes might therefore be a pre-requisite step.¹⁷⁰

In terms of the various study outcomes associated with delirium management, and the recognized economic cost associated with delirium in other settings, we were unable to find any studies that reported an economic cost associated with delirium and its management in PC settings. Although delirium has a reported reversibility of 50% for episodes in an acute PC unit,¹⁰⁰ and vigorous pursuit of reversal is often appropriate, it is also the case in clinical practice that delirium reversal is often inappropriately pursued with potentially burdensome and expensive investigations in the absence of externally validated predictive models or risk scores to guide the most appropriate level of therapeutic intervention. There is therefore a need to link an economic evaluation of delirium management with the intensity of the therapeutic attempts at delirium reversal. Some researchers have already begun to work towards developing a common core set of predefined delirium outcomes, albeit that some outcomes will be setting specific.¹⁷¹ Future primary studies will require broad collaborative input with substantive interdisciplinary involvement and for larger, adequately powered trials, multicentre collaboration is essential. Furthermore, mixed methods approaches that capture the experiences of patients and families and engage knowledge-users to inform and define the most meaningful outcomes in rigorously designed controlled trials and other studies, would be well suited to address the complexity of delirium and its management in the PC setting.¹⁷²

Conclusion

In examining the scope and nature of the published scientific literature that addresses the assessment, management, outcomes and impact of delirium in PC settings, primary studies are required to address many

existing gaps: lack of external validation of delirium risk prediction models; lack of reports on the comparative effectiveness and harms of prevention strategies and psychomotor classification of delirium; no data on the degree of variability in delirium management and related outcomes across the various types of PC settings, advanced directive and substitute decision-maker input, the experiential impact of transition of care location in relation to delirium management; and lack of external validation of predictive models in estimating delirium reversibility. Based on the number of studies, it appears feasible to conduct systematic reviews in relation to some aspects: the epidemiological burden (incidence and prevalence) of delirium, the risk factors for and diagnosis of delirium, the test performance of delirium psychomotor classification strategies, the pharmacological and non-pharmacological management of delirium, and the prediction of delirium reversibility. The scoping review's broad appraisal of study quality and limited external validity of some studies, based on population selection, together raised some preliminary concerns that warrant a more in-depth analysis and also reflect the importance of rigor in future studies. In addition, future studies will require broad collaboration from a multicentre, interdisciplinary and administrative knowledge user perspective. Mixed methods approaches incorporating experiential outcomes for patient, family and professional caregivers will be required to address some of the more complex aspects of delirium.

This scoping review's findings will hopefully guide researchers and assist us towards the long-term goal of studies in the SUNDIPS research program: to generate knowledge synthesis and translation, inform guidelines and policy for delirium management and thus improve the experience of patients (and their families) with or at risk of delirium in PC settings and across the spectrum of end-of-life care.

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Declaration

All authors have no conflicts of interest to declare

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Table 1 Research domains and questions related to analytic framework in Figure 1**Epidemiological burden of delirium**

1. What are the incidence and prevalence rates of delirium in the various palliative care settings (acute care, inpatient hospice and hospital care, and community palliative services)?

Delirium Prediction and prevention

2. What are the baseline and precipitating risk factors for onset of delirium?
3. What is the performance of the various delirium risk prediction models under current standards of care and how do they compare with each other?
4. Does the model have transportability or external validity?
5. What are the comparative effectiveness and harms of the various delirium-preventative management strategies (including but not limited to management guided by delirium risk prediction) among themselves or between them and a no delirium-preventative management option?

Screening for Delirium in PC settings

6. What is the test performance of the various delirium screening tests (e.g. cognitive active screening, informal caregiver observational passive screening, etc.) and how do they compare with each other?
7. What are the comparative effectiveness and harms of the various delirium screening tests/strategies among themselves or between them and a no screening option (e.g. cognitive active screening of all patients versus cognitive active screening triaged by nurse/informal caregiver observational passive screening for important delirium associated outcomes)?

Diagnosis and classification of Delirium

8. What is the diagnostic performance of the various validated delirium diagnostic and classification tools (in current use) and how do they compare with each other?
9. What are the comparative effectiveness and harms of the various validated delirium diagnostic and classification tools/strategies (in current use) among themselves or between them and a no diagnostic testing option or no classification option, respectively?

Management of Delirium

10. What is the extent of variability in management of delirium across the various care settings (acute care, inpatient hospice and hospital care, and community palliative services)?
11. Is the variability in management of delirium across the various care settings (acute care, inpatient hospice and hospital care, and community palliative services) associated with important differences in outcomes of benefits and harms?
12. What are the comparative effectiveness and harms of delirium management strategies that incorporate advanced directives and/or substitute decision maker input versus those that do not?
13. What are the comparative effectiveness and harms of the various pharmacologic symptom directed interventions among themselves, against non-pharmacologic therapies or a no therapy option?
14. What are the comparative effectiveness and harms of the various nonpharmacologic symptom directed interventions among themselves, against pharmacologic therapies or a no therapy option?
15. For patients in community settings (private home, nursing home, long-term care facility) who develop delirium in the context of predominantly palliative goals of care, what is the comparative effectiveness (e.g. higher probability of reversal of delirium; quality of life gain; reduction of family caregiver burden) and harms (undue invasive procedures, break in continuity of care, burdensome transition; potential separation from family) of transfer to hospital care settings (emergency or inpatient care) or inpatient hospice care for subsequent management versus continued care in their community settings? What patient or environmental factors might explain any observed heterogeneity in outcomes across studies?

Prediction of response to management and treatment of Delirium

16. In patients with established delirium, what are the risk factors that predict its non-reversibility or its complete or partial reversibility and sustainability of response?
17. What is the performance of the various risk prediction models that predict complete or partial reversibility of delirium under current standards of care and how do they compare with each other?
18. Does the model have transportability or external validity?
19. What are the comparative effectiveness and harms of patient management guided by models predicting delirium reversibility among themselves or between them and a no delirium prediction-based management option?

Table 2 Eligibility criteria for delirium scoping review

1. Inclusion criteria: a record was included if it provided an answer to at least one of the 19 questions (see **Table 1**) in the analytic framework (see **Figure 1**) and meets none of the exclusion criteria.

2. Exclusion criteria: a record was excluded if it met one or more of the criteria (a-i); reviewers selected a single best response.

- a) Availability:** insufficient information to ascertain relevance beyond title (neither abstract nor full text are available)
- b) Language:** abstract and/or full text of record is in a language other than English
- c) Sample size:** less than 20 participants
- d) Population:** not adult (exclusively or as an analytic subgroup) or does not meet the contextual criterion of patients in palliative care settings (admitted to an inpatient palliative care or hospice unit; followed by a hospital consult palliative care team; having cancer or AIDS as a progressive life-threatening illness and unequivocally eligible for palliative care referral but assessed by an oncology, psychiatry, psycho-oncology or supportive care service; or under the care of a community hospice or palliative care program)
- e) Diagnosis of delirium:** is not clearly defined according to standard criteria such as one or more of the following: Diagnostic and Statistical Manual (DSM) of Mental Disorders criteria for delirium, International Classification of Diseases (ICD) diagnostic criteria, a diagnostic cut-off score on a validated assessment (diagnostic or screening) tool such as the Confusion Assessment Method (CAM), or standard psychiatric assessment
- f) Design:** it is not a systematic review, randomized controlled trial or analytic observational study (cohort, case-cohort, nested case-control, case-control or time series)
- g) Investigational intent (primary or secondary):** does not aim to empirically investigate any of the following:
 - incidence or prevalence estimates of delirium or its level of reversal (complete, partial or non-reversal)
 - risk factors for delirium onset or its reversal (complete, partial or non-reversal)
 - accuracy, performance, effectiveness or harms of medical tests for screening, diagnosis or classification of delirium

- development, performance, validation, effectiveness or harms of risk prediction models for delirium onset or its reversal (complete, partial or non-reversal)
 - comparative effectiveness or harms of delirium-preventative management strategies
 - variability in management of delirium across palliative care settings
 - comparative effectiveness or harms of delirium management or treatment, transfer to hospital care settings (emergency or inpatient care) or inpatient hospice care for subsequent management
 - cost-effectiveness of delirium screening, diagnosis, classification, prognosis, or management/treatment
- h) Insufficient information:** investigational intent, study design, population, or sample size remains unclear due to insufficient information in full text or abstract only records
- i) Other reason(s):** as documented by reviewers

Table 3 Aggregate summary of study characteristics of included studies (N=104)

Study characteristics	Studies N=104 (%)
Geographic origin	
USA ^{45-57,60,63-66,69-71,73-75,94,104,106,120-122,128,133,134,136,139,141,142}	37 (35.6)
Japan ^{42, 97,107,108,112-115,117,118,130,137,138,140}	14 (13.5)
Canada ^{76-83,100,101}	10 (9.6)
Multiple countries ^{62,91,93,95,109,110}	6 (5.8)
Australia ^{40,41,92,105,127,132}	6 (5.8)
UK ^{44,59,89,126,135}	5 (4.8)
Other ^{43,58,61,67,68,72,84-88,90,96,98,99,102,103,111,116,119,123-125,129,131,143}	26 (25)
Palliative indicator diagnosis*	
Cancer in all or ≥ 90% ^{40,42,43,45-53,55-57,60,61,63-66,68-73,77-81,83,85-88,90-94,96-108,111-118,122,125,127,129-133,135-138,140}	74 (71.2)
Heterogeneous mix of life-threatening illnesses ^{41,44,62,76,119,120,128,134}	8 (7.7)
AIDS ^{54,75,141}	3 (2.9)
AIDS or cancer (systematic reviews, each included reference #54) ^{59,95,124}	3 (2.9)
Hepatic failure ¹³⁹	1 (1)
Dementia ¹²¹	1 (1)
Unclear or unreported ^{58,67,74,82,84,89,109,110,123,126,142,143}	12 (11.5)
Care setting or service	
Single inpatient Palliative Care Unit (PCU)	48 (46.2)
Hospital-based ^{44,58,67,69,74,88,92,96,98,99-101,103,108,111,112,114,115,117,118,125,136,143}	23 (22.1)
Hospice-based ^{57,72,78,79,84,102,107,109,110,121,123,126-129,135}	16 (15.4)
Cancer center-based ^{65,66,85-87,93,94,133}	8 (7.7)
Institutional base unclear ¹⁴¹	1 (1)

Inpatient PCU combined with either ≥ 1 other inpatient PCU or a non-inpatient PC setting	6 (5.8)
Inpatient PCUs ^{40,41,43,61,77}	5 (4.8)
Inpatient PCU with community PC setting ¹²⁰	1 (1)
Other specific PC settings	11 (10.6)
Hospital PC consult service ^{63,71,89,113,116,138,142}	7 (6.7)
Community PC settings ^{64,76,134}	3 (2.9)
Hospital PC outpatient setting ¹⁰⁴	1 (1)
Multiple PC settings in formal systematic reviews and systematic literature reviews ^{62,90,91,95,124,131}	6 (5.8)
Psychiatry service referrals in eligible population ^{42,45-48,53-56,59,60,75,97,106,122,130,139}	17 (16.3)
Hospitalized oncology patients ^{49-52,68,73,80-83,105,119,132,137,140}	15 (14.4)
Cancer center emergency department ⁷⁰	1 (1)
Study design	
Formal systematic review ^{59,62,90,91,95}	5 (4.8)
Randomized controlled trial ^{41,54,57,94,103}	5 (4.8)
Uncontrolled nonrandomized trial or cohort with one or more groups	70 (67.3)
Prospective ^{40,56,61,67-69,72,73,75,77,78,81-88,93,96-98,100,102,105-107,112,116-118,121,123,125,126,128-130,140,143}	41 (39.4)
Mixed prospective cohort and cross-sectional parts ¹³⁵	1 (1)
Secondary analysis of prospective data ^{45-53,66,80,134}	12 (11.5)
Retrospective ^{42,58,63,64,71,74,104,108,115,119,122,133,137,138,141}	15 (14.4)
Unclear or unreported ¹¹¹	1 (1)
Cross-sectional study ^{43,55,60,65,70,76,79,92,99,101,109,113,114,120,127,132,136,139}	18 (17.3)
Case-control study ^{110,142}	2 (1.9)
Uncontrolled before-after study ^{44,89}	2 (1.9)
Non-formal systematic review study with systematic literature review ^{124,131}	2 (1.9)
Demographics of study sample subjects	

Age		
Age mixed / not age selected	^{41,42,45-49,53-64,66-73,75-88,91-94,96-103,105-113,117-120,122,123,125,127-130,132-138,141-143}	83 (79.8)
Age ≥ 65	^{50,51,52,74,140}	5 (4.8)
Age < 59	¹³⁹	1 (1)
Unclear or unreported	^{40,43,44,65,89,90,95,104,114-116,121,124,126,131}	15 (14.4)
Sex		
Mixed / not sex selected	^{41,42,45,46,48-57,59,61-64,66,68-73,76-78,81,83-88,91-94,96-101,103,105-113,117,118,120,122,123,125-130,132,133,135-138,140}	74 (71.2)
Male only selected	^{75,134,141,142}	4 (3.8)
Female only selected	⁶⁰	1 (1)
Unclear or reported	^{40,43,44,47,58,65,67,74,79,80,82,89,90,95,102,104,114-116,119,121,124,131,139,143}	25 (24)

*In 2 additional studies,^{102,136} cancer was the principal palliative indicator diagnosis in 87.2% and 79% of subjects, respectively.

†Both of these reviews involved systematic literature searches and addressed some of the AF questions but lacked a quality appraisal of their included studies, and by definition were not formal systematic reviews.

Table 4 Studies that addressed the epidemiological burden, prediction and prevention of delirium

Research domains and related questions (Q)†		Study Reference Number	Studies N=104 (%)
Epidemiological burden of Delirium			
Q 1	Prevalence investigated	42,44,50,52,58,60,63-65,70-72,75,76,78-83,87-93,96-98-100,104-107,111-114,116,120,126,135,136,139-141,143	48 (46.2)
	Incidence investigated	50,52,58,60,66-68,73,75,77-82,88,91,98,100,105,106,114-116,119,125-127,134,137,142	31 (29.8)
Prediction and Prevention			
Q 2	Investigates risk factor(s) for onset of delirium (risk association study)	40,48,50,52,53,58,61,66,68,73,75,81,83,84,88,98-100,104-108,114,115,118,119,122,125,126,130,134,135,137,139-142	38 (36.5)
Q 3	Involved development of delirium risk prediction model (or score)	73,81,83,105,114,119,134,141,142	9 (8.7)
Q 4	Investigates transportability or external validity of risk prediction model		0 (0)
Q 5	Investigates effectiveness and/or harms of delirium-preventative management strategies guided by risk prediction		0 (0)
	Compares effectiveness and harms of other delirium-preventative management strategies with each other or routine care?	57, 77	2 (1.9)

†Domains and questions (Q1-Q5) from the analytic framework as presented in Table 1 and Figure 1

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Table 5 Studies that addressed screening, diagnosis and classification of delirium

Research domains and related questions (Q)†		Study reference numbers	Studies N=104 (%)
Screening			
Q 6	Investigates screening to detect subsyndromal and/or full syndromal delirium	44,62,64,67,72,78,80,82,89,90,121,126-129,132,136,139	18 (17.3)
	Investigates the diagnostic performance of a delirium screening test vs a reference standard	62,64,67,78,90,129,136	7 (6.7)
	Investigates the comparative diagnostic performance of delirium screening tests (Test A vs reference standard; Test B vs same reference standard)	62,80,82,132,139	5 (4.8)
Q 7	Investigates comparative effectiveness and/or harms of screening tests among themselves or between them and routine patient care	44,62,72,80,89,121,126-128	9 (8.7)
Diagnosis and Classification			
Q 8	Investigates the establishment of delirium diagnosis	43,55,82,89,90,101,110,113,123	9 (8.7)
	Investigates the diagnostic performance of a delirium diagnostic test vs a reference standard	43,55,90,101,110,123	6 (5.8)
	Investigates the comparative diagnostic performance of delirium diagnostic tests (Test A vs reference standard; Test B vs same reference standard)	82,110	2 (1.9)
Q 9	Investigates comparative effectiveness and/or harms of diagnostic tests among themselves or between them and routine	89, 101, 113	3 (2.9)

	patient care		
Q 8	Investigates diagnostic performance of 1 or more psychomotor classification test(s) of delirium	84,109,131	3 (2.9)
Q 9	Investigates comparative effectiveness/harms of 1 or more psychomotor classification test(s) of delirium		0 (0)

†Domains and questions (Q6-Q9) from the analytic framework as presented in Table 1 and Figure 1

Table 6 Studies that addressed the management of delirium and prediction of response

Research domains and related questions (Q)†		Study reference numbers	Studies N=104 (%)
Management approach			
Q 13	Investigates comparative effectiveness and/or harms of ≥ 1 pharmacological management approach to delirium	41,45-48,53,54,56,57,59,69,74,75,85,86,94,95,97,103,107,117,122,124,133	24 (23.1)
Q 14	Investigates comparative effectiveness and/or harms of ≥ 1 non-pharmacological management approach to delirium	131,138	2 (1.9)
Prediction of response to management			
Q 16	Prediction of response (reversibility) to management of delirium	49,51,53,56,68,98,100,102,111,118,122,124,130	13 (12.5)
Q 17	Investigates model development for predictors of delirium reversibility	98,100,102,111	4 (3.8)

†Domains and questions (Q10-Q19) from the analytic framework as presented in Table 1 and Figure 1: none of the included studies mapped onto the following questions: Q 10-12, Q 15, Q 18 and Q 19.

Table 7 Future research recommendations regarding delirium in palliative care settings

Research strategy	AF domain/questions (Qs)	Relevant focus or recommendation
Systematic review (SR)	Epidemiological burden (Q1)	<ul style="list-style-type: none"> • Incidence and prevalence; pooled estimates
	Prognosis (Q2-3)	<ul style="list-style-type: none"> • Predictive model and risk association studies
	Screening (Q6)	<ul style="list-style-type: none"> • Screening test performance and CEH
	Diagnosis (Q8-9)	<ul style="list-style-type: none"> • Diagnostic test performance and CEH
	Classification (Q8)	<ul style="list-style-type: none"> • Sufficient studies for test performance only
	Management (Q13-14) and reversibility (Q16-17)	<ul style="list-style-type: none"> • CEH; current formal SRs require updating • Predictive model and risk association studies
Primary studies	Risk factor identification and prevention strategies (Q2-5)	<ul style="list-style-type: none"> • Predictive models for delirium occurrence; predictive score to determine risk; CEH of such models/scores • RCTs of preventive strategies, particularly non-pharmacological interventions to prevent delirium
	Screening, diagnosis and classification (Q6-9)	<ul style="list-style-type: none"> • Diagnostic performance studies of assessment tools in these domains • CEH studies of screening, diagnosis and psychomotor classification
	Management issues (Q10-19)	<ul style="list-style-type: none"> • Variability across PC settings and related outcomes • Advanced directives and goals of care designation • Community studies and impact of transition of care setting for delirium management

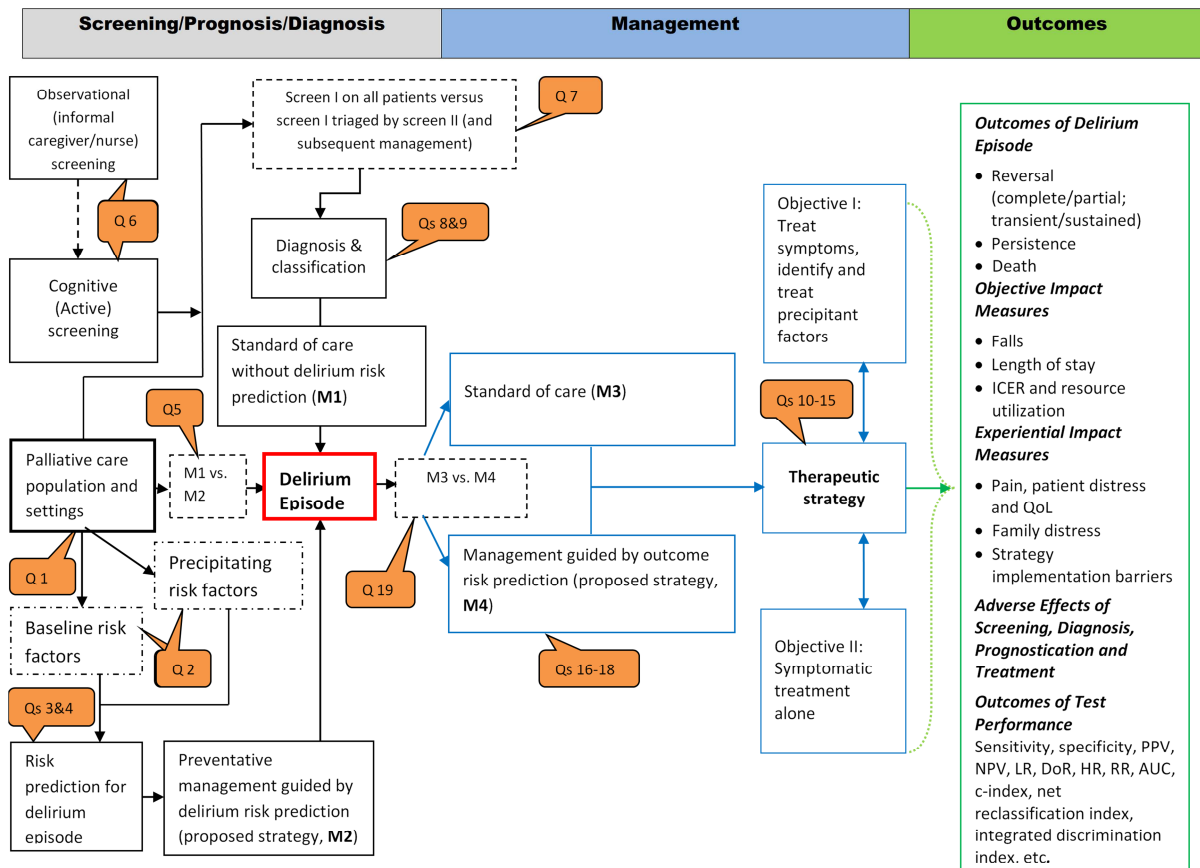
		<ul style="list-style-type: none"> • Pharmacological and particularly non-pharmacological intervention; both RCTs and PTs
		<ul style="list-style-type: none"> • Externally validated predictive models for reversibility
	Outcomes needing further evaluation (related to Q2-19 in AF)	<ul style="list-style-type: none"> • CEH in general, including assessment and management interventions • Experiential (patient/family/professional caregiver) • Economic cost

AF: analytic framework; CEH: comparative effectiveness or harms; RCT: randomized controlled trial; PC: palliative care; PT: pragmatic trial

Table 8 Additional methodological considerations regarding future research

Methodological issue	Recommendation
Defining a palliative care population	<ul style="list-style-type: none"> • Reality is that the PC population is becoming increasingly heterogeneous; some studies (eg, risk factor evaluation) may benefit from selecting a more homogeneous sample regarding palliative indicator diagnosis; alternatively, consider stratification or subgroup analysis
Delirium diagnosis	<ul style="list-style-type: none"> • Use ICD/DSM standard criteria or standard cut-off score on a tool validated against ICD/DSM criteria • Diagnostic algorithm for chart diagnosis/coding in database studies
Baseline documentation of dementia status	<ul style="list-style-type: none"> • Document due to potential impact on outcomes and their evaluation; consider stratification or subgroup analysis on the basis of dementia status
Baseline documentation of Parkinson's disease status	<ul style="list-style-type: none"> • Document particularly in studies of antipsychotics; potential to cause extrapyramidal side-effects
Outcomes: definition; evaluation of additional outcomes	<ul style="list-style-type: none"> • Definition of core outcomes • Experiential outcomes for patients, families and professional caregivers; mixed methods approach will likely be required for some aspects
Collaboration	<ul style="list-style-type: none"> • Consider multi-centre collaboration to facilitate recruitment for RCTs and PTs • Consider interdisciplinary and knowledge user collaboration

PC: palliative care; ICD: International Classification of Disease;^{9,10} DSM: Diagnostic Statistical Manual of Mental Disorders⁸ RCT: randomized controlled trial; PT: pragmatic trial;



ICER=incremental cost-effectiveness ratio; QoL=quality of life; PPV=positive predictive value; NPV=negative predictive value; LR=likelihood ratio; DoR=diagnostic odds ratio; c-index= concordance index; AUC=area under the curve. Boxes with broken lines are not steps in the care pathway but describe either a relevant clinical equipoise or determinants of a pathway step. M1 and M2 are pre-delirium management strategies; M3 and M4 are strategies to manage established delirium.

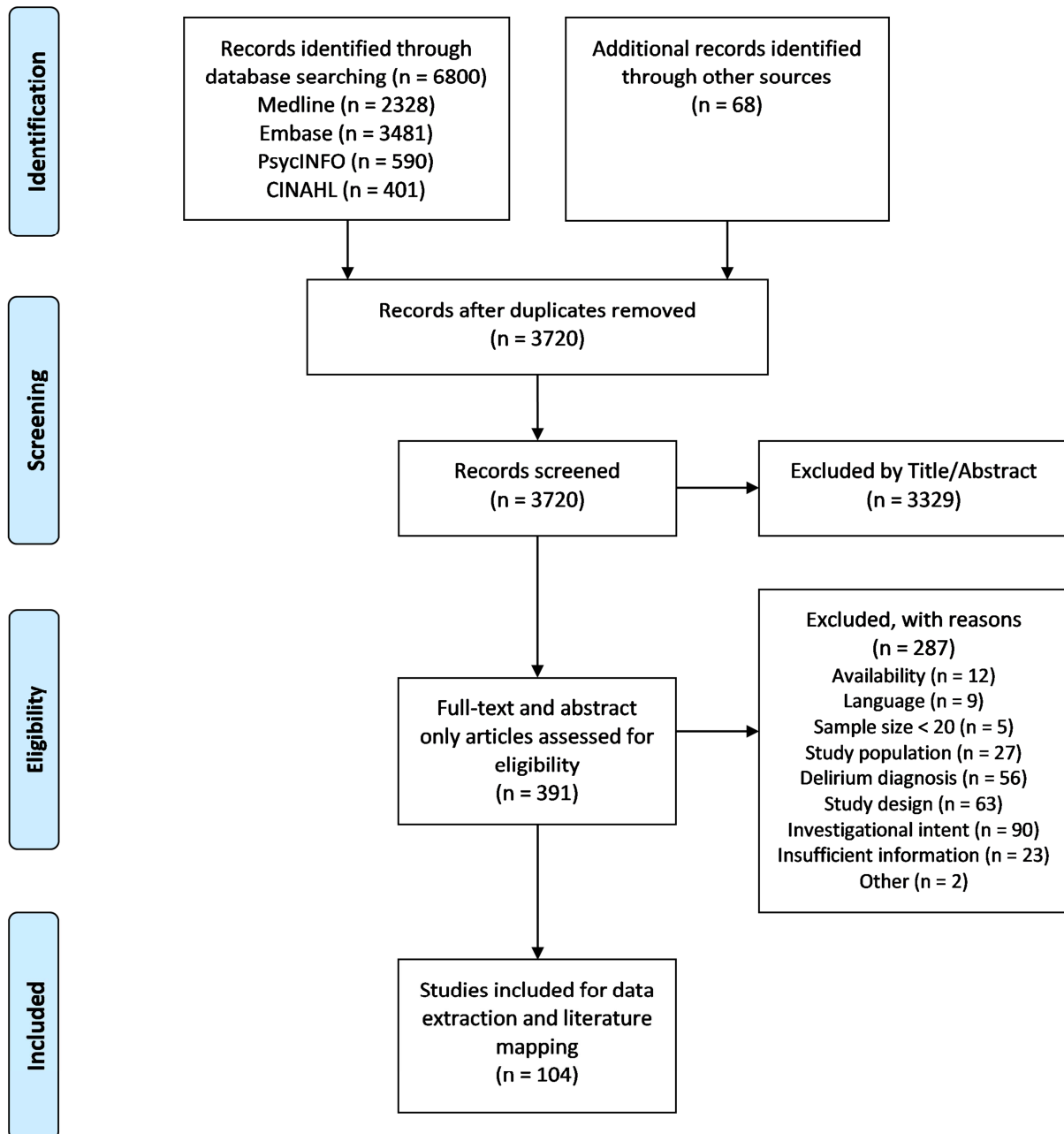


Figure 2 PRISMA Flow diagram for delirium scoping review