Risk factors for delirium in adult patients receiving specialist palliative care: A systematic review and meta-analysis

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Abstract

Background: Delirium is common and distressing for patients receiving palliative care. Interventions targeting modifiable risk factors in other settings have been shown to prevent delirium. Research on delirium risk factors in palliative care can inform context-specific risk-reduction interventions.

Aim: To investigate risk factors for the development of delirium in adult patients receiving specialist palliative care.

Design: Systematic review and meta-analysis (PROSPERO CRD42019157168).

Data sources: CINAHL, Cochrane Database of Systematic Reviews, Embase, MEDLINE and PsycINFO (1980-2021) were searched for studies reporting the association of risk factors with delirium incidence/prevalence for patients receiving specialist palliative care. Study risk of bias and certainty of evidence for each risk factor were assessed.

Results: Of 28 included studies, 16 conducted only univariate analysis, 12 conducted multivariate analysis. The evidence for delirium risk factors was limited with low to very low certainty.

Potentially modifiable risk factors: Opioids and lower performance status were positively associated with delirium, with some evidence also for dehydration, hypoxaemia, sleep disturbance, liver dysfunction and infection. Mixed, or very limited, evidence was found for some factors targetted in multicomponent prevention interventions: sensory impairments, mobility, catheter use, polypharmacy (single study), pain, constipation, nutrition (mixed evidence).

Non-modifiable risk factors: Older age, male sex, primary brain cancer or brain metastases and lung cancer were positively associated with delirium.

Conclusions: Findings may usefully inform interventions to reduce delirium risk but more high quality prospective cohort studies are required to enable greater certainty about associations of different risk factors with delirium during specialist palliative care.

Keywords

Risk factors, delirium, palliative care, systematic review, meta-analysis

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What is already known about the topic?

- Delirium is common and distressing in patients receiving palliative care.
- Studies of multicomponent interventions targeting modifiable delirium risk factors have reported delirium risk reduction in other settings.
- There is uncertainty about which delirium risk factors to address in patients receiving palliative care.

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> **What this paper adds?**
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> - A number of studies have examined delirium risk factors for patients receiving palliative care but the overall evidence is limited with low to very low certainty.
> - Potentially modifiable risk factors reported to be positively associated with delirium included opioids and lower performance status, with some evidence of association for dehydration, hypoxaemia, sleep disturbance, liver dysfunction and infection.
> - The evidence for several risk factors commonly targeted in preventative interventions in other settings was mixed or reported in a single study only.
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> **Implications for practice, theory or policy**
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> - There is a need for more high quality prospective cohort studies to enable greater certainty in the association of different risk factors with delirium.
> - The limited evidence may be used to inform interventions to reduce the risk of delirium in the palliative care context.

Introduction

Delirium is a distressing condition that is common in patients with advanced illness and associated with serious adverse outcomes.[1–3] It is a manifestation of underlying and multifactorial pathophysiological abnormalities and is characterised by acute and fluctuating disturbances in attention, awareness and cognition.[4,5] Multicomponent interventions targeting modifiable risk factors reduce the risk of delirium by around one in three cases during hospitalisation.[6,7]

Systematic reviews suggest that although many risk factors for delirium are common across different patient populations and settings, their types and strengths of association vary. Reviews in older hospitalised patients[8] and Intensive Care Units[9] both found strong associations with older age, dementia and illness severity, but other significant risk factors differed and some were setting-specific, such as mechanical ventilation in intensive care. Vasilevskis et al.[10] and Ahmed et al.[8] have highlighted this variability between clinical settings and patient populations. Therefore, it is important to identify specific delirium risk factors, and the strengths of their association, for patients receiving palliative care. For example, palliative care patients' risk of delirium may be increased due to factors related to advanced disease and multi-organ dysfunction[11] and their frequent exposure to iatrogenic risk factors such as opioids. However, to our knowledge, no systematic review of delirium risk factors in patients receiving palliative care has yet been reported.[12]

Synthesis of evidence on potentially modifiable risk factors is important to inform the design of interventions to reduce the risk of developing delirium. The term, 'potentially modifiable' is used in this review as the modifiability of some delirium risk factors in the palliative care context may vary, depending on factors such as the patients' illness trajectory and goals of care. This evidence may also be used, in conjunction with that on non-modifiable risk factors, to develop predictive models of patient groups most likely to develop delirium.[11]

This systematic review aimed to investigate risk factors for delirium in adult patients receiving specialist palliative care and address the research questions:

1. What possible risk factors for delirium have been measured in studies of adult patients receiving specialist palliative care?
2. What is the strength of association of identified risk factors with delirium incidence or prevalence in adult patients receiving specialist palliative care?

Methods

The protocol is registered on PROSPERO on 11.11.2019 (CRD42019157168).[13] The review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[14] Review guidance specific to observational studies of aetiology also informed its conduct.[15] The definition of a risk factor as, 'A factor that is causally related to a change in the risk of a relevant health process, outcome or condition'[16] was used.

Eligibility criteria

Eligibility criteria were framed according to PECO (Participants, Exposures, Comparators, Outcomes) criteria.[15] Eligible participants were adult patients (≥18 years) receiving specialist palliative care services, including in-patient care in a hospice or hospital palliative care unit, palliative care consultation teams and specialist out-patient and community services. Studies needed to report the association of a possible risk factor with delirium incidence or prevalence, or data permitting its calculation.

Studies that included only risk markers *per se* (non-causal predictive factors e.g. educational level) were excluded. Eligible studies needed to report delirium diagnosis using Diagnostic and Statistical Manual (DSM) or International Classification of Diseases (ICD) diagnostic criteria or a diagnostic cut-off score on a validated assessment (diagnostic or screening) tool. Studies needed to

compare occurrence of delirium in those exposed and not exposed to the potential risk factor.

Study designs eligible for inclusion included prospective and retrospective cohort studies, case-control, cross-sectional studies and randomised controlled trials. Case studies, case series, qualitative studies, opinion pieces and reviews were excluded. Studies published from 1980 onwards were included (when delirium was first included in DSM-III).[17] No language restrictions were imposed. Abstracts were excluded if no full text was available.

Study retrieval and selection

The following databases were searched: CINAHL, Cochrane Database of Systematic Reviews (CDSR), Embase, MEDLINE and PsycINFO. The search strategy was developed with a Health Sciences Information Specialist. Key terms were: 'Palliative Care' and 'Delirium'. A validated search filter for palliative care was used with minor adaptations.[18] Delirium search terms were derived from recent relevant reviews.[12,19] The search was conducted in June 2019 and updated in April 2020 using the full search and screening strategy (Supplemental File 1). A final rapid update (March 2021) was conducted using an accepted method[20] (single reviewer, MEDLINE only, as it was the source of 83% of included studies in previous searches). Reference lists of included studies, relevant reviews identified through the search and delirium guidelines were examined for additional eligible studies.

Search results were screened in two stages: title and abstract and full text screening, using Covidence software.[21] Two reviewers independently screened each result (IF, RW, JB, AH, PL) using Google Translate for non-English papers. At full text stage, reviewers selected a reason for exclusion from a hierarchical list. Where needed, translators, contacted through the Centre for Reviews and Dissemination (University of York), assisted in clarifying eligibility and enabling data extraction and risk of bias assessment. Disagreements were resolved through discussion to reach consensus or consultation with a third reviewer. When no full-text paper could be found, study authors were contacted.

Data extraction

Relevant data were extracted by one reviewer (IF) using a pre-piloted data extraction table in Excel[22] and checked by a second reviewer (RW) (See Supplemental File 2 for data extraction items). Delirium occurrence was recorded as: point prevalence (delirium at a time point, such as admission); period prevalence (delirium on admission and during study period); or incidence (new cases during study period).

Risk of bias assessment

Validity and risk of bias were assessed independently by two reviewers (IF, GR, RW) using a modified version of the Quality in Prognosis Studies (QUIPS) tool.[23] The following domains were assessed: study participation; attrition; risk factor measurement; confounding measurement and account; outcome measurement; analysis and reporting. Consensus on ratings was reached through discussion. QUIPS assessments were conducted only in relation to study data relevant to this review, therefore they should not be interpreted as assessments of the studies' overall risk of bias *per se*. This informed decisions about whether study results should be included in meta-analysis; the narrative synthesis of results; and the GRADE (Grading of Recommendations Assessment, Development and Evaluation)[24] ratings of the evidence for each risk factor.

Data synthesis

Clinical and methodological heterogeneity were assessed to decide whether to conduct meta-analyses. Studies evaluating the same risk factor were assessed to determine the extent of variability in relation to participants and settings; measurement of the risk factor and delirium outcome, including type of delirium occurrence; study design; risk of bias; and whether only univariate or multivariate analysis was conducted.[25] Statistical heterogeneity was assessed using the I^2 statistic.[26]

The principal summary measures used in the review were odds ratios (95% confidence interval (CI)) for dichotomous risk factors and mean differences (95% CI) for continuous risk factors.[27] Data were transformed to present a common statistic across studies where possible.

Revman software[28] was used to conduct meta-analyses using a random effects model (DerSimonian and Laird inverse variance) due to heterogeneity between studies.[25] Where studies provided only the odds ratio and 95% confidence interval, the log odds ratio and standard error was calculated for all studies in the comparison and generic inverse variance was used for meta-analysis.[25] Forest plots were used to present the results. Subgroup analyses were conducted to explore heterogeneity in relation to the type of delirium occurrence measured (point prevalence, period prevalence, incidence).

Narrative synthesis was used when meta-analysis could not be conducted. Studies examining each possible risk factor were grouped, their characteristics tabulated, and a common statistic presented across studies where possible. Potential moderator variables, including measurement of the risk factor and delirium outcome, were examined and a narrative interpretive summary was produced.[29]

GRADE assessment

The GRADE approach,[24] with guidance on its adaptation for reviews of prognostic factor research,[30,31] was used to assess the certainty of the body of evidence for the association of each risk factor with delirium. Downgrading of
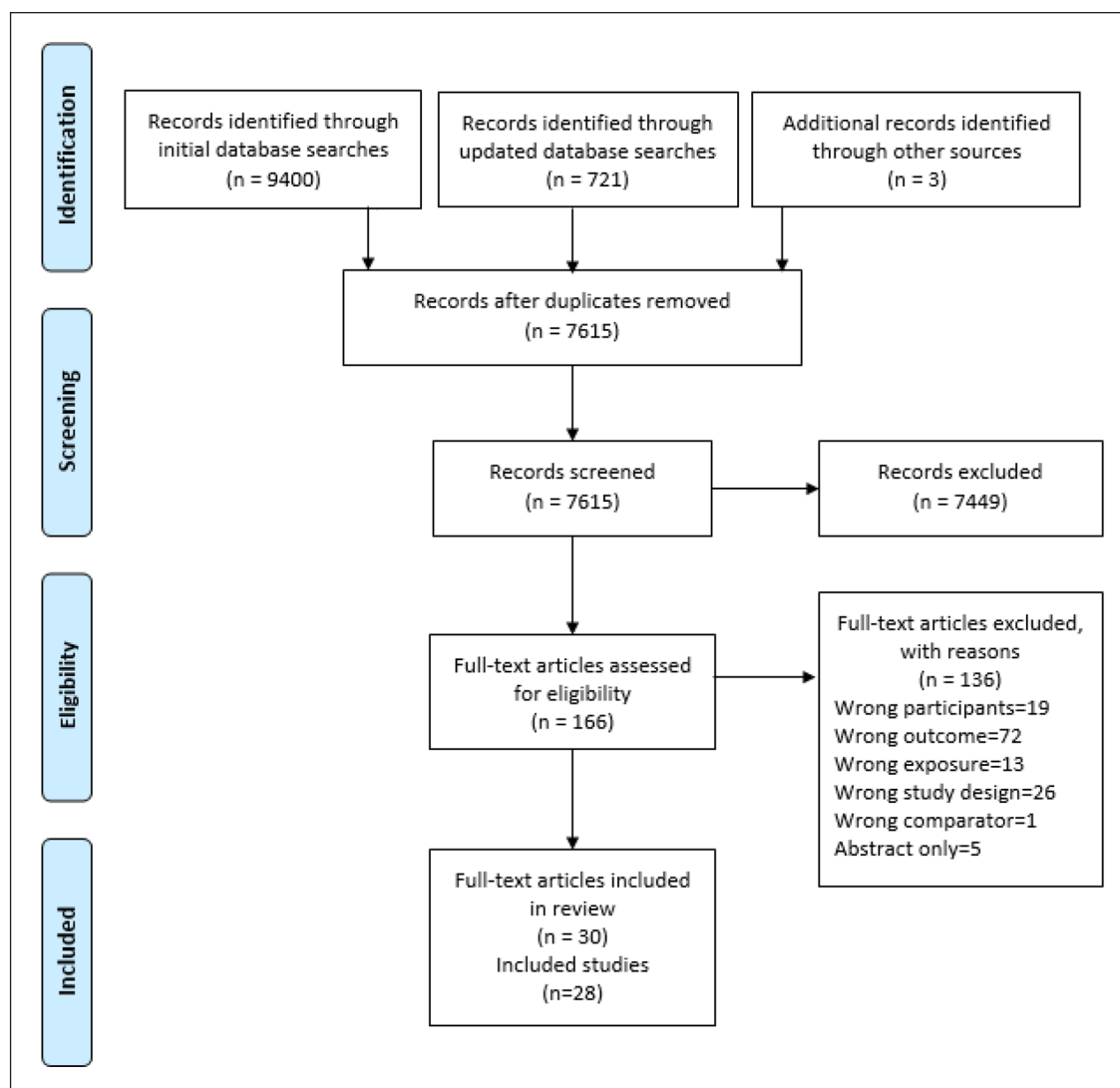
Figure 1. PRISMA diagram.

the level of certainty was based on assessment of five domains (risk of bias, inconsistency, indirectness, imprecision and publication bias) and upgrading was based on large effects or exposure-response gradient.[24]

Results

Study selection

Twenty eight studies reported in 30 articles were included (Figure 1). Three studies were each reported in two articles[32–38], two studies were reported in one article.[39]

Study characteristics

Supplemental File 3 shows detailed study characteristics.

Included studies were from the USA (n = 7),[37,40–45] Japan (n = 4),[46–49] Italy[32,33,50] and Spain (each n = 3),[51–53]

Canada,[54,55] South Korea[56,57] and the UK[39] (each n = 2) and Taiwan,[58] Germany,[59] Mexico,[60] Turkey[61] and Switzerland (each n = 1).[62] Twenty five studies were reported in English; two in Spanish[52,53], one in Japanese.[47]

Most studies included inpatient specialist palliative care units in hospitals (n = 21)[32,37,39,41,42,44,46,48–53,55–62] or hospice (n = 5).[33,39,47,51,54] Three studies each included palliative care consultation teams[40,45,49] and palliative care community services[33,41,43]

In 23 studies, all participants had a primary cancer diagnosis,[32,33,37,40–42,46–62] three studies included cancer and non-cancer diagnoses[39,43,44], two studies did not report diagnoses.[39,45] Participants in 24 studies were in the late stages of illness (e.g. advanced or terminal cancer),[32,33,37,39–42,46–62] while in the remaining four studies participants' stage of illness was unclear.[39,43–45]

In 14 studies, only cross-sectional data was eligible for the review.[32,33,39,41,42,44,47,48,50,51,56,57,60] There were two

Table 1. QUIPS results.

Study	Risk of bias domains					
	1. Study participation	2. Study attrition	3. Risk factor measurement	4. Outcome measurement	5. Study confounding	6. Statistical analysis and reporting
Barahona et al.[51]	High	N/A	High	Moderate	High	High
Braiteh et al.[40]	Moderate	Low	High	Moderate	High	High
Caraceni et al.[50]	Moderate	N/A	Moderate	Low	Moderate	Moderate
De la Cruz et al.[37,38]	Low	Low	Low	Moderate	High	High
Diaz Garcia et al.[52]	High	Moderate	Moderate	Moderate	High	High
Fadul et al.[41]	Moderate	N/A	Low	Moderate	High	High
Fang et al.[58]	High	Low	Low	Moderate	High	High
Farriols Danés et al.[53]	Low	Low	High	High	High	High
Gagnon et al.[54]	Low	Moderate	Moderate	Moderate	High	High
Kang et al.[56]	Moderate	N/A	Moderate	Low	Moderate	Moderate
Kim et al.[57]	Moderate	N/A	High	Moderate	High	High
Lawlor et al.[55]	Low	Low	Moderate	Moderate	High	High
Matsuo et al.[49]	Low	Low	Moderate	Moderate	Moderate	Moderate
Matsuoka et al.[46]	High	Low	Moderate	High	Moderate	Moderate
Mercadante et al.[32,34]	Moderate	N/A	Moderate	Low	Low	Moderate
Mercadante et al.[33,35]	High	Moderate	Moderate	Moderate	Moderate	Moderate
Minagawa et al.[48]	Moderate	N/A	Moderate	Moderate	High	High
Morita et al.[47]	High	N/A	Moderate	High	High	High
Plaschke et al.[59]	Moderate	High	Moderate	Moderate	Moderate	Moderate
Rodriguez-Mayoral et al.[60]	Moderate	N/A	Moderate	Low	High	High
Sarhill et al.[42]	Moderate	N/A	Moderate	High	High	High
Seiler et al.[62]	High	High	Moderate	High	High	Moderate
Senel et al.[61]	Moderate	Low	High	Moderate	High	High
Slatore et al.[43]	High	High	Moderate	Moderate	High	Moderate
Spiller and Keen[39]	Moderate	N/A	High	Moderate	Moderate	Moderate
Spiller and Keen[39]	Moderate	N/A	High	Moderate	High	High
Stillman and Rybicki[44]	High	N/A	Moderate	Moderate	High	High
Zimmerman et al.[45]	Moderate	Low	Moderate	High	Moderate	Low

Level of assessed risk of bias = low (green)/moderate (amber)/ high (red); N/A = Not applicable (white).

prospective[43,49], one retrospective[45] cohort studies (measuring delirium incidence); eight other prospective studies[52–55,58,59,61,62], three retrospective chart reviews[36,37,40] (measuring delirium period prevalence). Sixteen studies conducted only univariate analysis (for the data eligible for the review)[37,39–42,44,48,51–55,57,58,60,61] and 12 also conducted multivariate analysis.[32,33,39,43,45–47,49,50,56,59,62]

Risk of bias within individual studies

Table 1 presents the ratings for the QUIPS risk of bias domains for individual studies.

Several studies excluded patients at high risk of delirium such as those with dementia/cognitive impairment (five studies[46,52,56,59,61]) and severely ill/dying patients (seven studies[32,33,42,46,48,52,56]).

Routine data on risk factors were often used and their measurement not clearly defined. The timing of exposure in relation to outcome measurement was unclear in many studies (cross-sectional or measuring delirium period prevalence).[39,47,57,59,61,62] All included studies used validated delirium assessment tools or criteria but the methods and frequency of assessment were variable.

Sixteen studies included only univariate data on the association between risk factors and delirium, so made no adjustment for confounding.[37,39–42,44,48,51–55,57,58,61] Many of the studies which conducted multivariate analysis had adjusted for some, but not all, important potential confounding factors.[39,43,45–47,49,50,59,60,62]

Several included studies selectively reported results, including six studies which only reported multivariate analysis results that were statistically significant.[39,49,50,56,59,60]

Potentially modifiable risk factors. Additional forest plots for study results included in meta-analyses are presented in Supplemental File 4. Due to heterogeneity between studies, most results could not be combined and are tabulated in Supplemental File 5.

Medications and treatment risk factors. **Opioids (*n* = 12):** Three studies reported statistically significant positive associations between opioid use and delirium in univariate analysis,[46,49,61] which persisted in multivariate analysis in Matsuo et al.'s[49] study (OR 3.7, 95% CI 1.0, 13.0) but not in Matsuoka et al.'s[46] study (OR 2.85, 95% CI 0.82, 9.90). Plaschke et al.[59] reported no statistically significant association with morphine use.

Regarding opioid dose (*n* = 5), two studies[54,56] reported higher mean opioid dose in the delirium group and one[57] reported a higher median dose, although these results were not statistically significant. Morita et al.[47] reported that higher opioid use (cut off unclear) was significantly associated with delirium and Mercadante et al.[33] reported a statistically significant correlation between opioid dose and delirium on admission.

All three studies examining 'opioid toxicity'[32,39] reported a statistically significant positive association with delirium.

Steroids (*n* = 6): Four out of five studies examining steroid use (yes/no) in univariate analysis reported a positive association with delirium which reached significance in three of the studies,[33,46,47,50,61] Two studies used multivariate analysis and found no statistically significant association.[33,46] In Matsuo et al.[49] no statistically significant association was found between higher dose of corticosteroid treatment (>3 mg initial daily dose as betamethasone equivalent) and delirium incidence (unadjusted OR 0.90, 95% CI 0.43, 1.88).

Anticholinergics (*n* = 6): Five studies[42,47,49,59,61] reported mixed results from univariate analysis of association between anticholinergic medications/load and delirium. Zimmerman et al.[45] reported that delirium incidence following hospital admission was significantly higher in participants whose Anticholinergic Risk Scale score increased from baseline in multivariate analysis (OR 1.43, 95% CI 1.04, 1.94).

Anxiolytics/hypnotics (*n* = 4): Results of four studies examining anxiolytics/ hypnotics[49,56,59,61] were mixed, but overall suggested a small positive association with delirium. These results could not be pooled due to differing definitions of medication types.

Other medications: Two studies reported statistically significant associations of antiepileptic/anticonvulsant drugs with delirium in univariate analysis but significance was not retained in multivariate analysis in Matsuoka et al. 's[46,61] study (OR 3.42 95% CI 0.58, 20.01).Antipsychotics [57]; beta blockers[59] and antihistamine drugs[46] were each examined in one study with statistically significant associations with delirium reported in univariate analysis. Significance was retained in multivariate analysis for beta blockers (OR 3.95 95% CI 1.642, 9.479) but not for antihistamine drugs (OR 1.28 95% CI 0.14, 11.37). Plaschke et al.[59] found no association between antibiotic use and delirium.

In univariate analysis, Şenel et al.[61] reported a statistically significant positive association between polypharmacy (more than three drugs) and delirium period prevalence (unadjusted OR 26.39, 95% CI 12.70, 54.82).

Cancer treatments (*n* = 4): In univariate analysis, two studies[32,48] found non-significant positive associations between radiotherapy and delirium point prevalence. Mixed results were reported for hormonal therapy (two studies),[32,50] surgery (two studies)[32,48] and chemotherapy (three studies[32,46,48]).

Other treatments: One study found no significant association of delirium with blood transfusion.[50] Matsuo et al.[49] examined the association between indwelling urinary catheter use and delirium incidence in univariate analysis and found a positive association close to statistical significance (OR 2.25, 95% CI 0.97, 5.22).

Physiological risk factors. **Nutrition-related risk factors (*n* = 11):** The pooled mean difference in the Edmonton Symptom Assessment System (ESAS) lack of appetite score between those with and without delirium on admission from three studies[32,33,56] (Figure 2) was statistically but not clinically significant (less than 1 point difference in ESAS score).[63] Results from two further studies of ESAS lack of appetite score, not included in meta-analysis, were mixed,[33,37] as were the results of two studies examining the association of malnutrition[61,62] and of low Body Mass Index[56,59] with delirium. Two studies examining anorexia in univariate analysis,[49,50] and cachexia in multivariate analysis (OR 3.44, 95% CI 1.55, 7.63[33] and OR 3.24, 95% CI 0.747, 14.096[62]) suggested an association with delirium.

Infection-related risk factors (*n* = 7): Three studies examining association between infection and delirium[39,46,61] reported statistically significant positive associations in univariate analysis, although this was not retained in Matsuoka et al. 's[46] multivariate analysis (OR 2.83, 95% CI 0.79, 10.12). Two studies reported statistically significant positive associations between fever and delirium.[47,49] One study found a statistically significant positive association between sepsis and delirium period prevalence [62]; but no association with pneumonia.[62]

Dehydration (*n* = 5): Five studies examining the association between dehydration and delirium in univariate
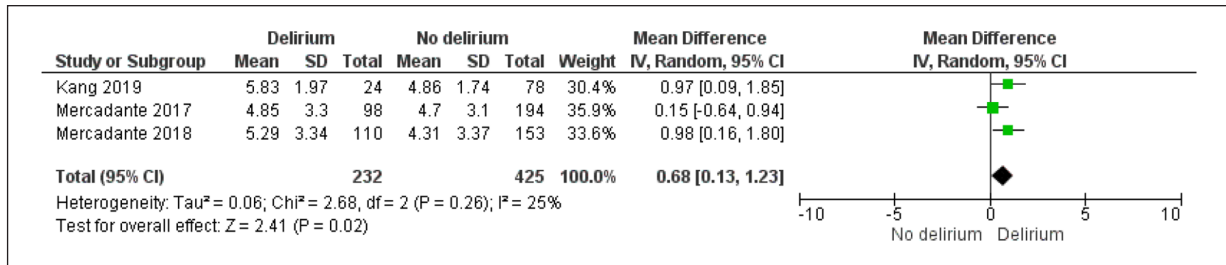
Figure 2. Forest plot: ESAS lack of appetite and delirium point prevalence (mean difference).
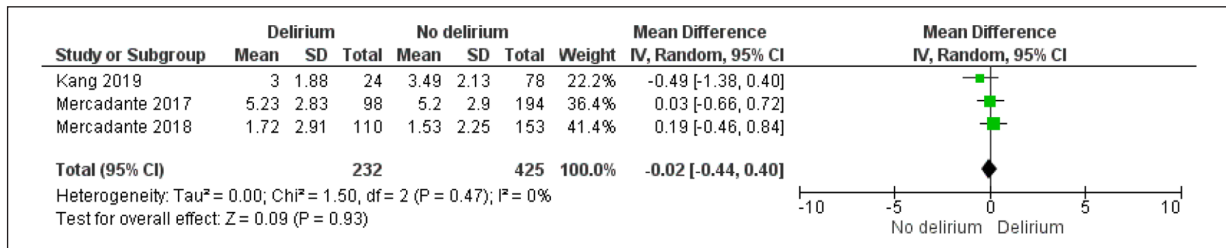

Figure 3. Forest plot: ESAS pain score and delirium point prevalence on admission (mean difference).

analysis,[33,39,46,61], two using multivariate analysis, (OR 5.16, 95% CI 1.83, 14.59[46] and OR 2.50, 95% CI 1.17, 5.34[33]) reported positive associations.

Hypoxaemia (*n* = 5): Of the five studies which examined association between hypoxaemia and delirium in univariate analysis,[39,46,49,57,61] four reported positive associations, of which three reached significance. However, in the one multivariate analysis[46] this was no longer associated (OR 0.93, 95% CI 0.28, 3.13).

Liver and renal dysfunction (*n* = 4): Four studies reported on risk factors related to liver and renal dysfunction.[47,49,61,62] In univariate analysis, delirium was positively associated with several markers of liver dysfunction including raised bilirubin[47,49,61] and low serum albumin levels.[47,49] One study reported a non-significant positive association of delirium with liver failure[62] and one reported a statistically significant association with renal and/or liver failure.[61] In multivariate analysis, one study[62] reported no association between delirium period prevalence and chronic renal disease (OR 0.81, 95% CI 0.26, 2.53), but a statistically significant positive association with acute renal failure (OR 6.79, 95% CI 1.06, 43.41).

Leucopoenia (*n* = 4): In univariate analysis, three out of four studies reported positive associations that did not reach significance between delirium and high leucocyte count[47,49,50,59], two studies[49,50] found no association with low lymphocytes.

Calcium/sodium abnormalities (*n* = 2): Two studies reported no significant associations of calcium and sodium abnormalities with delirium in univariate analysis.[47,49]

Oedema (*n* = 3): In univariate analysis, no significant association was found between lung oedema and delirium in one study.[62] In one study, no association was found with peripheral oedema,[49] but another found very

increased odds of delirium for those with oedema in the lower leg or upper arm (OR 10.92, 95% CI 5.21, 22.89).[47]

Pleural effusion (*n* = 2): No significant associations were found between delirium and pleural effusion in two studies.[49,62]

Anaemia (*n* = 2): Two studies reported non-significant positive associations of anaemia with delirium period prevalence.[46,61]

Sensory impairment (*n* = 1): One study reported statistically significant associations of hearing impairment[62] (OR 3.52, 95% CI 1.721, 7.210) and vision impairment[62] (OR 3.15, 95% CI 1.765, 5.607) with delirium period prevalence in multivariate analysis.

One study each reported statistically significant associations of numbness[47] and pressure sores[62] with delirium.

Symptom risk factors. (Reported in order of ESAS, except loss of appetite reported in nutrition-related risk factors above)

Symptom burden (total ESAS score): Two studies examined the association of symptom burden (total ESAS score) and delirium with mixed results.[32,33]

Pain (*n* = 8): Pooling three studies[32,33,56] comparing the ESAS pain scores of patients with and without delirium on admission found no difference (Figure 3). Two studies[37,59] reported a higher mean pain score in participants without delirium during the study whereas two studies[53,62] reported a positive association of pain with delirium period prevalence in univariate analysis, which was close to significance in Seiler et al. 's[62] multivariate analysis (OR 2.42, 95% CI 0.95, 6.23, *p* = 0.07). Overall, the evidence on the association of pain with delirium was mixed.
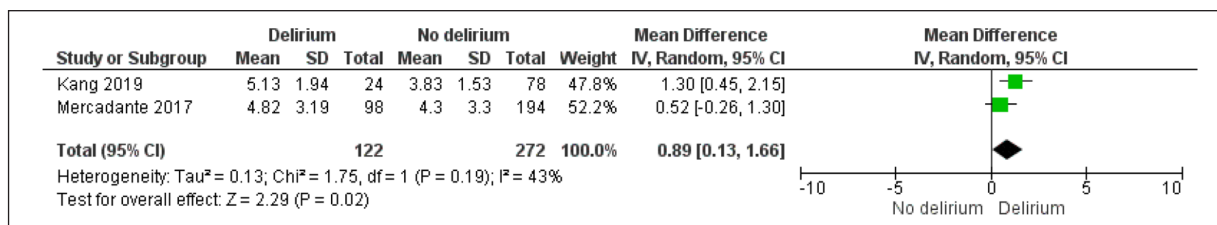
Figure 4. Forest plot: ESAS sleep disturbance and delirium point prevalence (mean difference).

Fatigue/weakness (*n* = 5): Overall, the evidence from five studies did not find a significant association of fatigue/weakness with delirium[32,33,37,49,56] (Appendices 4 and 5).

Drowsiness (*n* = 5): In univariate analysis in four studies,[32,33,37,56] the evidence of an association between drowsiness and delirium was mixed but multivariate analysis in three studies[33,49,56] found statistically significant positive associations (Appendices 4 and 5).

Nausea (*n* = 6): Six studies that examined the association of nausea and delirium in univariate analysis reported mixed results.[32,33,37,47,49,56]

Breathlessness (dyspnoea) (*n* = 7): Meta-analysis of mean difference in dyspnoea ESAS score in three studies,[32,33,56] found no association with delirium (0.05, 95% CI –0.56, 0.65) (Supplemental File 4). Three of the four studies reporting unadjusted odds ratios,[47,49,50,53] reported positive associations of breathlessness with delirium of variable size.

Depression, anxiety and decreased wellbeing: Overall, the evidence from five studies examining depression and anxiety[32,33,37,51,56] did not support a clinically significant association with delirium. Four studies examining the association of decreased wellbeing with delirium had mixed results.[32,33,37,56]

Sleep disturbance (*n* = 5): Combined mean difference in ESAS sleep disturbance score between those with and without delirium on admission from two studies was statistically, but not clinically, significant (Figure 4).[32,56] One study[37] reported a non-significant negative association between ESAS sleep disturbance and delirium period prevalence. One study[49] reported a non-significant positive association of insomnia with delirium incidence. Slatore et al.[43] reported a hazard ratio for developing delirium for each 1 point worse sleep quality in the last month as 2.37 (95% CI 1.50, 3.74).

Constipation (*n* = 4): Two studies[39,61] reported statistically significant positive associations between constipation and delirium in univariate analysis and two studies[39,49] found no association.

Behavioural disorders. Association of smoking,[56] alcohol misuse[32] and substance use disorder[62] with delirium were examined in one study each and no statistically significant associations were found.

Performance status, illness severity and prognostic assessments. Eighteen studies reported that lower performance status was strongly associated with delirium, using either Karnofsky Performance Status (eight studies)[32,33,44,48,50,53,59,60]; Eastern Cooperative Oncology Group (ECOG) Performance Status (seven studies)[37,39,46,49,56,57,60] or the Palliative Performance Scale (five studies).[47,49,51,52,61] One study[61] reported a statistically significant positive association between immobilisation and delirium period prevalence in univariate analysis.

Two studies found no significant difference in Charlson Comorbidity Index scores.[52,62] One study[45] found no statistically significant association between illness severity (APACHE III) and delirium incidence; while one study each found that admission for end of life care[32] and higher palliative prognostic index scores[61] were associated with delirium.

Non-modifiable risk factors. Additional forest plots for study results included in meta-analyses are presented in Supplemental File 6. Results are tabulated in Supplemental File 7.

Age. (*n* = 18). Meta-analysis of mean difference in age reported by nine studies suggested that participants with delirium were on average 3.08 (95% CI 1.01, 5.16) years older than those without delirium (Figure 5).[32,33,44,53,55,56,59,61,62] This was higher in studies measuring delirium point prevalence (5.62 years, 95% CI 2.97, 8.27 years). Unadjusted odds ratios from six studies[45–47,49,50,62] and adjusted odds ratios from four studies[33,45,46,56] report either a small association of older age with delirium or no significant association.

Sex. (male/female) (*n* = 18). The summary unadjusted odds ratio from 15 studies suggests that male palliative care patients were slightly more likely to have delirium than female patients (OR 1.39, 95% CI 1.23, 1.57) (Figure 6).[32,33,37,44,50,52–59,61,62] Results of three further studies not included in meta-analysis were consistent with this.[46,48,49]

Cancer-related risk factors. Three cancer-related risk factors were examined in this review: lung cancer (*n* = 12); brain cancer/ brain metastases (*n* = 12) and metastases (overall) (*n* = 4). Patients with lung cancer may be slightly more likely to have delirium than those without (pooled
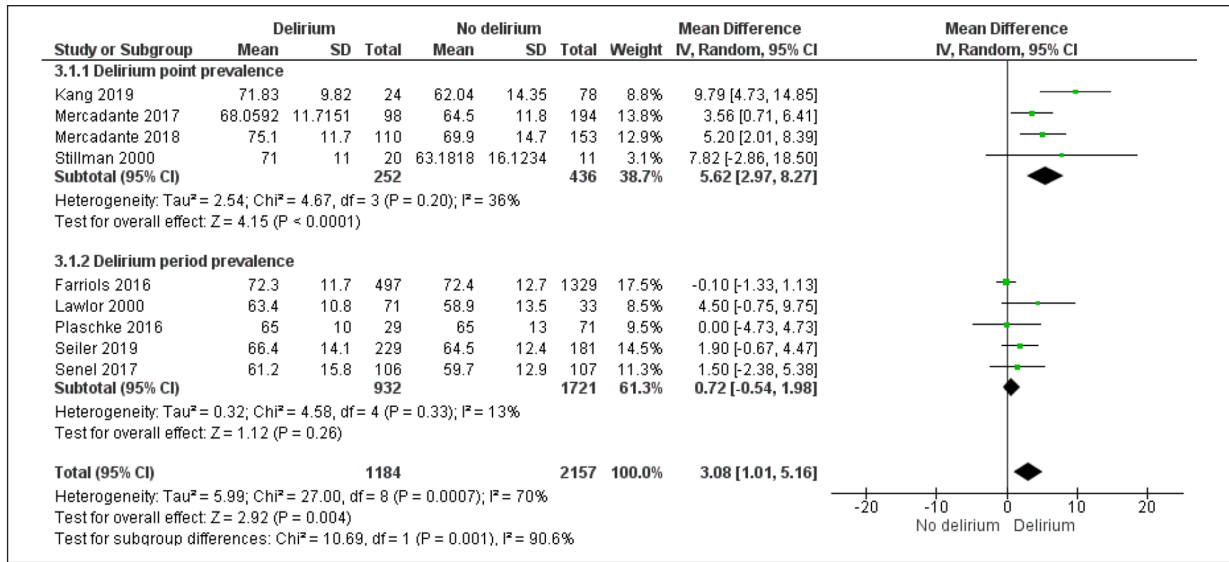
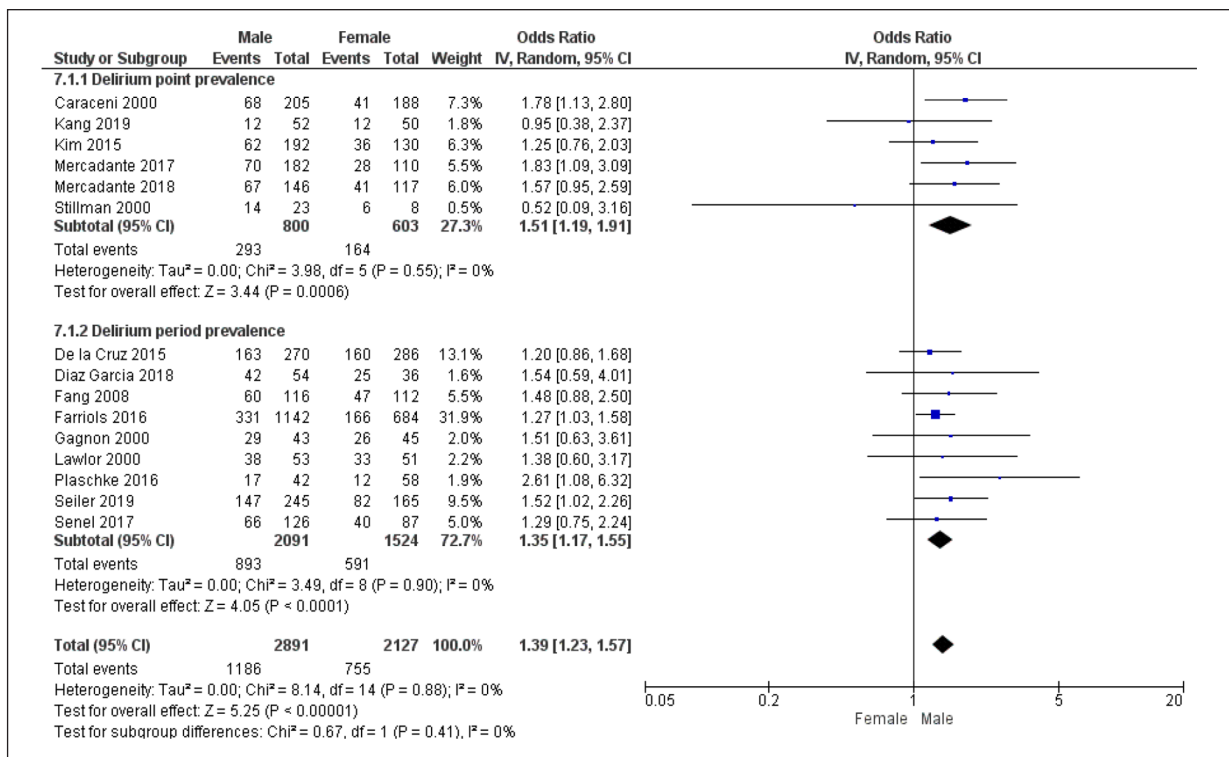**Figure 5.** Forest plot: age (years) and delirium (mean difference).

Figure 6. Forest plot: sex (male/female) and delirium (unadjusted OR).

OR 1.29, 95% CI 0.99, 1.68) (Supplemental Files 6 and 7).[32,33,48–50,52,53,55–58,62]

Twelve studies examined the association between primary brain cancer and/or brain metastases and delirium.[42,45,47–50,52,53,55,58,61,62] Positive associations were found in meta-analyses of univariate analyses between delirium and primary brain cancer (OR 2.01, 95% CI 0.98, 4.14)[52,53,62] and brain metastases (OR 3.16, 95% CI 1.85, 5.40)[42,47,48,50] (Supplemental File 6). Seiler et al.[62] found a positive association with primary brain cancer in multivariate analysis (OR 3.63, 95% CI 1.03, 12.77). Three further univariate analyses of brain metastases, from

studies not included in meta-analysis,[45,49,58] two studies that combined primary brain cancer and brain metastases as a single risk factor,[55,61] reported mixed results.

Seven studies reported positive associations between other neurological/ cerebral risk factors and delirium.[39,40,44,46,51,61,62] As these were defined in different ways they could not be combined for meta-analysis. One study each reported a statistically significant association of 'neurological diseases'[61]; 'cerebral disease'[39]; 'focal neurological deficit'[44] and 'myoclonus'[40] with delirium.

In meta-analysis of univariate data from four studies, presence of metastases (overall) was not associated with delirium period prevalence (OR 0.83, 95% CI 0.66, 1.05) (Supplemental File 6).[52,53,55,61]

GRADE assessment of the certainty of the evidence for risk factors' association with delirium

The certainty of the evidence for the following risk factors was graded as low: gender, lung cancer, metastases (overall), primary brain cancer, performance status, opioid use, dehydration, infection and drowsiness. For all other risk factors, certainty was rated as very low (Supplemental File 8). The evidence for most risk factors was downgraded for risk of bias, based upon the QUIPs assessments and lack of adequate adjustment for confounding factors in analysis. The evidence for many risk factors was also downgraded for inconsistency, due to unexplained heterogeneity between study results, and for imprecision of the results.[24]

Discussion

Main findings

We found that the evidence from 28 included studies regarding the association of possible risk factors with delirium in adults in palliative care settings was limited, particularly for many potentially modifiable risk factors, and was of low or very low certainty.

In relation to potentially modifiable risk factors, there is evidence of positive associations between delirium and both opioids and lower performance status and suggestive evidence for dehydration, hypoxaemia, sleep disturbance, liver dysfunction and infection. Positive associations with delirium were reported in only one study for each of the following: polypharmacy, sensory impairment, immobility, pressure sores and indwelling catheter use.

There was more mixed evidence about the association of delirium with pain, dyspnoea, anticholinergics, drowsiness, anxiolytics/ hypnotics, steroid use, constipation and nutrition-related risk factors.

In relation to non-modifiable risk factors, the evidence suggests positive associations of delirium with older age; male sex; primary brain cancer or brain metastases and lung cancer.

Strengths and limitations of the review

To our knowledge, this is the first systematic review conducted of risk factors for delirium in palliative care settings. Rigorous review methods were used. Particular strengths were the inclusion of studies that only used validated delirium assessment tools or criteria; inclusion of non-English language papers; screening and risk of bias assessment conducted by two independent reviewers and GRADE assessment of the certainty of evidence for each risk factor.[24]

Most included studies were not high quality cohort studies comparing delirium incidence between those exposed/ not exposed to the risk factor. Identifying delirium risk factors was not the primary aim of most included studies. Many provided only cross-sectional data, or measured delirium period prevalence, so timing of risk factor exposure in relation to delirium development was unclear. Little evidence was reported on several potentially modifiable risk factors recommended in delirium risk reduction guidelines.[64,65]

Delirium can result from a complex interplay between multiple risk factors[5] and this was not adequately accounted for in the included studies which mostly used only univariate analyses. Due to the multiple risk factors for delirium, it is difficult to account for all potential confounding and, as Zaal et al.[9] (p. 69) noted, 'It is poorly established which confounders should be incorporated in multivariable risk factors models' for delirium. Multivariate analysis adjusted for some, but not all, potentially important confounding factors. For example, those examining associations between pain and delirium did not adjust for opioid use.

We separately reported the results for those risk factors that are clearly non-modifiable (e.g. age, sex) and those which may potentially be modifiable. However, what is modifiable is uncertain, for example, it might not be possible to modify risk factors such as liver and renal dysfunction and performance status. In palliative care contexts, the modification of many risk factors may not be possible due to factors such as the patient's stage of illness and their goals of care.[11]

Most studies in this review were conducted in in-patient palliative care settings with participants with late-stage cancer, so results may be less generalisable to other patients receiving palliative care services. The definition of the eligible population as patients in receipt of specialist palliative care services could be clearly operationalised to conduct this review. However, it led to the exclusion of some possibly relevant studies, such as those of delirium risk factors for terminally ill patients in the general hospital setting.[66,67]

What this study adds

Delirium guidelines, not specific to palliative care contexts, such as NICE[64] and SIGN,[65] and systematic reviews of multicomponent interventions,[6,7] recommend delirium

risk reduction through targeting modifiable risk factors. The evidence from this review suggests positive associations between delirium and opioid use, higher opioid dose and toxicity in palliative care settings. This supports the importance of medication review and use of the minimum effective dose, in line with delirium guidelines.[64,65] The limited evidence of associations of other modifiable risk factors with delirium, provides some support for targetting risk factors included in guidelines and interventions from other settings,[6,7,64,65] including dehydration, hypoxaemia, sleep disturbance and infection, to reduce delirium in palliative care.

The low or very low certainty of the evidence must be taken into account in drawing clinical implications from our findings. Several potentially modifiable risk factors targetted in guidelines and interventions from other settings,[6,7,64,65] including sensory impairments, mobility, catheter use and polypharmacy, were each examined in only one study, which reported positive associations with delirium. A systematic review found these to be statistically significant risk factors for delirium incidence for older hospitalised patients.[8] We found mixed evidence regarding several other risk factors- pain, constipation and nutrition- which are commonly targetted in delirium prevention strategies. This highlights the need for further, high quality research focussed on the association of potentially modifiable risk factors with delirium in palliative care settings.

Although performance status was strongly associated with delirium in this review, it is not a single modifiable risk factor. It could be useful, in conjunction with evidence on other modifiable/non-modifiable risk factors, in developing predictive models of patient subgroups most likely to develop delirium. In relation to non-modifiable risk factors, this review's results support the association between older age and delirium found in other settings.[8,9] Associations between delirium and male sex, brain cancer/metastases and lung cancer were also identified in palliative care contexts. Notably, dementia, which is strongly associated with delirium in other settings,[8,9] was only examined by one study in this review. However, as delirium prevalence in palliative care patients is very high (58%– 88% in the last weeks of life),[1] it is arguably more of a priority to develop population-level preventative interventions targeting modifiable risk factors, than to predict subgroups of patients at elevated risk in order to target interventions for them.

In treating an established episode of delirium, modifiable causes are also targeted (in accordance with the patient's goals of care), to attempt to reduce the length and severity of the episode. A study in an acute palliative care unit found 49% of delirium episodes could be reversed.[55] Although the primary focus of our review was on factors affecting the risk of developing delirium, its findings could also be used to inform further research to identify modifiable factors to target in delirium treatment. Several additional studies have investigated delirium reversibility through systematic investigation of multiple precipitating risk factors in palliative care patients who have developed delirium.[55,68–70] Their data were excluded from this review because they did not include a comparator group without delirium, but may be informative in research to identify factors associated with delirium reversibility.

Conclusion

The limited evidence from this systematic review offers some support for the use of interventions that target modifiable risk factors to reduce the risk of delirium for palliative care patients. However, there is a need for high quality prospective cohort studies with more comprehensive and robust delirium risk factor measurement along with adequate adjustment for important confounding factors through multivariate analysis. This will enable much greater certainty in the evidence regarding the strength of the association of different risk factors with delirium, to inform the design of multicomponent interventions to reduce risk of delirium, and clinical decision-making regarding competing risks, in the palliative care context.

Ethical approval

No ethical approval was required for this research, as it was a review of existing published articles with no new primary data collected.

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Data management and sharing

All of the papers included in this review are available through their respective journals.

Supplemental material

Supplemental material for this article is available online.

References

1. Hosie A, Davidson PM, Agar M, et al. Delirium prevalence, incidence, and implications for screening in specialist palliative care inpatient settings: a systematic review. *Palliat Med* 2013; 27: 486–498.

2. Watt CL, Momoli F, Ansari MT, et al. The incidence and prevalence of delirium across palliative care settings: a systematic review. *Palliat Med* 2019; 33: 865–877.

3. Salluh JI, Wang H, Schneider EB, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. *BMJ* 2015; 350: h2538.

4. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 5th ed. Washington: American Psychiatric Association Publishing, 2014.

5. Inouye SK. Delirium in hospitalized older patients: recognition and risk factors. *J Geriatr Psychiatry Neurol* 1998; 11: 118–125; discussion 157.

6. Siddiqi N, Harrison JK, Clegg A, et al. Interventions for preventing delirium in hospitalised non-ICU patients. *Cochrane Database Syst Rev* 2016; 3: CD005563.

7. Hshieh TT, Yue J, Oh E, et al. Effectiveness of multicomponent nonpharmacological delirium interventions: a meta-analysis. *JAMA Intern Med* 2015; 175: 512–520.

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

9. Zaal IJ, Devlin JW, Peelen LM, et al. A systematic review of risk factors for delirium in the ICU. *Crit Care Med* 2015; 43: 40–47.

10. Vasilevskis EE, Han JH, Hughes CG, et al. Epidemiology and risk factors for delirium across hospital settings. *Best Pract Res Clin Anaesthesiol* 2012; 26: 277–287.

11. Lawlor PG, Davis DHJ, Ansari M, et al. An analytical framework for delirium research in palliative care settings: integrated epidemiologic, clinician-researcher, and knowledge user perspectives. *J Pain Symptom Manag* 2014; 48: 159–175.

12. Lawlor PG, Rutkowski NA, MacDonald AR, et al. A scoping review to map empirical evidence regarding key domains and questions in the clinical pathway of delirium in palliative care. *J Pain Symptom Manag* 2019; 57: 661–681.e12.

13. Featherstone I, Sheldon T, Johnson M, et al. *A systematic review of risk factors for delirium in adult patients receiving specialist palliative care*. PROSPERO: International prospective register of systematic reviews. 2019. Report no. CRD42019157168. Centre for Reviews and Dissemination, University of York.

14. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009; 151: 264–269, W64.

15. Dekkers OM, Vandenbroucke JP, Cevallos M, et al. COSMOS-E: guidance on conducting systematic reviews and meta-analyses of observational studies of etiology. *PLoS Med* 2019; 16: e1002742.

16. International Epidemiological Association. *A dictionary of epidemiology*. 6th ed. New York, NY: Oxford University Press, 2016.

17. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 3rd ed. Washington: American Psychiatric Association Publishing, 1980.

18. Rietjens JA, Bramer WM, Geijteman EC, et al. Development and validation of search filters to find articles on palliative care in bibliographic databases. *Palliat Med* 2019; 33(4): 470–474.

19. Siddiqi N, Clegg A, Todd OM, et al. Non-pharmacological interventions for managing delirium in hospitalised patients. *Cochrane Database Syst Rev* 2017, Issue 4. https://doi.org/10.1002/14651858.CD005995.pub2

20. Datla S, Verberkt CA, Hoye A, et al. Multi-disciplinary palliative care is effective in people with symptomatic heart failure: a systematic review and narrative synthesis. *Palliat Med* 2019; 33: 1003–1016.

21. Veritas Health Innovation. *Covidence systematic review software*. Melbourne, Victoria, Australia: Veritas Health Innovation.

22. Microsoft Excel. Microsoft Corporation, 2018, https://office.microsoft.com/excel

23. Hayden JA, van der Windt DA, Cartwright JL, et al. Assessing bias in studies of prognostic factors. *Ann Intern Med* 2013; 158: 280–286.

24. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; 336: 924–926.

25. Higgins JP, Thomas J, Chandler J, et al. *Cochrane handbook for systematic reviews of interventions*. 2nd ed. Chichester: John Wiley & Sons, 2019.

26. Higgins JPT and Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21: 1539–1558.

27. Borenstein M, Hedges L, Higgins J, et al. *Introduction to meta-analysis*. Chichester: John Wiley and Sons, 2009.

28. Review Manager (RevMan) Computer Program. 5.4 ed. London: The Cochrane Collaboration, 2020.

29. Popay J, Roberts H, Sowden A, et al. *Guidance on the conduct of narrative synthesis in systematic reviews*. ESRC methods programme. Lancaster University. 2006.

30. Huguet A, Hayden JA, Stinson J, et al. Judging the quality of evidence in reviews of prognostic factor research: adapting the GRADE framework. *Syst Rev* 2013; 2(1): 71.

31. Foroutan F, Guyatt G, Zuk V, et al. GRADE guidelines 28: use of GRADE for the assessment of evidence about prognostic factors: rating certainty in identification of groups of patients with different absolute risks. *J Clin Epidemiol* 2020; 121: 62–70.

32. Mercadante S, Adile C, Ferrera P, et al. Delirium assessed by Memorial Delirium Assessment Scale in advanced cancer patients admitted to an acute palliative/supportive care unit. *Curr Med Res Opin* 2017; 33: 1303–1308.

33. Mercadante S, Masedu F, Balzani I, et al. Prevalence of delirium in advanced cancer patients in home care and hospice and outcomes after 1 week of palliative care. *Support Care Cancer* 2018; 26: 913–919.

34. Mercadante S, Adile C, Ferrera P, et al. Symptom expression in patients with advanced cancer admitted to an acute supportive/palliative care unit with and without delirium. *Oncologist* 2019; 24: e358–e364.

35. Mercadante S, Masedu F, Maltoni M, et al. Symptom expression in advanced cancer patients admitted to hospice or home care with and without delirium. *Intern Emerg Med* 2019; 14: 515–520.

36. Cruz-Jentoft AJ, Boland B and Rexach L. Drug therapy optimization at the end of life. *Drugs Aging* 2012; 29: 511–521.

37. De la Cruz M, Ransing V, Yennu S, et al. The frequency, characteristics, and outcomes among cancer patients with delirium admitted to an acute palliative care unit. *Oncologist* 2015; 20: 1425–1431.

38. de la Cruz M, Yennu S, Liu D, et al. Increased symptom expression among patients with delirium admitted to an acute palliative care unit. *J Palliat Med* 2017; 20(6): 638–641.

39. Spiller JA and Keen JC. Hypoactive delirium: assessing the extent of the problem for inpatient specialist palliative care. *Palliat Med* 2006; 20: 17–23.

40. Braiteh F, El Osta B, Palmer JL, et al. Characteristics, findings, and outcomes of palliative care inpatient consultations at a comprehensive cancer center. *J Palliat Med* 2007; 10: 948–955.

41. Fadul NA, El Osta B, Dalal S, et al. Comparison of symptom burden among patients referred to palliative care with hematologic malignancies versus those with solid tumors. *J Palliat Med* 2008; 11: 422–427.

42. Sarhill N, Walsh D, Nelson KA, et al. Assessment of delirium in advanced cancer: the use of the bedside confusion scale. *Am J Hosp Palliat Care* 2001; 18: 335–341.

43. Slatore CG, Goy ER, O'hearn DJ, et al. Sleep quality and its association with delirium among veterans enrolled in hospice. *Am J Geriatr Psychiatr* 2012; 20: 317–326.

44. Stillman MJ and Rybicki LA. The bedside confusion scale: development of a portable bedside test for confusion and its application to the palliative medicine population. *J Palliat Med* 2000; 3: 449–456.

45. Zimmerman KM, Salow M, Skarf LM, et al. Increasing anticholinergic burden and delirium in palliative care inpatients. *Palliat Med* 2014; 28: 335–341.

46. Matsuoka H, Yoshiuchi K, Koyama A, et al. Chemotherapeutic drugs that penetrate the blood-brain barrier affect the development of hyperactive delirium in cancer patients. *Palliat Support Care* 2015; 13: 859–864.

47. Morita T, Tsunoda J, Inoue S, et al. [Risk factors of delirium in terminally ill cancer patients: a prospective study]. *Seishin Igaku* 1998; 40: 823–829.

48. Minagawa H, Uchitomi Y, Yamawaki S, et al. Psychiatric morbidity in terminally ill cancer patients. A prospective study. *Cancer* 1996; 78: 1131–1137.

49. Matsuo N, Morita T, Matsuda Y, et al. Predictors of delirium in corticosteroid-treated patients with advanced cancer: an exploratory, multicenter, prospective, observational study. *J Palliat Med* 2017; 20: 352–359.

50. Caraceni A, Nanni O, Maltoni M, et al. Impact of delirium on the short term prognosis of advanced cancer patients. Italian multicenter study group on palliative care. *Cancer* 2000; 89: 1145–1149.

51. Barahona E, Pinhao R, Galindo V, et al. The diagnostic sensitivity of the Memorial delirium assessment scale-spanish version. *J Pain Symptom Manag* 2018; 55: 968–972.

52. Díaz García V, López Pérez M and Zuriarrain Reyna Y. Prevalencia de delirium mediante la escala Memorial Delirium Assessment Scale (MDAS) en pacientes oncologicos avanzados ingresados en una Unidad de Cuidados Paliativos. Factores de riesgo, reversibilidad y tratamiento recibido [Prevalence of delirium using the Memorial Delirium Assessment Scale (MDAS) in advanced oncology patients admitted to a palliative care unit. Risk factors, reversibility and treatment received]. *Med Paliativa* 2018; 25: 245–254.

53. Farriols Danés C, Landa Teran CP, Ruiz Ripoll AI, et al. Prevalencia del delirium en pacientes con enfermedad oncologica avanzada ingresados en una unidad de cuidados paliativos [Prevalence of delirium in patients with advanced cancer admitted to a palliative care unit]. *Med Paliativa* 2016; 23: 165–171.

54. Gagnon P, Allard P, Mâsse B, et al. Delirium in terminal cancer: a prospective study using daily screening, early diagnosis, and continuous monitoring. *J Pain Symptom Manag* 2000; 19: 412–426.

55. Lawlor PG, Gagnon B, Mancini IL, et al. Occurrence, causes, and outcome of delirium in patients with advanced cancer: a prospective study. *Arch Intern Med* 2000; 160: 786–794.

56. Kang B, Kim YJ, Suh SW, et al. Delirium and its consequences in the specialized palliative care unit: validation of the Korean version of Memorial Delirium assessment scale. *Psychooncology* 2019; 28: 160–166.

57. Kim S-Y, Kim S-W, Kim J-M, et al. Differential associations between delirium and mortality according to delirium subtype and age: a prospective cohort study. *Psychosom Med* 2015; 77: 903–910.

58. Fang C-K, Chen H-W, Liu S-I, et al. Prevalence, detection and treatment of delirium in terminal cancer inpatients: a prospective survey. *Jpn J Clin Oncol* 2008; 38: 56–63.

59. Plaschke K, Petersen KA, Frankenhauser S, et al. The impact of plasma cholinergic enzyme activity and other

risk factors for the development of delirium in patients receiving palliative care. *J Pain Symptom Manag* 2016; 52: 525–532.

60. Rodríguez-Mayoral O, Reyes-Madrigal F, Allende-Pérez S, et al. Delirium in terminal cancer inpatients: short-term survival and missed diagnosis. *Salud Ment* 2018; 41: 25–30.

61. Şenel G, Uysal N, Oguz G, et al. Delirium frequency and risk factors among patients with cancer in palliative care unit. *Am J Hosp Palliat Care* 2017; 34: 282–286.

62. Seiler A, Schubert M, Hertler C, et al. Predisposing and precipitating risk factors for delirium in palliative care patients. *Palliat Support Care* 2020; 18(4): 437–446.

63. Hui D, Shamieh O, Paiva CE, et al. Minimal clinically important differences in the Edmonton Symptom Assessment Scale in cancer patients: a prospective, multicenter study. *Cancer* 2015; 121: 3027–3035.

64. National Institute for Health and Care Excellence. *Delirium: prevention, diagnosis and management. CG103*. Manchester: National Institute for Health and Care Excellence, 2010.

65. Scottish Intercollegiate Guidelines Network. *Risk reduction and management of delirium*. Edinburgh: Scottish Intercollegiate Guidelines Network, 2019.

66. Uchida M, Okuyama T, Ito Y, 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: 934–940.

67. Suzuki H, Hirashima T, Kobayashi M, et al. Impact of pneumonia on hyperactive delirium in end-stage lung cancer patients. *Support Care Cancer* 2013; 21(1): 281–285.

68. Morita T, Tei Y, Tsunoda J, et al. Underlying pathologies and their associations with clinical features in terminal delirium of cancer patients. *J Pain Symptom Manag* 2001; 22: 997–1006.

69. Matsuda Y, Nakao Y, Yabe M, et al. Association of the clinical subtype and etiology for delirium with the outcome after risperidone monotherapy in patients having cancer. *Osaka City Med J* 2016; 62: 19–28.

70. Leonard M, Raju B, Conroy M, et al. Reversibility of delirium in terminally ill patients and predictors of mortality. *Palliat Med* 2008; 22: 848–854.