Journal of Critical Care 56 (2020) 257–264

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Risk factors and outcomes among delirium subtypes in adult ICUs: A systematic review

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ARTICLE INFO

Keywords:
Delirium
Critical care
Subtype
Risk factors
Systematic review

ABSTRACT

Purpose: Use systematic review methodology to summarize risk factors and outcomes for each delirium subtype (hypoactive, hyperactive and mixed) in an adult ICU population.
Materials and methods: We searched the MEDLINE, Embase, CINAHL, SCOPUS, Web of Science and PsycINFO databases from database inception until August 13, 2018, with no restrictions.
Results: Of 9635 abstracts, 20 studies were included. Older age was not associated with any delirium subtype in 4/7 (57%) studies. Sex was not associated with any delirium subtype in 4/4 (100%) studies. Mortality was consistently associated with hypoactive delirium in 4/7 (57%) studies. The evidence supporting the association of APACHE-II score, mechanical ventilation, length of stay, duration of delirium and removal of tubes were inconsistent across studies.
Conclusions: Although included studies reported on many subtype-specific risk factors and outcomes, heterogeneity in reporting and methodological quality limited the generalizability of the results and the evidence for many subtype-specific risk factors or outcomes is inconsistent across studies. Standardized methodology and the creation of a universal template for collecting data in ICU delirium studies are essential moving forward; helping to identify subtype-specific risk factors or outcomes and strengthen the association of potential risk factors or outcomes.

1. Background

Delirium is a common acute onset organ dysfunction in the intensive care unit (ICU) and is associated with extended hospital stays [1], increased risk of mortality [2-4] and long term cognitive impairment [5-7]. Delirium can fluctuate in both its severity and its presentation, and can be categorized according to one of three motoric subtypes: hyperactive (agitation, restlessness, hallucinations and aggression), hypoactive (lethargy, inattentiveness and motor slowness) and mixed (fluctuating between hyperactive and hypoactive subtypes) [8-10].

Two recent systematic reviews and meta-analyses identified risk factors (i.e., older age, dementia, hypertension, pre-ICU emergency surgery or trauma, Acute Physiology and Chronic Health Evaluation II (APACHE-II) score, mechanical ventilation, metabolic acidosis, delirium on the prior day and coma) [11] and outcomes (i.e., increased mortality, cognitive impairment; longer durations of mechanical ventilation and longer lengths of stay in the ICU) [12] for delirium *overall* in the ICU. However, there is a growing number of studies suggesting that there may be important differences in risk factors and outcomes among delirium *subtypes* [13-33]. Given the variability in the prevalence of the three motoric subtypes of delirium (hypoactive 17%, mixed 10% and hyperactive 4%) [10], knowledge of subtype-specific delirium risk factors could be useful for the development of risk prediction models to target pharmacological prophylaxis/management and effective non-pharmacological interventions to prevent delirium in high-risk patients. This may advance clinical care of patients with delirium by stratifying risk (according to subtype), such as prioritizing a patient at high risk for hypoactive delirium for delirium screening and detection as the

Abbreviations: PRISMA, preferred reporting items for systematic review and meta-analyses; CAM-ICU, Confusion Assessment Method for the ICU; ICDSC, Intensive Care Delirium Screening Checklis; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-IV; OR, Odds Ratio; ICU, Intensive Care Unit; APACHE-II, Acute Physiology and Chronic Health Evaluation II; 95% CI, 95% confidence interval.

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https://doi.org/10.1016/j.jcrc.2020.01.017

hypoactive form of delirium is difficult to detect and may be missed [34]. The aim of this systematic review was to summarize, compare and evaluate risk factors and outcomes for delirium subtypes in an adult ICU setting.

2. Methods

2.1. Search strategy

This systematic review was conducted according to established methodological standards and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [35,36]. In consultation with content experts and an academic librarian with expertise in systematic reviews, a search strategy was developed (Additional File 1). A second librarian conducted a peer review of the search strategy using the Peer Review of Electronic Search Strategies (PRESS) checklist [37]. No restrictions were placed on the date of publication or the language. References were exported and managed using EndNote X7 [38]. Search terms included ICU, delirium, motor subtype, risk factor, outcome and all related synonyms and Boolean logic (for a detailed search strategy, see Additional File 1). Prior to the initial search, the systematic review study protocol and the full-search strategy were registered in PROSPERO (registration number CRD42016041403) [39]. The search was executed on August 13, 2018 and included six bibliographic databases (MEDLINE, EMBASE, Scopus, WOS, CINAHL and PsycINFO). Reference lists of all included articles and proceedings from the past three years of relevant conferences (American Thoracic Society, Society for Critical Care Medicine) were manually searched to identify additional studies.

2.2. Study selection

All abstracts and titles from the search were independently screened in duplicate by two reviewers (KMF and KDK) using EndNote X7 [38] to identify potentially relevant studies. The full-text articles of potentially relevant studies were subsequently reviewed by two reviewers (KMF and KDK), who independently reviewed and applied the inclusion/exclusion criteria; disagreements were resolved by discussion or consensus with a third reviewer. Studies were included if they were: original research, conducted in adult patients admitted to any medical, surgical or specialty ICU, of cross-sectional or cohort study design and reported on risk factors for different delirium subtype(s) or outcomes associated with the subtype(s). Diagnoses of delirium could be determined using any method (e.g., screening tool, clinical diagnosis, validated chart review). Inter-rater agreement (kappa-statistic) was calculated for each selection stage using Stata software version 14.0 for Windows (Stata Corp LP, College Station, Texas, USA). The agreement was interpreted as fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80) and almost perfect (0.81–1.00) [40].

2.3. Study quality and risk of bias assessment

Two reviewers (KMF and KDK) independently assessed the quality of included studies using the Scottish Intercollegiate Guidelines Network (SIGN) quality checklists for cohort studies and cross-sectional studies [11,41]. Each study was assigned a score from one to ten, based on ten quality criteria that critiqued selection of subjects, delirium assessment, outcome measures, confounders and statistical analysis. For each criterion, a point was given if the criterion was met and no point given if it was not met. If the study contained insufficient information about a specific criterion, the item was stated as "?" for cannot say, and no point was given. Similar to the adaptation of the SIGN criterion used by Zaal et al., only tools validated in the ICU against the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) were given a point for the detection bias criterion. This includes the Confusion Assessment Method for the ICU (CAM-ICU) [42], Intensive Care Delirium Screening Checklist (ICDSC) [43] and NEECHAM [44,45] delirium screening tools. We determined the overall quality of each study, as high (7–10 points), acceptable (5–6 points) or low quality (≤ 4 points).

2.4. Data synthesis

All data from included articles were independently extracted and agreed upon by two authors using a standard electronic data form. The following data were extracted: study information (author, year), population demographics (mean/median age, sex/gender, location and time of data collection), condition information (ICU type, delirium definition, delirium screening tool, frequency of screening, delirium assessor(s)), sample size, prevalence/incidence of delirium subtype(s), subtype-specific risk factors and outcomes (including statistical analysis). After data extraction, all studies evaluating the same risk factor or outcome were further compared. Because of the heterogeneity of risk factors and outcomes and lack of reporting of effect sizes, we did not statistically pool any data. Studies reporting on the same risk factor or outcome were grouped, to semi-quantitatively compare the risk factors and outcomes between the studies [11]. Studies were only included for semi-quantitative analysis if they reported on more than one delirium subtype and compared risk factors and outcomes between delirium subtypes (i.e., between hyperactive and hypoactive delirium, between hyperactive and mixed delirium or between hypoactive and mixed delirium). We evaluated each risk factor or outcome adapting previously described criteria [41]: 1) the number of studies evaluating a specific risk factor or outcome; 2) the quality (high, acceptable or low) of each study evaluating this risk factor or outcome and 3) the consistency of the reported association between each risk factor or outcome and the delirium subtype. Due to the number of studies with small sample sizes, we did not depend solely on statistical significance in univariable analysis. To consider whether a risk factor or outcome represented a true subtype-specific "association", the odds ratio, confidence intervals and statistical significance (p-values) were considered. Only the risk factors and outcomes that were evaluated in more than one study were included in data analysis. All other risk factors and outcomes are listed in Additional File 2.

3. Results

3.1. Results of the search

A total of 9635 unique studies were identified by the search (Fig. 1). After the initial screen (kappa = 0.30 [fair], 86.4% agreement), 488 papers met the criteria for full-text review, of which 468 were excluded (kappa = 0.61 [substantial], 94.6% agreement). The two most common reasons for exclusion were results not presented according to subtype (170/468, 36%) and no subtype-specific risk factor/outcome being reported (111/468, 24%).

3.2. Description of studies

Additional File 2 presents the characteristics of the 20 included studies. The settings varied with seven studies evaluating mixed ICU patients [15-18,20,21,29,31], six cardiovascular/cardiac surgery ICU patients [19,22,25-28], two each in neurological [33,46] and surgical ICU patients [13,30] and one each in anaesthesiology, oncology ICU [14] and respiratory ICU patients [32]. Only three studies included multiple centers [16,20,21,26]. Most studies used the Confused Assessment Method for the ICU (CAM-ICU) for delirium screening (14/20, 70%) [13,14,17,18,20-22,25-29,31,46]. Of these, 11 (11/14, 79%) used the Richmond Agitation-Sedation Score (RASS) to identify delirium subtype [13,14,17,18,20-22,27,29,31,46]. All other tools used to screen for delirium and determine delirium subtype are listed in Additional File 2. Delirium assessments were most often conducted by nurses in eight

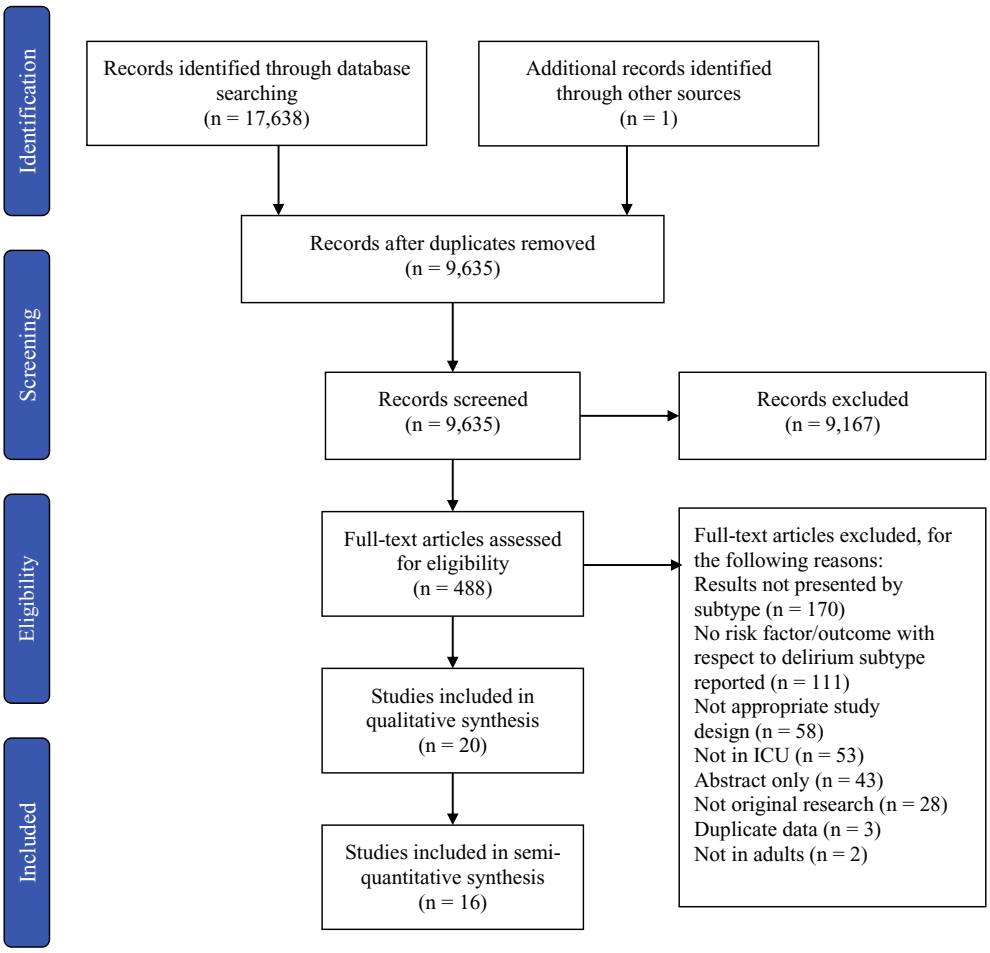

Fig. 1. PRISMA diagram of study selection.

(8/20, 40%) studies followed by physicians or research assistants (each 3/20, 15%) [13,15,17,22,26,27,29,46].

The range of prevalence of hyperactive (0.3% to 6.5%,), hypoactive (7.3% to 29.2%) or mixed delirium (1.3% to 33.6%) varied across the 20 studies (Additional File 2). Twelve studies (12/20, 60%) categorized delirium into three subtypes: hyperactive, hypoactive and mixed. Four studies (4/20, 20%) categorized delirium into two subtypes: hypoactive and hyperactive/mixed [13], hyperactive and non-hyperactive [15], delirium with agitation and delirium without agitation [46] or hyperactive and hypoactive delirium [31]. Four studies (4/20, 20%) reported on one delirium subtype [16,28,33] or reported on all three subtypes, but did not identify risk factors for the hyperactive and mixed subtypes (because the prevalence estimates were too low for statistical analysis) [19]. Sixteen studies (16/20, 80%) reported on risk factors/outcomes of multiple delirium subtypes and were included in the semi-quantitative analysis. However, they will be counted as 15 studies because the studies by van den Boogaard used the same data, but reported on different risk factors/outcomes [20,21].

3.3. Study quality assessment

The quality of the included studies varied (Additional File 3) and scores ranged from 4/10 to 8/10, with a median score of six (interquartile range (IQR): 1). Four studies (4/20, 20%) were graded as high quality, thirteen studies (13/20, 65%) as acceptable quality and three (3/20, 15%) studies as low quality. Only two studies accounted for performance bias by assessing delirium at the time of ICU admission [31] or excluding participants with delirium at study onset [14]. Two studies reported on delirium, but did not report which screening tool was used [16,33] and two evaluated patients for delirium using an instrument that, to our knowledge, is not validated for use in the ICU against the DSM-IV [15,31]. Most prospective cohort studies did not account for attrition bias (8/15, 53%). The majority of studies did not describe blinding of delirium or outcome assessors (19/20, 95%) (detection bias) or provide 95% confidence intervals (95% CI) (12/20, 60%).

4. Risk factors

Eight (8/15, 53%) studies reported on the risk factors associated with a delirium subtype using either multivariable or univariable analysis. Risk factors that were included in more than one study were: age, sex/gender and APACHE-II score. The results for the best-evidence synthesis of these risk factors are presented in Table 1.

4.1. Age

Seven (7/8, 87%, 9892 patients; 1702 with delirium) studies reported on age as a risk factor with respect to delirium subtype (Table 1) [13,15,17,18,21,27,30]. The mean age of the included patients in these studies varied between 52.5 and 68.2 years. Four (4/7, 57%) studies (three acceptable, one low quality) found no significant difference ($p > .05$) in mean or median age between reported delirium subtypes (Table 1) [13,15,21,30]. Two (2/7, 29%) studies (one high, one acceptable quality) determined that hypoactive delirium groups were significantly older when compared to other subtypes (Table 1). In the study by Robinson et al., univariable analysis demonstrated that patients with hypoactive delirium had a higher mean age of 71 years (standard deviation [SD]: 9) compared to patients with mixed delirium

Table 1
Overview of identified risk factors for delirium subtypes by univariable and multivariable statistical analysis.

Author (year)	Risk Factors		
	Age	Sex	APACHE-II
Bui (2016)	*U*	*U*	–
Heymann (2007)	*U*	*U*	*M*(hyperactive)*
Horacek (2016)	U	–	–
Khan (2016)	–	–	–
Lee (2018)	*U*(between motor subtypes)*	*U*	*U*(between motor subtypes)*
Peterson (2006)	*M*(hypoactive)*	–	*M*(hyperactive & mixed)*
Robinson (2011)	*U*(hypoactive)*	–	–
van den Boogaard (2012)	*U*	*U*	U*(mixed > hyper)

All acceptable/high quality studies are italicized.
U: included in univariable analysis of risk factor, but no significant difference between subtypes.
U*: identified as an independent risk factor (no correction for confounders).
M: included in multivariable analysis of risk factor, but no significant difference between subtypes.
M*: confirmed this factor as an independent risk factor for delirium (after correction for confounders).

(mean age: 65 years, SD: 9, $p = .002$) [18]. In the study by Peterson et al., multivariable analysis showed that older patients (≥65 years of age) had increased odds of developing hypoactive delirium (odds ratio: 3.0, 95% CI 1.7–5.3, $p < .001$) and the percentage of patients with hypoactive delirium was significantly higher in patients ≥65 years of age (41%) compared to patients who were < 65 years of age (21.6%, p < .001) [17]. The study by Lee et al. reported a difference between the motor subtypes, but there were no confidence intervals to indicate whether the difference in the mean age was significant between delirium subtypes [27]. There were consistent findings in four (4/7, 57%) large studies (sample sizes ranging from 1055 to 5642 participants) of no association of age as a risk factor for any delirium subtype.

4.2. Sex/Gender

Four (4/8, 50%, 3464 patients; 1113 with delirium) studies reported on sex (biological sex at birth; female/male) [47] or gender (role, behaviour or perception of self; woman/man) [47] with respect to delirium subtype [13,15,21,27] (Table 1). As sex or gender were not identified in their primary research question, we assume two (2/4, 50%) studies unintentionally used the term gender to refer to sex [15,21]. The proportion of females in the studies ranged between 31.2% and 51%. Using univariable analysis, all four (4/4, 100%) studies found no association for sex as a risk factor for any delirium subtype ($p > .05$). Sex associations were consistent, and two of the studies were considered high quality and there is no evidence of an association between sex and any delirium subtype.

4.3. APACHE-II score

Four (4/8, 50%, 4078 patients; 1488 with delirium) studies reported on mean APACHE-II score with respect to delirium subtype [15,17,21,27] (Table 1). Two (2/4, 50%) studies (both high quality) used univariable analysis. In the study by van den Boogaard et al., the authors found a significantly higher median APACHE-II score in patients with mixed delirium (18, IQR: 14-23) compared to patients with hyperactive delirium (16, IQR: 13–19, $p = .03$) [21], but not when compared to patients with hypoactive delirium (18, IQR: 14–22, $p = .47$). The study by Lee et al. found a significant difference in median APACHE-II score across all three subtypes (hyperactive: 16 (IQR: 12.0-20.0; hypoactive: 15.5 (IQR: 12.0–19.3); mixed: 17.0 (IQR: 14.0-20.0), $p < .001$) but there were no confidence intervals to indicate whether the difference in APACHE-II scores between delirium subtypes was significant [27]. Two (2/4, 50%) studies (both acceptable quality) used multivariable analysis. In the study by Heymann et al., the authors found the APACHE-II score to be significantly associated with hyperactive delirium (OR = 1.21; 95% CI 1.11–1.31, $p = .000$) while the authors in the study by Peterson et al. found the APACHE-II score to be associated with both hypoactive (OR = 1.04; 95% CI 1.01–1.07, $P < .05$) and mixed (OR = 1.08; 1.04–1.11, p < .001) delirium. There are inconsistent findings for APACHE-II score as a risk factor for any delirium subtype.

5. Outcomes

Outcomes associated with a delirium subtype were reported in nine (9/15, 60%) studies using either multivariable or univariable analysis. Outcomes that were included in more than one study were: mechanical ventilation, length of ICU/hospital stay, mortality, duration of delirium and inadvertent tube/line removal. The results for the best-evidence synthesis of these outcomes are presented in Table 2.

5.1. Mechanical ventilation

Five (5/9, 56%, 9615 patients; 1208 with delirium) studies reported on mechanical ventilation as an outcome with respect to delirium subtype [13,15,21,22,27] (Table 2). The percentage of patients mechanically ventilated among these studies ranged from 25% to 78.5%. All five studies (three acceptable, two high quality) used univariable analysis. One study (1/5, 20%) reported on the proportion of mechanically ventilated patients, wherein patients with hyperactive/mixed delirium were more likely to be on mechanical ventilation than patients with hypoactive delirium (59% vs. 40%, $p < .001$) [13]. Four studies (4/5, 80%) reported on the duration of mechanical ventilation. One study reported that the duration of mechanical ventilation was significantly longer for patients with hyperactive delirium (mean: 677.7 h, SD: 112.4) compared to patients with non-hyperactive delirium (mean: 340.6 h, SD: 56.8, $p = .01$) [15]. A different study reported that the median days of mechanical ventilation was significantly longer in patients with mixed delirium (6.9 days, IQR: 1.7–13.8) compared to patients with hypoactive delirium (3 days, IQR: 0.8–7.7, p < .001) and patients with hyperactive delirium (0.6 days, IQR: 0.3–2.1, p < .001) [21]. Two studies reported that the duration of mechanical ventilation differed significantly across delirium subtypes [22,27], but there were no confidence intervals or between-subtype *p*-values, and no indication where the subtype differences are significant. There are inconsistent findings in risk or duration of mechanical ventilation as an outcome of delirium subtypes.

5.2. Length of stay

Six (6/9, 67%, 4085 patients; 1319 with delirium) studies reported on length of stay in the ICU [LOS(ICU)] [13,15,18,21,22,27] (Table 2). The LOS(ICU) among studies ranged from a median LOS(ICU) 24.4 hours to a mean LOS(ICU) of 38.3 days. Five (5/6, 83%) studies (two high, three acceptable quality) reported univariable analysis [13,15,18,21,22] and one (1/6, 17%, high quality) multivariable analysis [27]. The high quality study that reported univariable analysis reported no significant difference in the mean LOS(ICU) between patients with delirium subtypes ($p > .05$) [18]. The three acceptable quality studies and one high quality study reported inconsistent findings. One study reported a significantly longer mean LOS(ICU) for patients with hyperactive/mixed delirium (11 days, SD: 12) compared to patients with hypoactive delirium (5 days, SD: 5, $p < .001$) [13]. One study reported a significantly longer mean LOS(ICU) for patients with hyperactive delirium (38.31 days, SD: 4.73) compared to patients with non-hyperactive delirium (13.8 days, SD: 1.5, p < .001) [15]. One study

Table 2
Overview of identified outcomes for delirium subtypes by univariable and multivariable statistical analysis.

Author (year)	Outcomes					
	Mechanical Ventilation	LOS (ICU)	LOS (hospital)	Mortality	Duration of Delirium	Removal of tubes
Bui (2016)	*U*(mixed/hyperactive)*	*U*(mixed/hyperactive)*	*U*(mixed/hyperactive)*	*U*	–	–
Falsini (2017)	–	–	–	*U*(hypoactive, in-hospital)*	–	–
Heymann (2007)	*U*(hyperactive)*	*U*(hyperactive)*	–	*U*(hyperactive)*	–	–
Horacek (2016)	–	–	–	–	U*(hyperactive)	–
Lee (2018)	*U*(between motor subtypes)*	*M*(between motor subtypes)*	*M*(between motor subtypes)*	*M*	*U*(between motor subtypes)*	–
Robinson (2011)	–	*U*	*U*	*U(30 days), U* (hypoactive, 6 months)*	*U*	*U(mixed)*
Sharma (2012)	–	–	–	U*(hypoactive)	–	–
van den Boogaard (2012)	U*(mixed)	*U*(mixed)*	*U*(mixed)*	U*(mixed and hypoactive)	*U*(mixed)*	U* (hyperactive)
Zhang (2016)	*U*(between motor subtypes)*	*U*(between motor subtypes)*	*U*	–	–	–

All acceptable/high quality studies are italicized.
U: included in univariate analysis of outcome, but no significant difference between subtypes.
U*: identified this factor as an independent outcome for a delirium subtype (no correction for confounders).
M: included in multivariable analysis of outcome, but no significant difference between subtypes.
M*: confirmed this factor as an outcome for a delirium subtype (after correction for confounders)

reported that patients with mixed delirium had a significantly longer median LOS(ICU) (9 days, IQR: 3–17) compared to patients with hypoactive delirium (5 days, IQR: 2-9, p < .001) and patients with hyperactive delirium (3 days, IQR: 1-5, p < .001)[21]. Two studies found that the median LOS(ICU) stay differed significantly between patients with delirium subtypes, but there were no 95% CIs or *p*-values to indicate which subtype had a significantly longer LOS(ICU) [22,27]. There are inconsistent findings in LOS(ICU) as an outcome of delirium subtypes.

Five (5/9, 56%, 3889 patients, 1123 with delirium) studies reported on length of stay in the hospital [LOS(hospital)] with respect to delirium subtype [13,18,21,22,27] (Table 2). The LOS(hospital) among studies ranged from a mean of 10 to 24 days. The subtype association with LOS(hospital) was similar to LOS(ICU) except that the study by Zhang et al. found no significant difference in the median LOS(hospital) between subtypes [22] wherein there was in LOS(ICU). There are inconsistent findings in LOS(hospital) as an outcome of delirium subtypes.

5.3. Mortality

Seven (7/9, 78%, 4502 patients, 1373 with delirium) studies reported on mortality with respect to delirium subtype (Table 2)[13,15,18,21,26,27,32]. Using univariable analysis, four (4/7, 57%) studies (one high, three acceptable quality) found an association between hypoactive delirium and increased mortality. In the study by Falsini et al., the authors found that patients with hypoactive delirium had significantly higher in-hospital mortality (42.9%) compared to patients with hyperactive delirium (12.5%, $p = .022$), mixed delirium (4.5%, $p = .016$) and no delirium (2.5%, $p < .0001$). In the study by Robinson et al., the authors found that patients with hypoactive delirium had a significantly higher 6-month mortality (32%) compared to the mixed group (8.7%, $p = .04$). In the study by van den Boogaard et al., the authors found that patients with hypoactive delirium had a significantly higher in-hospital mortality (18.9%) compared to patients with hyperactive delirium (6.8%, p = .04). In the same study, patients with mixed delirium had higher in-hospital mortality (19.2%) compared to patients with hyperactive delirium (6.8%, $p = .03$). The difference between the patients with hypoactive delirium and patients with mixed delirium was not significant ($p = .53$). Only one study found that the in-hospital mortality was higher in patients with hyperactive delirium (22%) compared to patients with non-hyperactive delirium (5.7%, $p = .02$) [15]. In the study by Bui et al., the authors found that in-hospital mortality did not differ significantly between the patients with hyperactive/mixed delirium (15%) and hypoactive delirium (10%, $p = .162$). Mortality was consistently associated with hypoactive delirium in 4/7 (57%) studies (one high and three acceptable quality).

5.4. Duration of delirium

Four (4/9, 44%, 8027 patients; 708 with delirium) studies reported on delirium duration with respect to subtype [21,27,30,18] (Table 2). One study reported that the hyperactive subtype of delirium was associated with a prolonged median duration of delirium (hyperactive: 76.2 h, SD: 40.5, hypoactive: 54.5 h, SD: 28.4, mixed: 61.2 h, SD: 37.9) [30]. One study reported that patients with mixed delirium had significantly longer duration of delirium (median: 4 days) compared to patients with hyperative or hypoactive delirium (each 1 day, p<.001) [21]. One study reported that the mean duration of delirium did not differ between the hypoactive (mean: 2.8 days, SD: 1.4) and mixed (mean 3.9 days, SD: 5.4, $p = .34$) groups [18]. The study by Lee et al. reported a difference between the motor subtypes, but there were no confidence intervals to indicate which subtype had a longer delirium duration [27]. There are inconsistent findings duration of delirium as an outcome of delirium subtypes.

5.5. Inadvertent tube/line removal

Two (2/9, 22%, 1,785 patients; 485 with delirium) studies reported on inadvertent tube/line removal; including catheters, peripheral intravenous lines and nasogastric tubes with respect to subtype (Table 2) [18,21]. Inadvertent tube/line removal was reported to be associated with the mixed [18] and hyperactive [21] subtypes of delirium. In the

study by Robinson et al., the authors found a significant difference in inadvertent tube or line removal in the mixed group (90.0%) versus the hypoactive group (22.2%, $p = .006$). The hyperactive delirium subtype was excluded from statistical comparison because of the small prevalence ($n = 1$) in that study sample. In the study by van den Boogaard et al., there was a significant increase in the re-intubation per 1000 delirium days of patients with hyperactive delirium ($n = 68$) compared to patients with hypoactive ($n = 22$, $p = .02$) and mixed delirium ($n = 16$, $p = .01$). The frequency of unplanned removal of tubes and catheters per 1000 delirium days was also significantly higher in patients with hyperactive delirium ($n = 386$) compared to patients with hypoactive delirium ($n = 88$, <0.001) and mixed delirium ($n = 86$, $p < .001$). There was no significant difference between the hypoactive and mixed subtypes ($p > .05$). There are inconsistent findings in subtype-specific inadvertent tube/line removal as an outcome of a delirium subtype.

6. Discussion

This systematic review included 26,442 adult ICU patients (3897 with delirium) and used semi-quantitative analyses to evaluate delirium subtype-specific risk factors and outcomes. The heterogeneous reporting of variables made it difficult to find subtype-specific risk factors and outcomes. Although risk factors (age, sex/gender, APACHE-II score) and outcomes (mechanical ventilation, length of ICU stay, mortality, delirium duration and inadvertent tube removal) were significantly associated with delirium subtypes in multiple studies, the subtype-specific association and quality of the studies varied. This highlights the challenge of identifying subtype-specific risk factors and outcomes for ICU delirium, reflecting the need for the standardization of delirium research reporting and methodologies.

The identification of subtype-specific risk factors and outcomes may help with the prevention, diagnosis and management of delirium in the critically ill. The delirium literature is vast and growing exponentially. This literature primarily includes risk factors and outcomes for overall delirium, which have been identified in recent systematic reviews and meta-analyses [11,49]. However, the current literature is inadequate to address whether any risk factor or outcome is associated with delirium subtypes (Table 3). This may be due in part to inconsistent reporting of risk factors and outcomes between studies and variation in statistical models used to analyse the data. To advance knowledge of delirium subtypes and progress toward evidence-based improvements in patient- and family-centered outcomes, delirium research must be conducted using consistent measures and standard methods across studies in similar populations. The results of this systematic review supports the recent aim of the delirium of core outcome sets (Del-COrS) group to develop a set of core outcomes for patient groups when studying delirium, including the critically ill [50]. This core outcome set should include measures that may be associated with delirium subtypes such as risk factors (e.g., age, sex/gender, APACHE-II score) and outcomes (e.g., duration of mechanical ventilation, length of ICU stay, mortality, delirium duration and inadvertent tube removal) for each patient in any delirium study. The development of a core outcome set should occur through international consensus, including consideration of risk factors and outcomes reported in systematic reviews, interviews with patients and families who experienced delirium and a Delphi process to agree upon delirium subtype core outcome measures. Consistent reporting of outcomes has the potential to identify subtype-specific risk factors and outcomes less equivocally.

Table 3
Identified delirium risk factors and outcomes and their reported association with delirium subtypes.

Delirium risk factors & outcomes	Hyperactive	Hypoactive	Mixed
Risk factors			
Age	⟺	⇑	⟺
Dementia	x	x	x
Hypertension	⇑	x	x
Pre-ICU emergency surgery or trauma	⇑	x	x
APACHE-II score	⇑	⟺	⇑
Mechanical ventilation	⇑	⟺	⇑
Metabolic acidosis	x	x	x
Delirium on the prior day	x	x	x
Coma	x	x	x
Outcomes			
Mortality	⇑	⇑	⇑
Duration of mechanical ventilation	⇑	⟺	⇑
Length of stay (hospital)	⇑	⟺	⇑
Length of stay (ICU)	⇑	⟺	⇑
Cognitive impairment	⇑	⟺	⟺

Abbreviations: APACHE II (Acute Physiology and Chronic Health Evaluation II); ICU (Intensive Care Unit).
x (risk factor or outcome subtype association not reported [in any included studies]); ⇑ (reported subtype association [in any included studies]); ⟺ (no reported subtype association [in any included studies]).

Most risk factors for delirium are not modifiable, though may provide information for a subtype-specific delirium prediction model, like the PREdiction of DELIRium for the Intensive Care patients (PRE-DELIRIC) model [51]. For example, the study by Lee et al. calculated the PRE-DELIRIC score for each participant and, using univariable analysis, found a significant difference in patients at risk between delirium subtypes ($p < .001$) [27]. However, the association of a PRE-DELIRIC score with a specific subtype is unknown. Adapting the PRE-DELIRIC model will require an observational study collecting delirium subtype-specific data on risk factors that contribute to the PRE-DELIRIC formula (i.e., age, APACHE-II score, coma, type of patient, infection, metabolic acidosis, use of morphine, use of sedatives, urea concentration and urgent admission). This data could then recalibrate the delirium prediction model for each delirium subtype, which may serve as a diagnostic adjunct to existing delirium screening tools. This may improve the detection of hypoactive delirium, which is more difficult to recognize than hyperactive delirium [52]. Patients with hypoactive delirium may have higher mortality than patients with hyperactive or mixed delirium [18,21,26,32]. All patients at high risk for hypoactive delirium should be prioritized for screening or detection as hypoactive delirium is difficult to detect and might be missed [34]. At the time of this review, one study reported that patients with hyperactive or mixed delirium have deficiencies in the mental health domain of a patient-reported survey of their health [20]. As such, patients who have any delirium during their ICU stay, especially mixed or hyperactive, could be flagged for post-ICU follow-up, but further studies including subtype-specific long-term mental health and cognitive outcomes are required.

Patients admitted to the ICU often have complex medical problems in addition to a variety of clinical factors that may contribute to the development of and detection of delirium subtypes [11,53]. The current study demonstrates the inconsistency in reporting, which limits the evidence available for subtype-associated risk factors and outcomes. Several studies did not account for analgesia or sedative used. This is important because analgesia and sedation practices vary across settings [54] and benzodiazepines have been identified as a delirium risk factor [55-57]. In addition, a patient may have altered mentation secondary to analgesia or sedation administration, which may confound a delirium diagnosis. Standardization in ICU delirium research methodology should include multivariable analysis that account for these factors when analysing subtype-associations of any risk factor or outcome. Currently, there is no standard set of variables that should be incorporated into a multivariable risk factor or outcome model. This is due in part to between study heterogeneity, which limits the generalizability across the studies. The standardized reporting of risk factors or outcomes will inform a potential common multivariable analyses that could be incorporated into the analysis of clinical data from future ICU delirium studies.

This systematic review has many strengths. It used established systematic review methodology and a pre-registered protocol. We searched six large online databases, without restrictions on language

or date of publication. Furthermore, the process of title/abstract screening, full-text selection, data extraction and study quality rating were performed in duplicate by two independent reviewers. Our systematic review also has limitations. Although we had a thorough search strategy, which included a grey literature search, it is possible that studies may have been missed. Given the heterogeneity in reported risk factors or outcomes and study methodology, it was not possible to do a pooled analysis on variables between studies. We therefore employed methodology described by Zaal et al. to semi-quantitatively compare risk factors between the 20 included studies. Future studies are unlikely to change the conclusions made in this investigation given the inconsistent application of delirium measurement tools in clinical settings; our paper provides the best available evidence regarding subtype-specific risk factors and outcomes.

7. Conclusions

This review examined risk factors and outcomes for delirium subtypes, identifying several risk factors and outcomes that may have a subtype-association, but require further investigation. This review also highlighted the need for the development of a standard set of clinically relevant risk factors and outcomes and research methodology for studies of delirium in the critically ill. It is unclear at present whether subtype-specific differentiation in risk factors and outcomes is important for understanding the epidemiology of delirium.

Funding

This work was supported by a New Investigator Seed Grant from the Critical Care Strategic Clinical Network of Alberta Health Services (to KMF).

Declaration of Competing Interest

The authors (KDK, HTS, EWE and KMF) do not have any conflicts of interest relevant to this manuscript.

Acknowledgements

Thank you to both Heather Ganshorn (University of Calgary) and Brooke Scott (Fraser Health) regarding the development and review of the search strategies. Thank you to Cassidy Codan, Lauren Doig and Megan Farris who provided assistance reviewing abstracts for this review.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2020.01.017.

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