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Review Article

Risk Factors for Acute Delirium in Critically Ill Adult Patients: A Systematic Review

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Background. Delirium is characterized by disturbances of consciousness, attention, cognition, and perception. Delirium is a serious but reversible condition associated with poor clinical outcomes. This has implications for the critically ill patient; the effects of delirium cause long term sequelae, principally cognitive deficits, and functional decline. *Objectives*. The objective of the paper was to describe risk factors associated with delirium in critically ill adult patients. *Methods*. Published and unpublished literature from 1990 to 2012, limited to English, was searched using ten databases. *Results*. Twenty-two studies were included in this paper. A large number of risk factors were presented in the literature; some of these were common across all settings whilst others were exclusive to the type of setting. Benzodiazepines and opioids were shown to be risk factors for delirium independent of setting. *Conclusion*. With regard to patients admitted to medical and surgical intensive care units, risk factors of older age and comorbidity were common. In the cardiac ICU, older age and lower Mini-Mental Status Examination scores were cited most often as risk factors for delirium, but other risk factors exclusive to the setting were also significant. Benzodiazepines were identified as the most significant pharmacological risk factor for delirium.

1. Introduction

Delirium is a syndrome characterized by disturbances of consciousness, attention, cognition, and perception [1]. Delirium has multiple aetiologies, but the predisposing risk factors most frequently cited are older age, cognitive impairment, severity of illness, and iatrogenic causes [2, 3]. Delirium has an acute onset. Symptoms fluctuate over a 24-hour period [4, 5]. Although its presentation is typically associated with symptoms of hyperactive delirium (restlessness, agitation) [4], two other subtypes exist, "hypoactive" and "mixed" [1]. Hypoactive delirium is characterized by lethargy, reduced activity, and apathy [5], whereas mixed delirium features characteristics of both hyperactive and hypoactive deliriums. Although associated with poor clinical outcomes, delirium is typically reversible [6, 7]. This has implications for management of the critically ill patient; not only is the patient's life threatened by the primary illness, but also the effects of delirium may cause long term sequelae, principally cognitive deficits, and functional decline [8]. Hypoactive and mixed deliriums often go unrecognized despite being more common than hyperactive delirium [3, 8], resulting in undertreatment and poorer outcomes [8, 9]. Such factors present a challenge to clinicians to identify factors and possibly to prevent delirium in critically ill patients.

2. Methods

This systematic paper is an abridged version of a full online publication available at the Joanna Briggs Institute Library of Systematic Reviews (http://connect.jbiconnectplus.org/JBIReviewsLibrary.aspx) [31].

2.1. Inclusion and Exclusion Criteria. This paper considered studies including randomised controlled trials, nonrandomised controlled trials, and before and after studies. In their absence, cohort and case control studies were considered for inclusion. Participants were adults (aged 21 years and above) presenting with delirium (hyperactive, hypoactive, and mixed) in the intensive care unit (ICU). Synonyms such

Table 1: Keyword categories.

	Keywords
Concept 1: factors	(i) Electrolyte imbalance (ii) Fever (iii) Urinary tract infection (iv) Sepsis (v) Pneumonia (vi) Anaesthetic (vii) Postoperative complication* (viii) Hypoxia (ix) Anoxia (x) Dementia (xi) Age (xii) Older* (xiii) Head injury (xiv) Subdural hematoma
Concept 2: acute delirium	(i) Delirium (ii) Confusion* (iii) Agitation* (iv) Attention* (v) Disorientation* (vi) Stupor (vii) Hallucination (viii) Incoherence* (ix) ICU psychosis (x) Acute confusional state (xi) ICU Syndrome
Concept 3: critically ill patients	(i) Critical care (ii) Intensive care unit

as ICU psychosis and ICU syndrome were included. Critically ill patients not in the ICU (e.g., those in the general ward) were excluded.

2.2. Search Strategy. A three-step search strategy was utilised. An initial search was undertaken using the search terms "factors," "delirium," and "critical care." A comprehensive search strategy was then developed using identified keywords and MeSH headings (Table 1). Finally, the reference lists of all identified studies were examined for additional studies relevant to the review. Published and unpublished literature from 1990 to 2012, limited to the English language, was searched using ten databases.

2.3. Search Results. Twenty-two studies were included in the paper (Figure 1; Table 2). The studies were conducted in medical, surgical, and cardiac intensive care units. Twenty studies were prospective and two retrospective cohort studies.

Fifteen studies used the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), with the Richmond Agitation Sedation Scale (RASS) for the diagnosis of delirium. The remaining studies used other delirium assessment tools: the Diagnostic Statistical Manual-IV (DSM-IV), Confusion Assessment Method (CAM), Intensive Care Delirium Screening Checklist (ICDSC), Nursing Delirium Screening Scale (Nu-DESC), and Delirium Rating Scale (DRS). Only one of the studies used randomized sampling [25], whilst the remainder predominantly used large cohort (range from 20 to 1367 patients) convenience sampling. Due to the heterogeneous nature of the included studies, findings are presented in a narrative review.

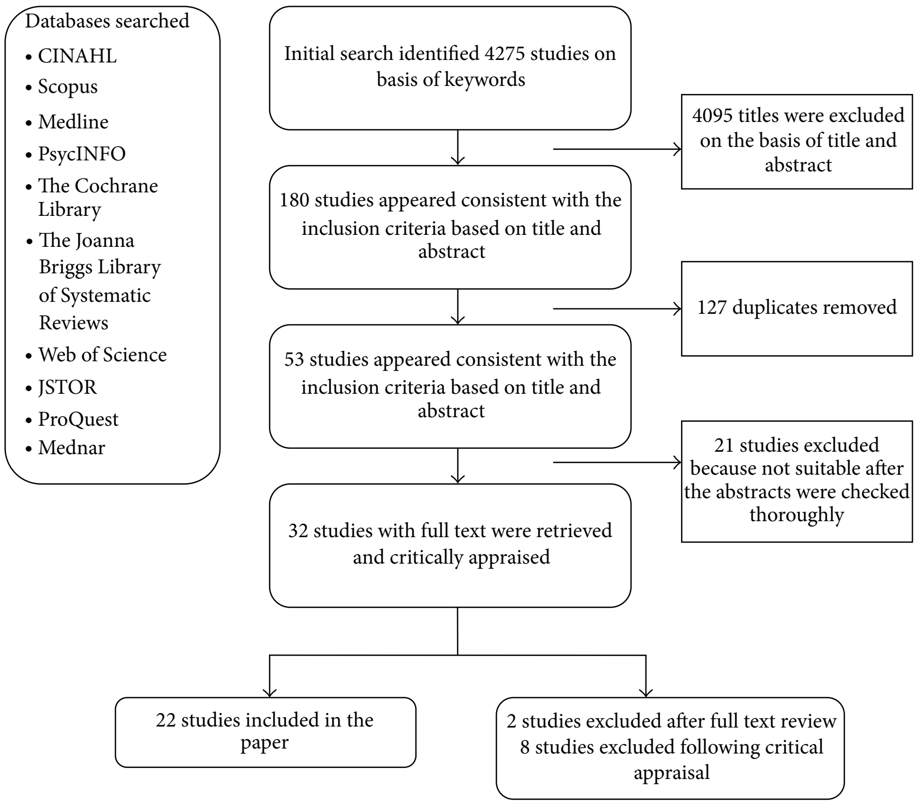
2.4. Assessment of Methodological Quality. Studies were identified for relevance via title, abstract, and keywords. Two independent reviewers assessed content relevance. Full texts of eligible studies were retrieved and reviewed using the appropriate critical appraisal instruments from the Joanna Briggs Institute (JBI) [31].

3. Results

3.1. Patients Admitted to the Medical Intensive Care Unit. Peterson et al. [25] examined delirium and its motoric subtypes in a medical ICU (MICU). Data on demographics (age, gender, and race), Acute Physiology and Chronic Health Evaluation-II (APACHE-II) scores, and intubation or extubation were collected from 614 randomised participants. Delirium assessments were extensive and rigorous, generating 7,323 CAM-ICU and 21,931 RASS assessments. Results show that patients aged 65 years and older ($n = 156$) experienced hypoactive delirium more frequently (71.8% versus 57.4%) than younger patients ($n = 458$), and older age was strongly associated with hypoactive delirium. Mixed type (hyper-, hypoactive) delirium was the most common (54.9%) amongst other subtypes.

In contrast, Lin et al. [20] examined risk factors for early-onset delirium in mechanically ventilated MICU patients. However, "early onset" was not defined in the study, and no time measures were recorded. Data was obtained from the medical records of 143 patients (including APACHE-II scores, patient's medical history, and alcohol use). Data collection was rigorous; the questionnaires used were previously pilot tested, and research procedures were standardised to ensure reliability. A stepwise logistic regression revealed hypoalbuminemia and presence of sepsis on admission as significant factors in the development of early onset delirium.

3.2. Patients Admitted to the Surgical Intensive Care Unit. Robinson et al. [27] recruited 144 patients who were listed for surgery and required postoperative ICU admission. A pilot study was conducted to assess interrater reliability using the CAM-ICU. A high interrater reliability (kappa statistic > 0.96) ensured internal validity of the results. It was shown that preoperative variables such as older age, hypoalbuminemia, impaired functional status, preexisting dementia, and preexisting comorbidities were significantly associated with delirium [27]. This supports the finding of Peterson et al. [25] who showed that preexisting dementia was the most significant risk factor for the development of postoperative delirium.



Search results and selection

Figure 1

Examining the course of delirium in older SICU patients, Balas et al. [15] recruited 117 participants. It contrasts with Robinson et al. [27] in that the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) was used to assess the presence of dementia. The IQCODE is a validated tool in which dementia is assessed by obtaining information from a surrogate. It was found that older adults admitted to the SICU were at high risk of developing delirium. 18.4% of the participants had dementia on admission, 28.3% of the participants developed delirium in the SICU, and 22.7% of the participants developed delirium in the post-SICU period. The study used descriptive statistics only. Furthermore, the effects of dementia were not explored.

Angles et al. [13] examined risk factors for delirium after major trauma in patients admitted to the trauma intensive care unit. Results from this group are reported because the majority of trauma patients require emergency surgery. The study had a small number of participants ($n = 59$). It was shown that a GCS of 12 or less, higher blood transfusions, and higher multiple organ failure score were significantly associated with delirium.

In a study examining the effect of hypoxia on cognition, Guillamondegui et al. [18] recruited 97 ICU patients with multiple traumas without evidence of intracranial haemorrhage. Data such as age, race, length of ICU stay, and injury severity score was recorded, and oxygen saturation was measured. Using the CAM-ICU, 57% of patients were "positive" for delirium. After adjusting for injury severity score, oxygen saturation, blood transfusions, and blood pressure, it was revealed that the number of ventilator days and ED pulse rate were significantly associated with delirium.

3.3. Patients Admitted to the Cardiac Intensive Care Unit. Afonso et al. [10] created a predictive model for postoperative delirium in 112 cardiac surgical patients. Surgery included coronary artery bypass graft (CABG), valve replacement, and aortic surgery. The incidence of delirium was 34%. Increased age and increased duration of surgery were the most significant risk factors for postoperative delirium.

Detroyer et al. [16] also examined postoperative delirium in 104 patients focusing on anxiety and depression as risk factors for postoperative delirium. Unlike Afonso et al. [10] the type of surgical procedure was not recorded. Prolonged intubation time and a low intraoperative lowest body temperature were the most significant predictors of delirium.

Similar to Afonso et al. [10], Bakker et al. examined predictors of delirium after cardiac surgery in 201 patients. A Mini-Mental Status Examination (MMSE) was conducted to assess "global cognitive functioning" [14] in the participants before surgery, and medical records were evaluated. In the final logistic regression model, lower MMSE scores, higher creatinine levels, and longer extracorporeal circulation time were independent predictors of delirium. Mortality during the first 30 days after surgery was significantly higher in

Table 2: Studies included in the paper.

Author(s)	Population	Intervention/control	Outcome measures	Results
Afonso et al., 2010 [10]	112 adult postoperative cardiac surgical patients	Patients w/out delirium	RASS and CAM-ICU scores	Increased age (OR = 2.5, C.I. = 1.6–3.9, and $P < 0.0001$, per 10 years) and increased duration of surgery (OR = 1.3, CI = 1.1–1.5, and $P = 0.0002$) were the most significant risk factors for postoperative delirium.
Agarwal et al., 2010 [11]	82 adult ventilated burn patients	Patients w/out delirium	CAM-ICU scores	Benzodiazepines were found to be independent risk factors for the development of delirium (OR = 6.8, CI = 3.1–15.0, and $P < 0.001$). Opiates ($P < 0.001$) and methadone ($P = 0.02$) appeared to have protective effects, being associated with a lower risk of delirium.
Andrejaitiene and Sirvinskas, 2011 [12]	90 patients with postoperative delirium after cardiac surgery on cardiopulmonary bypass	Nil	RASS and CAM-ICU scores	Administering a dose of fentanyl above 1.4 mg increased the possibility of developing severe delirium (OR = 29.4, CI = 4.1–210.3, and $P < 0.001$). Longer aortic clamping time was also noted as an independent predictor of severe delirium (OR = 8.0, CI = 1.7–37.2, and $P < 0.001$). Postoperative delirium prolonged the length of stay in the ICU by 8.4 days.
Angles et al., 2008 [13]	59 patients admitted to the trauma intensive care unit	Patients w/out delirium	CAM-ICU scores	A GCS of 12 or less (12 ± 1.0 versus 15 ± 0.1, $P < 0.01$), increased blood transfusions (2.8 ± 0.7 versus 0.5 ± 0.3, $P < 0.01$), and higher multiple organ failure scores (1.2 ± 0.2 versus 0.1 ± 0.1, $P < 0.01$) were significantly associated with delirium. Subjects with delirium had longer hospital and ICU stays and were more likely to require postdischarge institutionalization.
Bakker et al., 2012 [14]	201 patients who went for cardiac surgery aged 70 years and older	Patients w/out delirium	CAM-ICU scores and MMSE	63 patients developed delirium after cardiac surgery. Lower MMSE scores (OR = 2.32, CI = 1.20–4.46), higher creatinine levels (OR = 1.02, CI = 1.00–1.03), and longer extracorporeal circulation time (OR = 1.01, CI = 1.01–1.02) were independent predictors of delirium.
Balas et al., 2007 [15]	117 SICU patients	Patients w/out delirium	CAM-ICU scores	Older patients admitted to the SICU were at high risk for developing delirium during hospitalization.
Detroyer et al., 2008 [16]	104 patients admitted for elective cardiac surgery	Patients w/out delirium	CAM-ICU scores and DI	Prolonged intubation time (OR = 1.10, CI = 1.05–1.15) and a low intraoperative lowest body temperature (OR = 0.86, CI = 0.74–0.99) were the most significant predictors of delirium.
Eden et al., 1998 [17]	20 elderly patients in a critical care setting	Patients w/out delirium	DSM III and CAM scores	Comorbidity, presence of infection, a blood urea nitrogen/creatinine ratio of 18 or more, and age were the most significant variables, with a sensitivity of 100% and a specificity of 90%.
Guillamondegui et al., 2011 [18]	97 patients with multiple injuries, requiring ICU management	Patients w/out delirium	CAM-ICU scores	55 of 97 ICU patients were CAM-ICU positive for delirium. Number of ventilator days (OR = 1.16, CI = 1.05–1.29) and ED pulse rate (OR = 1.02, CI = 1.00–1.04) were significantly associated with delirium.
Hudetz et al., 2011 [19]	44 patients undergoing elective cardiac surgery aged 55 years or more	Nonsurgical controls and patients undergoing coronary artery bypass graft (CABG) alone	ICDSC scores	A univariate analysis showed that postoperative delirium occurred more frequently in patients undergoing valve surgery with or without CABG as opposed to CABG alone ($P = 0.01$).

Table 2: Continued.

Author(s)	Population	Intervention/control	Outcome measures	Results
Lin et al., 2008 [20]	143 mechanically ventilated patients	Patients w/out delirium	CAM-ICU scores	Hypoalbuminemia (OR = 5.94, CI = 1.23–28.77) and presence of sepsis on admission (OR = 3.65, CI = 1.03–12.9) are significant factors in the development of early onset delirium.
Norkiene et al., 2007 [21]	1367 adult patients undergoing CABG	Patients w/out delirium	DSM IV criteria	Eight factors were independent predictors of delirium, which were age more than 65 years (OR = 3.82, CI = 1.44–10.12), peripheral vascular disease (OR = 2.80, CI = 1.11–7.04), a EuroSCORE (European System for Cardiac Operative Risk Evaluation) more or equal to 5 (OR = 2.46, CI = 1.16–2.51), preoperative intra-arterial blood pressure support (OR = 8.51, CI = 1.81–40.03), blood product usage (OR = 4.59, CI = 2.10–10.06), and postoperative low cardiac output syndrome (OR = 8.04, CI = 1.1–60.6).
Ouimet et al., 2007 [22]	820 ICU patients	Patients w/out delirium	ICDSC and RASS scores	A history of hypertension (OR = 1.88, CI = 1.3–2.6), alcohol use (OR = 2.03, CI = 1.2–3.2), higher APACHE II score (OR = 1.25, CI = 1.03–1.07), and administration of sedative and analgesic drugs were associated with delirium (OR = 3.2, CI = 1.5–6.8).
Pandharipande et al., 2006 [23]	198 mechanically ventilated patients	Patients w/out delirium	RASS and CAM-ICU scores	Lorazepam was an independent risk factor (OR = 1.2, CI = 1.1–1.4) for daily transition to delirium. Midazolam ($P = 0.09$), fentanyl ($P = 0.09$), morphine ($P = 0.24$), and propofol ($P = 0.18$) were not significant, although they were "associated with trends towards significance."
Pandharipande et al., 2008 [24]	100 surgical and trauma ICU patients requiring mechanical ventilation for >24 hours	Patients w/out delirium	RASS and CAM-ICU scores	Midazolam (OR = 2.75, CI = 1.43–5.26, $P = 0.002$) was a strong risk factor for transition to delirium. Opiate exposure was inconclusive in that opiates such as fentanyl were a risk factor for delirium in the SICU ($P = 0.007$), but not in the TICU ($P = 0.936$). Opiates such as morphine were linked to a lower risk to delirium ($P = 0.024$).
Peterson et al., 2006 [25]	156 medical intensive care unit (MICU) patients	Younger MICU patients aged lower than 65	RASS and CAM-ICU scores	Patients 65 years and above experienced hypoactive delirium more frequently than younger patients (41.0% versus 21.6%, $P < 0.001$), and older age was strongly associated with hypoactive delirium (OR = 3.0, CI = 1.7–5.3). Mixed type (hyper-, hypoactive) delirium was the most common (54.9%) amongst other subtypes.
Ranhoff et al., 2006 [26]	401 sub intensive care unit patients 60 years and above	Patients w/out delirium	CAM and MMSE scores	Delirium was found in 29.2% of the patients, of which 13.7% developed delirium in the ICU. Heavy alcohol use (OR = 6.1, CI = 1.8–19.6), polypharmacy (7 or more drugs) (OR = 1.9, CI = 1.1–3.2), and the use of bladder catheter are predictors of delirium (OR = 2.7, CI = 1.4–4.9).
Robinson et al., 2009 [27]	144 patients older than 50 years admitted to postoperative intensive care unit	Patients w/out delirium	RASS and CAM-ICU scores	Several preoperative variables were significantly associated: older age ($P < 0.001$), hypoalbuminemia ($P < 0.001$), impaired functional status ($P < 0.001$), preexisting dementia ($P < 0.001$), and preexisting comorbidities ($P < 0.001$).

Table 2: Continued.

Author(s)	Population	Intervention/control	Outcome measures	Results
Schoen et al., 2011 [28]	231 patients scheduled for elective/urgent cardiac surgery	Patients w/out delirium	RASS, CAM-ICU and MMSE scores	Older age (OR = 4.30, CI = 1.54–12.04, and $P = 0.005$), lower MMSE scores (OR = 6.50, CI = 1.75–24.13, and $P = 0.018$), neuropsychiatric disease (OR = 6.22, CI = 2.02–19.16, and $P = 0.001$), and lower preoperative cerebral oxygen saturation scores (OR = 3.27, CI = 1.14–9.37, and $P = 0.027$) were independent predictors for postoperative delirium.
Shi et al., 2010 [29]	164 surgical intensive care unit patients after noncardiac surgery	Patients w/out delirium	Nursing Delirium Screening Scale	Predictive factors of delirium were increasing age (OR = 2.646, CI = 1.431–4.890), history of previous stroke (OR = 4.499, CI = 1.228–16.481), high APACHE II score on SICU admission (OR = 1.391, CI = 1.201–1.621), and high serum cortisol level (OR = 3.381, CI = 1.690–6.765) on the first postoperative day.
Taipale et al., 2012 [30]	122 participants requiring nonemergency surgery for coronary artery or valvular heart disease	Patients w/out delirium	RASS and CAM-ICU scores	The prevalence of delirium ranged from 37.7% to 44.3%. For every additional milligram of midazolam administered, patients were 7-8 % more likely to develop delirium (CI: 1.00–1.14, $P = 0.06$).
Uguz et al., 2010 [1]	212 coronary intensive care unit patients	Patients w/out delirium	DSM IV criteria and DRS	Independent predictors of delirium were advanced age ($B = 0.10$, $P = 0.02$), higher level of serum potassium at admission ($B = 1.37$, $P = 0.04$), and experience of cardiac arrest ($B = 4.85$, $P < 0.001$) during MI.

CAM-ICU: Confusion Assessment Method for the Intensive Care Unit.
DI: delirium index.
DSM: Diagnostic Statistical Manual.
DRS: Delirium Rating Scale.
ICDSC: Intensive Care Delirium Screening Checklist.
MMSE: Mini-Mental Status Examination.
RASS: The Richmond Agitation Sedation Scale.

delirious patients (14% versus 0%) as compared to nondelirious patients, and adverse events after surgery were more frequent.

In a retrospective study by Andrejaitiene and Sirvinskas [12] examining risk factors for early postcardiac surgery delirium, participants ($n = 90$) were studied as two distinct groups: light-to-moderate delirium and severe delirium. However, the criteria determining severity of delirium were not described. The term "early" was not defined. In addition, there is no comparator group, casting ambiguity on the "true" incidence of delirium (4.17%). As such, the assertion that delirium caused prolonged hospital stay cannot be justified. It was shown that administering a dose of fentanyl above 1.4 mg increased the possibility of developing severe delirium. Longer aortic clamping time was also noted as an independent predictor of severe delirium. New atrial fibrillation (AF) episodes also occurred more frequently in patients with severe delirium than those with light-to-moderate delirium.

The study by Schoen et al. [28] aimed to examine preoperative and intraoperative cerebral oxygen saturation and its association with postoperative delirium in patients undergoing on-pump cardiac surgery. 231 participants were recruited. Cerebral oxygen saturation was assessed using cerebral oximetry, detecting "imbalances in the cerebral oxygen supply/demand ratio" [28]. Older age, lower MMSE scores, neuropsychiatric disease, and lower preoperative cerebral oxygen saturation scores were independent predictors for postoperative delirium. However, the patient's sedatives, which may have a profound effect on the development of delirium, were not recorded.

3.4. Pharmacological Factors. Pandharipande et al. [23] examined sedatives and analgesics as risk factors for "patients' transition to delirium." One hundred and ninety-eight mechanically ventilated patients admitted to medical or coronary ICUs were recruited. Using a Markov regression model, it was found that lorazepam was an independent risk factor for daily transition to delirium. Other sedatives and analgesics, such as midazolam, fentanyl, morphine, and propofol, were not significant, although they were "associated with trends towards significance" [23].

In a follow-up study, Pandharipande et al. [24] investigated the effects of sedatives and analgesics in patients admitted to the surgical ICU (SICU) and trauma ICU (TICU). One hundred mechanically ventilated patients were recruited. Midazolam was found to be a strong risk factor for transition to delirium. However, opiate exposure was inconclusive in that opiates such as fentanyl were a risk factor for delirium in the SICU, but not in the TICU. In addition, opiates such as morphine were linked to a lower risk to delirium.

Agarwal et al. [11] recruited eighty-two adult ventilated patients in burns ICU. Benzodiazepines were found to be independent risk factors for the development of delirium. Results suggest that benzodiazepines were a strong risk factor for the transition to delirium. In comparison to the study by Pandharipande et al. [24], opiates and methadone appeared to have protective effects, being associated with a lower risk of delirium.

The association between nurse-administered midazolam and incident delirium was examined by Taipale et al. [30] in a prospective observational study. 122 participants undergoing cardiac surgery were recruited. In this ICU setting, there were no formal sedation protocols other than the physician's standing orders and sedatives which were administered pro re nata (PRN) by nurses. This study was notable in the creation of study variables when the diagnosis of delirium did not match those of the physicians' (overall agreement = 71.3%); this had not been done previously. There was also a detailed accounting of recruitment, and measures were taken to enhance reliability of CAM-ICU assessments between researchers. Results showed that, for every additional milligram of midazolam administered, patients were 7-8% more likely to develop delirium.

3.5. Evaluation by Other Instruments. In the medical ICU, three studies were reviewed. Eden et al. [17] applied four previously studied predictive models designed to predict susceptible ICU patients. This study used the CAM and DSM criteria for delirium diagnosis. Unlike other studies, this study has a small sample size; it has an elderly sample of ten delirious and ten control patients only. Fourteen independent variables were operationalised and incorporated into data collection tools. A composite of these predictive models was synthesized and showed that co-morbidity, presence of infection, a blood urea nitrogen/creatinine ratio of 18 or more, and age were the most significant variables, with a sensitivity of 100% and a specificity of 90%. Ranhoff et al. [26] conducted their study in a subintensive care unit for the elderly, recruiting 401 patients. The researchers also used the CAM to diagnose delirium. Delirium was found in 29.2% of the patients, of which 13.7% developed delirium in the ICU. Heavy alcohol use, polypharmacy (7 or more drugs), and the use of bladder catheter were predictors of delirium. Ouimet et al. [22] examined delirium in 820 ICU patients using the ICDSC. A history of hypertension, alcohol use (similar to the previous study by Ranhoff et al. [26]), higher APACHE II score, and administration of sedative and analgesic drugs was associated with delirium.

In the surgical ICU, one study was reviewed. Shi et al. [29] conducted a study in a Chinese ICU examining both the incidence and risk factors of delirium in 164 patients after noncardiac surgery. The researchers used the Nu-DESC, a delirium screening tool validated in the Chinese population. The results showed the predictive factors of delirium to be increasing age, history of previous stroke, high APACHE II score on SICU admission, and high serum cortisol level on the first postoperative day.

In the cardiac ICU, three studies were reviewed. Hudetz et al. [19] examined the incidence of delirium in patients undergoing valve surgery with or without CABG as compared to patients undergoing CABG alone. Forty-four "education balanced" patients were recruited from the ICU of one veteran affairs medical centre. The ICDSC was used to diagnose delirium before surgery and five days after surgery. Postoperative delirium occurred more frequently in patients undergoing valve surgery with or without CABG as opposed to CABG alone. Uguz et al. [1] conducted a study which measured the incidence of delirium as it relates to acute myocardial infarction (AMI) as opposed to surgical procedures. Two hundred and twelve patients who were admitted to the coronary intensive care unit were recruited and assessed using DSM-IV criteria and the DRS. Independent predictors of delirium were advanced age, higher level of serum potassium at admission, and experience of cardiac arrest during MI. The retrospective study by Norkiene et al. [21] had a very large sample size ($n = 1367$). The researchers studied the precipitating factors for delirium after CABG and screened for delirium using the DSM criteria. Eight factors were independent predictors of delirium, which were age more than 65 years, peripheral vascular disease, a EuroSCORE (European System for Cardiac Operative Risk Evaluation) more or equal to 5, preoperative intra-arterial blood pressure support, blood product usage, and postoperative low cardiac output syndrome.

4. Discussion

From the studies reviewed, there are a variety of candidate factors associated with delirium in the setting of the intensive care unit. Some are common across all settings, whereas others are exclusive to the type of setting. For example, the importance of valve surgery as a risk factor for delirium [10] is of key importance in a cardiac ICU but lacks importance in the medical ICU, where one is more likely to see cases of sepsis, acute respiratory failure, and renal disease.

In the medical ICU, older age, sepsis, co-morbidity, and heavy alcohol use were the most commonly cited risk factors. Older age is considered a highly significant risk factor for delirium due to a reduced synthesis of cerebral neurotransmitters [32]. Fluctuations in the neurotransmitter levels lead to impairment in neurotransmission, resulting in increased susceptibility to delirium in older patients. The mechanism by which sepsis causes delirium is poorly understood; however several theories have been postulated; these include brain activation by inflammatory mediators, oxidative stress, and blood-brain barrier breakdown [33]. It is possible that all these theories are valid; the manifestation of delirium is likely multifactorial, precipitated by cytokine pathways resulting in the derangement of neurological function. The presence of co-morbidity is not easily explained, although it might be expected that effects on increasing physiological burden may play a part. Heavy alcohol use is known to be associated with delirium tremens, a form of delirium caused by withdrawal of alcohol [34].

In the surgical ICU, older age, presence of co-morbidity (including previous history of stroke and dementia), and high APACHE-II score are the most cited risk factors. With a higher APACHE-II score, there is a greater physiological stress with concomitant increase in risk for delirium.

In the cardiac ICU, there were no factors which stood out more significantly than others (other than older age and lower MMSE scores). All other factors are likely to be equally significant. A study examining all these factors in a composite model is required to determine the most significant factors causing delirium in the CICU.

With regard to pharmacological factors, benzodiazepines were identified as a significant risk factor for ICU delirium. Benzodiazepines increase the effect of the neurotransmitter GABA, resulting in increased sedation and hypnosis [23]. The effect on GABA may cause an imbalance in the action and quantity of the other neurotransmitters, causing symptoms to manifest as delirium. In addition, benzodiazepines may cause behavioural disinhibition and aggression [24], symptoms similar to hyperactive delirium.

In this paper, two retrospective cohort studies were included in a majority of prospective studies. In comparison, prospective studies are preferred to retrospective studies as patients are available for accurate assessment and examination; in a retrospective review, it is not possible to confirm the patient's condition. A retrospective review further compounds a problem inherent in delirium: diagnosis. Physician's diagnoses may be subjective; as such, one physician may view a patient as delirious whilst another might regard it as preexisting dementia. The propensity for misinterpretation and incorrect diagnosis may be significant in clinical settings which do not use standardised criterion such as the CAM-ICU to determine diagnosis. Though the methodology and results of retrospective studies may be apocryphal, they are included in this paper for the sake of completeness.

4.1. Implications for Practice and Research

(i) By creating a predictive model for delirium, clinicians may be able to identify patients at risk of developing delirium and implement preemptive measures. This can be further developed into an ICU-specific model. For example, a patient in the medical ICU will have a different set of risk factors, such as the presence of sepsis, co-morbidity, and alcohol use, from a patient in the cardiac ICU. A protocol based on this model will assist the nurse in monitoring patients at higher risk for developing delirium, identifying modifiable risk factors to prevent or reduce the severity of delirium.

(ii) Clinicians should prescribe benzodiazepines judiciously, moderated by an understanding of the patient's mental status and propensity for developing delirium. Conversely, the precipitation of delirium in a patient prescribed benzodiazepines must be considered in the context of the patient's condition and not attributed to pharmacological reasons alone.

(iii) An alternative to using benzodiazepines as sedatives may be haloperidol. van den Boogard et al. [35] found that haloperidol prophylaxis resulted in lower delirium incidence and more delirium free days as compared to the control group. However, the results still need to be verified via a reliable randomised controlled trial.

(iv) Randomised control trials should be conducted to investigate the efficacy of other possible sedatives such as dexmedetomidine or opioids in comparison to benzodiazepines.

(v) Strength of studies could be further improved by increasing sample sizes, recruiting from more than one hospital and examining diverse factors in order to synthesise stronger evidence. Future studies may examine the effects of biomarkers on delirium in depth, possibly isolating key biomarkers in the pathway leading to delirium.

(vi) An examination of all the factors examined in the recent literature may be conducted, in order to create a composite model for predicting delirium. This predictive model can be used in future in tandem with research which examines interventions to reduce the incidence of delirium.

4.2. Limitations. This paper was limited by the parameters set in the search strategy; any relevant studies prior to 1990 were not included, possibly influencing the review findings. It was also limited by potential reporting bias, as "published studies tend to overreport positive and significant findings" [36]. Only studies written in English were included, possibly excluding relevant studies in other languages. Variability in the results may be attributed to the difference in sample sizes. Different study objectives, such as measuring pre- and postoperative variables and biomarkers, may have influenced the results of the studies.

5. Conclusion

Old age is a common risk factor for delirium in critically ill adult patients. In both medical and surgical ICUs, risk factors of older age and co-morbidity are significant, whilst heavy alcohol use and higher APACHE II scores are significant in medical and surgical ICUs, respectively. In the cardiac ICU, a variety of factors were significant, such as age and lower MMSE scores. Benzodiazepines are singled out as a significant risk factor for delirium.

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