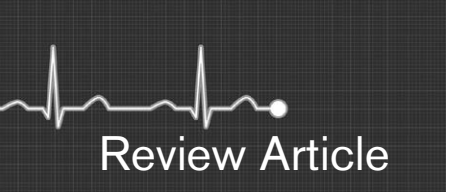

Delirium Monitoring in Neurocritically Ill Patients: A Systematic Review*

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Objectives: The Society of Critical Care Medicine recommends routine delirium monitoring, based on data in critically ill patients without primary neurologic injury. We sought to answer whether there are valid and reliable tools to monitor delirium in neurocritically ill patients and whether delirium is associated with relevant clinical outcomes (e.g., survival, length of stay, functional independence, cognition) in this population.

Data Sources: We systematically reviewed Cumulative Index to Nursing and Allied Health Literature, Web of Science, and PubMed.

Study Selection and Data Extraction: Inclusion criteria allowed any study design investigating delirium monitoring in neurocritically ill patients (e.g., neurotrauma, ischemic, and/or hemorrhagic stroke) of any age. We extracted data relevant to delirium tool sensitivity, specificity, negative predictive value, positive predictive value, interrater reliability, and associated clinical outcomes.

Data Synthesis: Among seven prospective cohort studies and a total of 1,173 patients, delirium was assessed in neurocritically patients using validated delirium tools after considering primary neurologic diagnoses and associated complications, finding a pooled prevalence rate of 12–43%. When able to compare against a common reference standard, *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, the test characteristics showed a sensitivity of 62–76%, specificity of 74–98%, positive predictive value of 63–91%, negative predictive value of 70–94%, and reliability kappa of 0.64–0.94. Among four studies reporting multivariable analyses, delirium in neurocritically patients was associated with increased hospital length of stay ($n = 3$) and ICU length of stay ($n = 1$), as well as worse functional independence ($n = 1$) and cognition ($n = 2$), but not survival.

Conclusions: These data from studies of neurocritically ill patients demonstrate that patients with primary neurologic diagnoses can meet diagnostic criteria for delirium and that delirious features may predict relevant untoward clinical outcomes. There is a need for ongoing investigations regarding delirium in these complicated neurocritically ill patients. (*Crit Care Med* 2018; 46:1832–1841)

Key Words: delirium; intensive care unit; neurocritical care; neurotrauma; stroke; traumatic brain injury

Delirium is a phenotypic syndrome manifested by the cardinal clinical features of fluctuations in mental status from baseline, inattention, altered level of consciousness, and disorganized thinking that represents acute cerebral dysfunction. Obviously in patients who have primary neurologic pathology (e.g., stroke, traumatic brain injury [TBI]), wholesale attribution of such clinical findings to delirium would be inappropriate without first considering the admission diagnostic injury or an extension of this injury. Indeed, it would be clinically dangerous to misattribute a patient's clinical deterioration to delirium when it was actually due to edema, vasospasm, rebleeding, seizures, and/or ischemia. That is precisely why the study of delirium, an extremely common malady possible in any hospitalized patient, is so difficult. Yet, we must acknowledge the medical-surgical ICU literature, which has shown how predictive delirium is for clinical outcomes like mortality and long-term dementia (1–4). These associations may also be applicable to the most neurologically vulnerable patients.

Instruments that are used to screen or diagnose delirium (5–8) in settings such as general medical or surgical ICUs could be adapted to a population of patients who have primary neurologic injury. For reference, in medical-surgical critical care, the clinician (e.g., nurse and physician) must consider new onset of delirium (e.g., fluctuations in mental status and inattention) as a potential indicator of an untreated primary illness. If this is unlikely after thorough evaluation, then delirium could indicate an untreated secondary ICU complication. Due to a plethora of data in nonneuro ICU patients, delirium has been considered a "canary in the coal mine" and has triggered clinical teams to consider other dangerous secondary events such as nosocomial sepsis, metabolic derangements, pharmacologic causes, and/or immobilization (9–12). Delirium during critical illness has had associations with survival, length of stay, cost, and long-term cognition (1–4, 13–16), although causation remains unproven, early recognition of delirium remains important.

The Society of Critical Care Medicine's guidelines for Pain Agitation and Delirium (17) recommend routinely monitoring delirium with the Confusion Assessment Method for the ICU (CAM-ICU) (5) or Intensive Care Delirium Screening Checklist (ICDSC) (6) in adult critically ill patients (grade 1B). However, the data were mostly derived from patients in medical, surgical, and cardiovascular ICUs rather than those with primary brain injury (e.g., stroke, neurosurgical resection, TBI). For example, it is known that severe disorders of consciousness (e.g., coma) currently preclude delirium assessment, yet clinicians might extend this logic to patients with diseases such as stroke and TBI and not bother to perform delirium monitoring in these ICU patients, even if they are noncomatose.

Thus, we hypothesized that delirium measured by known tools is often (but not always) assessable in those with neurocritical illness (i.e., ICU patients with acute pathoanatomic abnormalities on CT or MRI) and a marker for future adverse outcomes. To paraphrase for clarity, the primary objective of this article is to discuss the hypothesis that delirium is part of the larger risk profile of ongoing brain injury for many patients with primary diagnoses such as stroke or TBI and should be considered in the landscape of their clinical course. In order to demonstrate that formal scientific inquiry in this area is nascent and to stimulate more work in this field, we conducted a systematic review of the literature in neurocritically ill patients related to 1) delirium monitoring and 2) clinical outcomes associated with duration of delirium.

METHODS

Objective

In neurocritically ill patients with delirium versus without delirium (target condition), are there valid and reliable means

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by which to monitor for delirium (index test), as compared to a psychiatric reference standard when available (reference test)? And, in neurocritically ill patients with delirium versus without delirium, are there altered outcomes (e.g., survival, length of stay, functional independence, cognition)?

Study Eligibility

This review and associated protocol were registered with the PROSPERO international prospective register of systematic reviews (Registration Number: CRD42017074611). Inclusion criteria allowed any type of study design investigating delirium monitoring in neurocritically ill patients of any age. Our definition of neurocritically ill was restricted to and referred to ICU patients with acute intracranial injury (e.g., TBI, hemorrhagic stroke) or ischemic stroke. Reference lists of potentially included studies and review articles were also reviewed for additional citations pertinent to this search. Delirium assessments should have occurred at least daily using a delirium screening assessment tool with reporting of rate. When available, the criterion validity data (i.e., sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV]) were captured comparing delirium screening tools against psychiatric standard assessment using the Diagnostic and Statistical Manual (any edition) (18). If validation studies were done, then we also sought associated interrater reliability data (i.e., test-retest stability or kappa), but not those performed in isolation. Only English language studies and studies published in the peer-reviewed literature were eligible for inclusion. No date restriction was imposed on the search strategy. Exclusion criteria removed editorials, case reports, case-series, lay press articles, abstracts, and reviews.

Search Methods and Data Extraction

With the assistance of an experienced medical librarian (P.L.), we systematically searched Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, and PubMed from the National Center for Biotechnology Information (**Supplementary Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/D859). The search was not restricted by date. Reference lists of potentially included studies and review articles were reviewed for additional citations pertinent to this search. All of the abstracts of the studies identified by our search were independently examined by two authors who determined the eligibility of each study. A third author resolved any disagreements by consensus at each step as needed in the review process. Then, two authors reviewed the titles and abstracts of all remaining eligible studies to determine which required further inclusion. Two authors then retrieved and reviewed the manuscripts of the remaining articles and used data abstraction forms to collect the relevant study information. Captured data included study time period, sample size, subject sex characteristic, eligibility criteria, severity of illness markers, as well as delirium tool used, delirium prevalence, reference standard for delirium assessment with test characteristics (if present) (18). Note, the term "prevalence" was conservatively chosen as a more inclusive epidemiologic term encompassing old and new cases of delirium, although some articles reported incidence without clarifying how new cases were distinguished. We did not plan for a quantitative synthesis or meta-analysis given the anticipated heterogeneity of this emerging literature, delirium tools, and reference standards. For cohort studies, selection of the exposed and nonexposed groups, the comparability of the groups, the assessment of the outcomes, and the adequacy of follow-up were addressed using the Newcastle-Ottawa Scale.

RESULTS

A total of 1,460 relevant citations were screened from our search strategies (CINAHL, $n = 128$; Web of Science, $n = 888$; PubMed, $n = 441$; reference lists, $n = 3$), whereas 166 duplicates were excluded. Twelve-hundred sixty-one were excluded after title and abstract review because they did not meet inclusion criteria (**Fig. 1**). A total of 33 citations were reviewed at the article level, and we excluded 20 of those. Of these excluded articles, 19 were unrelated to our review (4, 15, 19–35), one was written in a non-English language (36), one was an editorial, and one was a review (19, 30). During data extraction, two articles were further excluded as they failed to provide outcome data relevant to delirium test characteristics or complications of delirium (37, 38). Of the remaining were 11 articles (39–49) without overlapping data, four final articles were excluded due to the ICU cohorts not exclusively composed of neurocritically ill patients (39–41, 49), thus leaving seven articles for qualitative synthesis.

Descriptive statistics were extracted from the seven prospective cohort designs, representing five single-center studies, and two dual-center studies (**Table 1**; and **Supplementary Table 2**, Supplemental Digital Content 2, http://links.lww.com/CCM/D860). In total, 1,173 subjects were represented across studies with a range from 61 to 527 (median 108) subjects per study. Sex characteristics were unclear or not stated for three of the cohorts. One study involved trauma and TBI patients, and six studies involved stroke patients and no trauma patients. Five studies did not state whether mechanical ventilation was affecting the study population, with the remaining two studies having mechanical ventilation rates from 7% to 66% (median 36%). Severity of illness was broadly defined and either used the Injury Severity Scale (score of 23.3 among one study), Glasgow Coma Scale (score range 13.9–14.5 with median 14 among three studies), National Institutes of Health Stroke Scale (score range 3–9 with median 8 among five studies), and/or the Acute Physiology and Chronic Health Evaluation II (score of 11.5 among one study); severity of illness was unclassified in one study.

Delirium was assessed most commonly by the CAM-ICU (five studies) with a prevalence rate of 24–43% (median 29%) when reported (**Table 2**). Other tools used were the ICDSC (prevalence not reported), 4-A Test (4-AT, prevalence 27%), and Confusion Assessment Method (CAM) (prevalence 12%). Four studies used a reference standard ($n = 61$–129; median, 104), mostly commonly the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV, three of four studies with a 28–46% prevalence with median 37%

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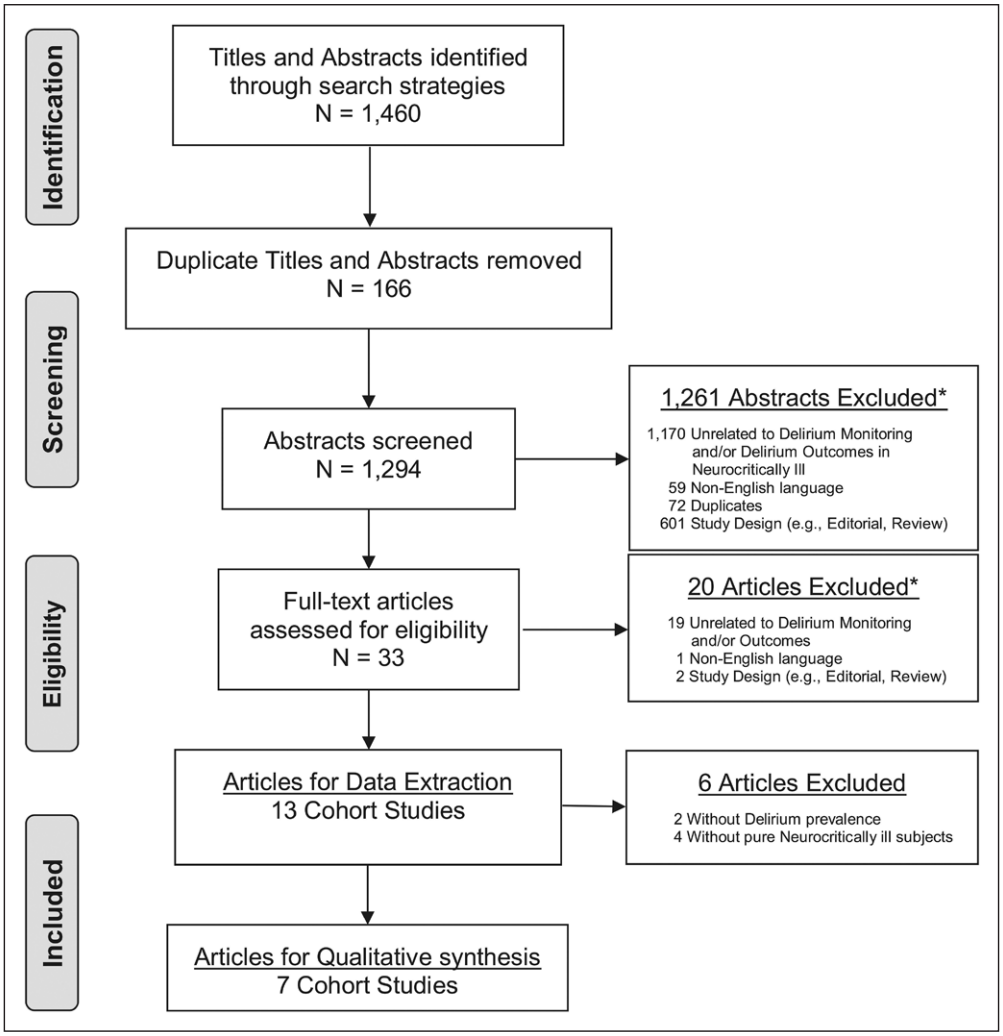

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for systematic review phases of delirium monitoring in neurocritically ill patients. *Multiple exclusions per abstract/article were allowed.

when reported), and the CAM (one study, 11% prevalence). Two studies used the CAM-ICU tool against a DSM-IV reference standard with sensitivities ranging 62–76% (median 69%), specificities ranging 74–98% (median 86%), PPVs ranging 63–91% (median 77%), and NPVs ranging 70–94% (median 82%). The ICDSC against a DSM-IV reference standard reported 64% sensitivity, 79% specificity, 74% PPV, and 69% NPV, whereas the 4-AT against a CAM reference standard reported 100% sensitivity, 82% specificity, 43% PPV, and 100% NPV. Reliability was assessed in two studies using the CAM-ICU with kappa range from 0.64 to 0.94 (median 0.79). The risk of bias was predominantly low (**Table 3**).

Across four studies (**Table 4**), the occurrence of delirium was studied with different outcomes including mortality, ICU length of stay, hospital length of stay, disposition, and neuropsychologic outcomes (e.g., disability, cognition, health-related quality of life). None of these studies reported delirium completely with test characteristics with a reference standard (above), and none reported all of these outcome domains. Four studies used multivariable analysis to associate delirium with selected outcome measures. For example, delirium independently prolonged ICU length of stay by a median 2.1 days (95% CI, 1.1–4.5; $p = 0.03$) after adjusting for age, admission National Institutes of Health Stroke Scale, and any benzodiazepine exposure (46). Similarly, delirium independently prolonged hospital length of stay in three studies (hazard ratio, 1.63; 95% CI, 1.11–2.38; $p = 0.013$ [45] and median 3.5 d longer; 95% CI, 1.5–8.3; $p = 0.004$ [46] and median 5.4 d longer; 95% CI, 2.1–8.6; $p < 0.001$ [47]). Also, delirium independently was associated with worse functional independence (by Barthel Index [49]) and cognition in two studies (by quality of life in neurologic disorders metric [46]).

DISCUSSION

These data from the first systematic review of delirium monitoring in the neurocritically ill patient show that, in these subsets of patients, it is possible to measure delirium in adult ICU patients with mild-moderate stroke (ischemic and/or hemorrhagic) or neurotrauma with existing delirium instruments. Important caveats include of course that the delirium prevalence rates and test characteristics were variable, as expected, likely due to diversity of patient populations and severity of illness, and also due to performance variations that exist depending on tool application (e.g., approach to determination of baseline mental status and attention testing) in this challenging and understudied population. In this nascent field, it is important that in four studies, the identification of delirium in neurocritically ill patients independently predicted poor clinical outcomes including longer length of stay and worse functional recovery and cognition. Among seven prospective cohort studies and a total of 1,173 neurocritically ill subjects, delirium was assessable using a myriad of tools (e.g., CAM-ICU, ICDSC, 4-AT) with a pooled prevalence rate of 12–43% and often validated against the DSM-IV. This work shows monitoring delirium in the neurocritically ill is relevant, has potential to improve ICU prognostics for this population, needs integration into ICU delirium guidelines, and requires further research.

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TABLE 1. Individual Study Inclusion, Sample Size, and Severity of Illness for this Systematic Review of Delirium Monitoring in the Neurocritically Ill

References; Time Period	Total *n* (*n* of Male Sex)	Inclusion	Percent Mechanically Ventilated of Sample	Severity of Illness
Frenette et al (42); unspecified	61 (47)	Two centers, trauma patients with mild/moderate TBI, age ≥ 18 yr, admitted to ICU > 48 hr	65.5	Mean Injury Severity Scale score = 23.3 ± 9.4; median GCS = 14 (IQR 3); mean Acute Physiology and Chronic Health Evaluation II score = 11.5 ± 6.4; 28% isolated TBI; 72% polytrauma and TBI
Kostalova et al (43); January 2009 to March 2010	100 (53)	One center, stroke patients in ICU with cerebral infarction or intracerebral hemorrhage; assessable ≤ 24 hr of stroke; approval of patient or surrogate	Not stated	Mean NIHSS = 8.8, and mean GCS = 13.9
Lees et al (44); April 2012 to June 2012	108 (unclear[a])	One center, stroke patients in ICU (ischemia and hemorrhage)	Not stated	Median NIHSS = 3 (IQR, 1–5); 38% with history of stroke
Mitasova et al (45); January 2009 to January 2010	129 (72)	One center, stroke patients in ICU (with ischemia or hemorrhage), assessment ≤ 24 hr of stroke; approval of patient or surrogate	7	Median NIHSS = 9.0 (no IQR); GCS = 14.5 (mean/median not specified)
Naidech et al (46); December 2009 to April 2013	98 (unclear[b])	One center, intracerebral hemorrhage by CT (neurologist verified) in neuro/spine ICU	Not stated	Not stated for cohort; but delirium group with median NIHSS = 8 (IQR, 3–15), and no delirium group with median NIHSS = 6 (IQR, 2–16)
Oldenbeuving et al (47); 1 yr period, unspecified	527 (288)	Two centers, stroke (neurologic deficit of sudden onset > 24 hr; ischemic or hemorrhagic) in ICU, age > 18 yr	Not stated	Median NIHSS = 5 (IQR, 0–36); 11% hemorrhage stroke
Rosenthal et al (48); December 2009 to October 2014	150 (unclear[c])	One center, intracerebral hemorrhage by CT (neurologist verified) in neuro/spine ICU	Not stated	Unclear[c]

IQR = interquartile range, GCS = Glasgow Coma Scale score, NIHSS = National Institutes of Health Stroke Scale score, TBI = traumatic brain injury.

[a]Men represented 55 of 111 subjects with cognitive assessment data; without sex further specified, 108 had 4-A test data relevant to this review.

[b]Women represented 52 of 114 subjects; without sex further specified, 98 in this study were assessable for delirium.

[c]Women represented 82 of 174 subject with long-term follow-up and of 174 subjects, NIHSS = 11 (IQR not provided); median GCS = 13.5 (IQR, 8–15); however, without sex or severity of illness further specified, 150 subjects in this study were assessable for delirium.

n refers to sample size of cohort assessed for delirium.

We warn the readership that it is important to use the delirium monitoring information as a complement to the neurologic examination and to expand the differential diagnosis when there is a change in the neurologic examination. In this complicated patient population, it is critical to acknowledge that a positive screen for delirium may be due to the underlying neurologic disease or its sequelae (e.g., edema, vasospasm, seizures, rebleeding, ischemia) requiring very different treatments than delirium and often with urgent or emergent time pressure to avoid further brain damage. Only once these have been evaluated as a primary cause for the neurologic decline, should delirium rise on the differential diagnosis.

These encouraging data are limited regarding the reliability of delirium tools (two studies; 0.64–0.94; median 0.79) in a neurocritical care population. However, another two studies have corroborating reliability data on delirium monitoring in the neurologically injured patient, which were excluded from our review's eligibility criteria (i.e., studies that did not measure delirium incidence or prevalence). Soja et al (38) implemented delirium monitoring in a trauma ICU with a subset of patients with TBI, representing over one third of

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TABLE 2. Delirium Prevalence and Delirium Tool Psychometrics for this Systematic Review of Delirium Monitoring in the Neurocritically Ill

References	Delirium Prevalence[a], %	Delirium Tool (Reference Standard)	Sensitivity, %	Specificity, %	Positive Predictive Value, %	Negative Predictive Value, %	Kappa (Unit of Interrater Reliability)
Frenette et al (42)	Not stated for tool (45.9% by reference standard delirium assessment)	CAM-ICU (DSM-IV); Intensive Care Delirium Screening Checklist (DSM-IV)	62 (95% CI, 44–76); 64 (95% CI, 49–77)	74 (95% CI, 59–85); 79 (95% CI, 63–89)	63 (95% CI, 45–78); 74 (95% CI, 55–87)	70 (95% CI, 55–82); 69 (95% CI, 54–81)	0.64; 0.68
Kostalova et al (43)	43% (not stated for reference standard delirium assessment)	CAM-ICU (DSM-IV)	–	–	–	–	–
Lees et al (44)	27% (11% by reference standard delirium assessment)	4-A Test (CAM)	100 (95% CI, 74–100)	82 (95% CI, 72–89)	43 (no CI)	100 (no CI)	–
Mitasova et al (45)	24% (28% by reference standard delirium assessment)	CAM-ICU, Czech (DSM-IV)	76 (95% CI, 55–91)	98 (95% CI, 93–100)	91 (95% CI, 70–99)	94 (95% CI, 88–98)	0.94 (95% CI, 0.83–1.0)
Naidech et al (46)	27%	CAM-ICU (N/A)	–	–	–	–	–
Oldenbeuving et al (47)	11.8%; 95% CI, 9.0–15.1	CAM (N/A)	–	–	–	–	–
Rosenthal et al (48)	30%	CAM-ICU (N/A)	–	–	–	–	–

CAM = Confusion Assessment Method, CAM-ICU = CAM for the ICU, DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, N/A = not available.

[a]The term "prevalence" was conservatively chosen as a more inclusive epidemiologic term encompassing old and new cases of delirium, although some articles reported incidence without clarifying how new cases were distinguished.

Dashes indicate no data.

observations. An expert evaluator performed 1,011 random CAM-ICU assessments within 1 hour of the bedside nurse's assessments. Overall agreement (kappa) between nurses and expert evaluator was 0.75 (0.667–0.829; $p < 0.0001$) in TBI patients, attesting to the ease of delirium monitoring in patients with polytrauma. Also, Yu et al (37) evaluated 151 patients from neurologic, neurosurgical, and trauma ICUs. In the 439 assessments performed by bedside staff and researchers, pain and sedation were always assessable with excellent interrater reliability (intraclass correlation, 0.86). Patients were sufficiently alert for delirium screening 75% of the time, and delirium screening items had good concordance. Importantly, each additional ICDSC item present, in proportion to the total ICDSC score, was associated with a 10% increase in ICU length of stay. Ultimately, clinicians should feel confident that delirium tools have solid reliability in the neurocritical care setting.

Past ICU data show that delirium is independently associated with increased mortality, length of stay, cost of care, accelerated or acquired dementia-like cognitive impairment, and the inability to return to independent living (2, 3, 16, 50–57). Now, the literature is showing a similar pattern in the neurocritically ill population, except the lack of association of delirium with mortality, which may be unique to this population and/or due to better statistical risk-adjustment methods compared with past work. This work may shed light and provide structure to the care of the complex neurocritically ill patient given the utility and prognostics associated with delirium monitoring.

Unaddressed Challenges for Delirium Monitoring in the Neurocritically Ill

The neurocritically ill patient population is obviously more challenging than general medical and general surgical patients with respect to delirium assessment (58). Some are not testable for delirium due to decreased level of consciousness (i.e., coma) because of the primary neurologic injury or due to deep sedation (Richmond Agitation-Sedation Scale < –3)

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TABLE 3. Risk of Bias Assessment for Cohort Studies (Based on Modified Newcastle-Ottawa Scale) of Delirium Monitoring in the Neurocritically Ill

References	Cohort Selection	Comparability of Cohorts	Outcome Adequacy	Total Score
Frenette et al (42)	***	*	***	7/9
Kostalova et al (43)	***	*	***	7/9
Lees et al (44)	***	*	**	6/9
Mitasova et al (45)	***	**	***	8/9
Naidech et al (46)	***	*	***	7/9
Oldenbeuving et al (47)	***	*	***	7/9
Rosenthal et al (48)	***	*	***	7/9

Evaluation by the modified Newcastle-Ottawa Scale shows these cohorts have a low risk of bias. Stars (*) are awarded for each quality item. Higher total stars/score means lower risk of bias.

for high intracranial pressures. Stroke patients, for example, present with a high prevalence of cognitive and communication deficits such as aphasia that can make delirium assessments especially challenging (45). For example, it is not possible to do delirium assessments on receptive aphasic patients, but expressive aphasic patients can follow commands and indicate answers to questions with head nods or hand movements, thus can complete tests of attentiveness. Purely aphasic (expressive or receptive) patients do not have impaired arousal; however, aphasia often times is not an isolated finding. Level of arousal will depend on the degree of comorbid brain injury along with other covariates such as psychoactive medications, sleep deficits, degree of agitation. Psychiatric disorders, such as depression or catatonia, are other confounders that may mimic some hypoactive delirium symptoms in their most severe forms (59). Overall, it remains unclear which proportions of hypoactive or hyperactive delirium exist in neurocritical populations or subpopulations.

Similarly, nonconvulsive status epilepticus may also mimic some features of delirium and can only be diagnosed with an electroencephalogram. An unproven approach is that seizures should remain on the differential diagnosis when underlying neurologic abnormalities or common risk factors of delirium do not explain a patient's neurologic examination. Furthermore, patients afflicted by both blindness and deafness often pose challenges for delirium assessments, neurologic examination, and ICU care. Despite these difficulties, there is growing evidence that it is possible to assess delirium using tools such as the CAM-ICU or ICDSC in many (37) neurologically injured patients. This is done using serial assessments conducted to detect fluctuations in relationship to the postinjury "new" baseline mental status determined (i.e. feature 1 of the CAM-ICU).

Future Areas for Delirium Research in Neurocritically Ill Patients

There have been broader and well-done reviews relevant to delirium in stroke (58, 60), and our work is uniquely limited by our focus on the critically ill patient affected by primary neurologic conditions. Additionally, we acknowledge our review excluded four studies that were not confined to neurocritically populations (39–41, 49). We note that there is no study validating any delirium tool in the neurocritically ill against the newer *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, DSM-5 (61), which formally excludes coma from inattention (i.e. delirium) assessments but broadly classifies anything else as inattention. Also, the DSM-5 does not specify whether to include those with preexisting impaired cognition (i.e., delirium superimposed on dementia) (62), further complicating delirium assessments in neurocritically ill populations. Within any delirium tool, it is unclear which subfeatures (e.g., fluctuating mental status, inattention) are more prevalent in stroke and/or neurotrauma. The stroke and neurotrauma delirium data are not entirely comparable, as neither population has been studied under a single delirium protocol or framework. We also designed our review to be broad, inclusive of any age, yet we found no children have been studied in either stroke or neurotrauma population. Although assessment tools for the child have been created, such as the pediatric or preschool delirium assessment or Cornell Assessment for Pediatric Delirium (63–65), none of these have specifically been assessed for reliability and validity for the neurocritically ill child. Another significant knowledge gap appears to be that delirium prognostics are being inconsistently reported across studies, and no study provides comprehensive associations with clinical outcomes. We also acknowledge that there are no data available to the guide-specific treatment of delirium among neurologic ICU patients.

Stroke or neurotrauma studies consist of heterogeneous groups of neurocritically ill patients, use varying research and clinical environments, employ different diagnostic tools, and claim wide ranges about the assessable proportion of subjects. Also, the characteristics of any tool can be influenced by factors such as education and training of the rater (49, 66, 67). Further research is needed and has started on well-defined and homogenous subgroups of neurologically injured patients (68), like the PRospective Observational POLIsh Study on post-stroke delirium. Given the heterogeneity among patients,

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TABLE 4. Delirium Associations With Outcomes: Qualitative Results From a Systematic Review of Delirium Monitoring in the Neurocritically Ill

References	Death	ICU LOS	Hospital LOS	Disposition and Neuropsychologic Outcomes
Mitasova et al (45)	Unchanged 6-mo mortality (HR, 1.22; 95% CI, 0.48–2.98; $p = 0.668$)[a]	–	Increased length of hospital stay (HR, 1.63; 95% CI, 1.11–2.38; $p = 0.013$)[b]	–
Naidech et al (46)	–	Longer ICU LOS (mean 2.1 d longer; 95% CI, 1.1–4.5; $p = 0.03$)[c]	Longer hospital LOS (mean 3.5 d longer; 95% CI, 1.5–8.3; $p = 0.004$)[d]	Poor modified Rankin Scale at 28 d (OR, 8.7; 95% CI, 1.4–52.5; $p = 0.018$)[e]; worse HRQoL (domains of applied cognition—executive function and fatigue)[f]
Oldenbeuving et al (47)	Unchanged in-hospital mortality (OR, 2.0; 95% CI, 0.8–5.1, $p < 0.001$)[g]	–	Longer hospital LOS by 5.4 d (95% CI, 2.1–8.6; $p < 0.001$)[h]	Worse 1 mo. BI (median BI 20.0 vs 7.5; $p < 0.001$)[i]; unfavorable outcome (OR, 2.0; 95% CI, 1.0–4.0; $p < 0.001$)[j]
Rosenthal et al (48)	–	–	–	Worse cognitive function HRQoL at 28 d and 1 yr[k]

BI = Barthel Index, HR = hazard ratio, HRQoL = health-related quality of life using Neuro-QOL (quality of life in neurologic disorders) metric, IQR = interquartile range, LOS = length of stay, OR = odds ratio.

[a]Multivariable Cox regression model shown in table was adjusted for age, gender, prestroke dementia, National Institutes of Health Stroke Scale (NIHSS) at admission, first day Sequential Organ Failure Assessment, and aphasia; univariate data showed 6-mo mortality with delirium: 23.6% vs no delirium: 14.9%.

[b]Multivariable Cox regression model using time-dependent covariate analysis was adjusted for age, gender, prestroke dementia, NIHSS at admission, first day Sequential Organ Failure Assessment, and aphasia; univariate data showed hospital LOS with delirium: 18.0 d vs no delirium: 12.0 d.

[c]Multivariable data shown in table were adjusted for age, admit NIHSS, and any benzodiazepine exposure; univariate data showed ICU LOS with delirium: 7.0 d (IQR, 3.4–10.2 d) vs no delirium: 2.3 d (IQR, 1.1–6.7 d).

[d]Multivariable data shown in table were adjusted for age, admit NIHSS, and any benzodiazepine exposure; univariate data showed hospital LOS with delirium: 13.2 d (IQR, 7.9–24.2 d) vs no delirium: 6.4 d (IQR, 4.0–13.2 d)

[e]Multivariable data shown in table demonstrated an increased odds of poor outcome at 28 d of modified Rankin Scale (mRS) > 3 vs mRS < 2 and was adjusted for admission NIHSS and age.

[f]Multivariable data shown in table were adjusted for the NIHSS, age, benzodiazepine exposure, and time to follow-up.

[g]Multivariable data shown in table were adjusted for age, Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) score, and severity of stroke (NIHSS score); univariate data showed in-hospital mortality for delirium: 19.4% vs no delirium: 6.5%.

[h]Multivariable data shown in table was adjusted for age, Informant Questionnaire on Cognitive Decline in the Elderly score, and stroke severity; univariate showed a longer hospital stay with delirium: 23.7 d vs no delirium: 13.9 d.

[i]Univariate analysis only.

[j]Multivariable data shown in table defined unfavorable outcome at 1 mo as dead or BI < 12 (BI range 0–20) for those with delirium, and the OR was corrected for age, NIHSS, and IQCODE score; univariate data showed unfavorable outcome with delirium: 66.7% vs no delirium: 21.3%.

[k]Multivariable summary shown in table that controlled for age, NIHSS, time of assessment, and multiple comparisons; 28 d Neuro-QOL T-scores for delirium with agitation 20.9 ± 7.3, delirium without agitation 30.4 ± 16.5, agitation without delirium 36.6 ± 17.5, and neither agitated nor delirious 40.3 ± 15.9; $p = 0.03$) and at 1 yr ($p = 0.006$); agitation defined as Richmond Agitation-Sedation Scale score ≥ 2.

Dashes indicate no data.

future studies should expand our nascent understanding of the prevalence and long-term neuropsychiatric implications (e.g., cognitive impairment, mood disorders) of both duration and pattern of time spent in a delirious state in populations like stroke and trauma. The methodological rigor of such investigations must be high (e.g., biostatistical design must include time-varying covariates).

Although there are no acute imaging correlates for delirium seen acutely or in-hospital, MRI and other techniques offer promise to uncover the hidden consequences of this secondary acute brain dysfunction. Neuroimaging of ICU cohorts with delirium is being pursued but is still in its infancy. The VISualizing Icu SurvivOrs Neuroradiological Sequelae (VISIONS) MRI studies (14, 69) showed that medical and surgical ICU survivors with delirium were more likely to have brain atrophy in the prefrontal cortex and hippocampus as well as white matter abnormalities demonstrated via fractional anisotropy and diffusion tensor imaging. This suggests that there is indeed microstructural damage, and this cohort did prove to have subsequent cognitive impairment manifested by executive dysfunction and memory deficits. In patients with intracerebral hemorrhage, hematomas in specific locations are more likely to manifest delirium symptoms (70). Moving forward, it will be important to study the hypothesis that quantifiable delirium variables predict some portion of the long-term neuroimaging and clinical deficits seen in survivors of neurocritical illness.

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CONCLUSIONS

Data from adult neurocritical care investigations indicate that tools are available for delirium monitoring in stroke patients, as well as neurotrauma patients. In such patients, the clinical information is a complement to the neurologic examination. In this case, delirium tools serve to expand the differential diagnosis. Delirium tools are to be used only after first considering the underlying admitting neurologic diagnosis. The value of the delirium tool, therefore, rests both in earlier detection of expected causes of an abnormal neurologic examination in this population (e.g., edema, vasospasm, seizures, rebleeding, ischemia), as well as adding common causes of delirium that might not be considered early enough (e.g., sepsis or sedatives) into the daily diagnostic and therapeutic conversations for these high-risk patients. We hope this work provides the reader with a clinically applicable framework for neurologically critically ill patients that considers delirium as a manifestation of secondary brain injury potentially superimposed on major neurologic deficits seen after primary brain injury. It is incumbent on the medical field to generate more data and advance our understanding, so that we may develop specific preventative and treatment strategies that will allow us to serve our neurologically injured patients better tomorrow than we do today.

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