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Delirium etiology subtypes and their effect on six-month function and cognition in older emergency department patients

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ABSTRACT

Background: Delirium is heterogeneous and can vary by etiology.

Objectives: We sought to determine how delirium subtyped by etiology affected six-month function and cognition.

Design: Prospective cohort study.

Setting: Tertiary care, academic medical center.

Participants: A total of 228 hospitalized patients $\geq$ 65 years old were admitted from the emergency department (ED).

Measurements: The modified Brief Confusion Assessment Method was used to determine delirium in the ED. Delirium etiology was determined by three trained physician reviewers using a Delirium Etiology checklist. Pre-illness and six-month function and cognition were determined using the Older American Resources and Services Activities of Daily Living (OARS ADL) questionnaire and the short-form Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). Multiple linear regression was performed to determine if delirium etiology subtypes were associated with six-month function and cognition adjusted for baseline OARS ADL and IQCODE. Two-factor interactions were incorporated to determine pre-illness function or cognition-modified relationships between delirium subtypes and six-month function and cognition.

Results: In patients with poorer pre-illness function only, delirium secondary to metabolic disturbance (β coefficient = −2.9 points, 95%CI: −0.3 to −5.6) and organ dysfunction (β coefficient = −4.3 points, 95%CI: −7.2 to −1.4) was significantly associated with poorer six-month function. In patients with intact cognition only, delirium secondary to central nervous system insults was significantly associated with poorer cognition (β coefficient = 0.69, 95%CI: 0.19 to 1.20).

Conclusions: Delirium is heterogeneous and different etiologies may have different prognostic implications. Furthermore, the effect of these delirium etiologies on outcome may be dependent on the patient's pre-illness functional status and cognition.

Key words: delirium, etiology, subtypes, long-term function, long-term cognition

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Introduction

Delirium is a form of acute brain failure that is associated with a disturbance in attention and cognition that is not explained by pre-existing neurocognitive disorder such as dementia (American Psychiatric Association and American

Psychiatric Association. DSM-5 Task Force., 2013). Delirium occurs in approximately 8% to 17% of older patients in the emergency department (ED) (Han *et al.*, 2009; 2010) and 25% of older hospitalized patients (Francis *et al.*, 1990; Pitkala *et al.*, 2005). The adverse effects of delirium are well documented and include poorer long-term function and cognition, prolonged hospitalizations, and increased mortality (Vida *et al.*, 2006; Han *et al.*, 2009, 2010; Witlox *et al.*, 2010; Han *et al.*, 2011; Gross *et al.*, 2012; Grossmann *et al.*, 2014). However, the outcomes of delirium are highly variable, with negative consequences ranging from little or none to severe (Andrew *et al.*, 2005; Jackson *et al.*, 2016). The factors underlying variability in outcomes of delirium are incompletely understood.

Delirium is a heterogeneous syndrome in terms of its phenomenology, duration, severity, and presence of predisposing factors. Several studies suggest that variations in psychomotor activity, (Kiely *et al.*, 2007; Meagher *et al.*, 2011; Kim *et al.*, 2015; Jackson *et al.*, 2016) level of arousal, (Han *et al.*, 2017a) severity, (Kelly *et al.*, 2001; Inouye *et al.*, 2014; Jackson *et al.*, 2016; Vasunilashorn *et al.*, 2016a, 2016b) duration of delirium, prior cognitive impairment, and other comorbidities differentially affect outcomes of delirium (Jackson *et al.*, 2016; Davis *et al.*, 2017; Han *et al.*, 2017a). There is also some limited evidence that physiological variables, such as increased inflammatory biomarkers, may influence outcomes, (Vasunilashorn *et al.*, 2017) suggesting the possibility that particular triggers of delirium such as those inducing inflammatory states may have more impact on outcomes than other etiologies. However, to our knowledge, no study has specifically evaluated how delirium subtyped by etiology impacts such outcomes, especially long-term function and cognition. Therefore, we sought to explore how different delirium etiology subtypes affected six-month function and cognition in acutely ill older patients.

Methods

Study design and setting

This was a pre-planned secondary analysis of the Delirium in the Emergency Department and Its Extension into Hospitalization (DELINEATE) study, (Han *et al.*, 2017b) a prospective cohort study that sought to determine how delirium affected six-month function and cognition in hospitalized older patients admitted from the ED. This study was conducted at a tertiary care, academic hospital. The local institutional review board reviewed and approved this study. Informed consent was obtained from the patient or an authorized surrogate. Patients were deemed capable of consenting if: (1) they were able to carry a normal adult conversation and (2) they were able to recall aspects of the consent (e.g. Can you tell me the purpose of the study?). The patient was asked questions about the study to ensure they could comprehend study procedures. If they were unable to adequately answer these questions, then informed consent was obtained from an authorized surrogate.

Selection of participants

Patients were enrolled from the ED between March 2012 and November 2014. Consecutive enrollment occurred Monday through Friday at four randomly selected 4-hour blocks per week (8A – 12P, 10A – 2P, 12P – 4P, 2P – 6P) for a total of 16 hours per week. Patients were included if they were 65 years or older, in the ED for less than 4 hours at the time of enrollment, and unlikely to be discharged home according to the ED physician. Patients were excluded if they were non-English speaking, previously enrolled, deaf, comatose as defined by a Richmond Agitation Sedation Scale score of −4 or −5, non-verbal, or unable to follow simple commands prior to their current illness, were considered unsuitable for enrollment by the treating physician or nurse, were unavailable for enrollment with the 4-hour time limit secondary to clinical care (e.g. procedures, radiologic testing, etc.), or were discharged home from the ED. Patients who were unable to follow simple commands prior to their acute illness, as determined by surrogate interview or medical record review, were considered to have end-stage dementia and were excluded because the delirium assessment used in this study was not validated for this patient group.

During enrollment, research assistants (RAs) approached those who met inclusion criteria and determined if any exclusion criteria were present. While all delirious were enrolled, one out of six (~16.7%) randomly selected non-delirious older ED patients was enrolled to maximize the feasibility of our study. This proportion was chosen because it was anticipated that 83% to 92% of older enrolled ED patients would be non-delirious (Han *et al.*, 2009; 2010).

Methods of measurement

Delirium was assessed in the ED at the time of enrollment (0 hours) and at 3 hours. A patient was considered to be delirious in the ED if either the 0- or 3-hour delirium assessment was positive. Delirium was determined by trained RAs who were involved in the validation of the

delirium assessments used in this study (Han *et al.*, 2014, 2016). In non-mechanically ventilated patients, delirium was ascertained using a modified version of the Brief Confusion Assessment Method (bCAM), a brief (<2 minutes) delirium assessment (Han *et al.*, 2016). The modified bCAM is 82% to 86% sensitive and 93% to 96% specific for delirium as diagnosed by a psychiatrist and its κ is 0.87, indicating excellent inter-observer reliability (Han *et al.*, 2016). In mechanically ventilated patients, the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) was used to ascertain delirium (Han *et al.*, 2013). The CAM-ICU is 93% to 100% sensitive and 98% to 100% specific for delirium in these patients, with a κ of 0.96, indicating excellent inter-observer reliability (Ely *et al.*, 2001).

The Delirium Etiology Checklist was used to categorize delirium etiologies (Table S1, available as supplementary material attached to the electronic version of this paper at www.journals.cambridge.org/jid_IPG) (Trzepacz *et al.*, 2009). This tool categorizes potential causes into drug intoxication, drug withdrawal, metabolic disturbance, organ dysfunction, traumatic brain injury, seizures, intracranial infections, systemic infection, intracranial neoplasm, systemic neoplasm, cerebrovascular, other CNS, and other. The other category included etiologies such as pain, fractures, immunosuppression, heat stroke, and hypothermia. Some delirium etiology categories had very few events and were collapsed accordingly to facilitate analysis. Drug intoxication and withdrawal were collapsed into one category (drug intoxication/withdrawal). Traumatic brain injury, seizures, intracranial infections, intracranial neoplasm, cerebrovascular, and other CNS were also collapsed into one category (CNS insults). Two trained physician reviewers (JC and CN) independently determined the etiology of delirium. These physicians received training from a physician (JHH) who has expertise in delirium. Training entailed didactic lectures about delirium, including its precipitating factors. For each enrolled patient, they reviewed the ED and inpatient history and physical examination notes, consultant notes, laboratory, and radiology results, and any other data relevant to the etiology of the delirium episode that originated in the ED. In-hospital data was reviewed because the etiology is occasionally not readily apparent until the diagnostic workup (e.g. blood cultures or magnetic resonant imaging) has been completed during the hospital course. For each delirium etiology category, the physician reviewer determined if it was the (1) definite cause, (2) likely cause, (3) possibly contributory to delirium, (4) present but not contributory to delirium, or (5) ruled out/not present. A delirium etiology category was considered to have precipitated the delirium episode if they were rated as definite, likely, or possibly contributory. Patients were able to have multiple delirium etiologies as prior studies have found older patients often have more than one etiology (Francis *et al.*, 1990; Laurila *et al.*, 2008). All disagreements were adjudicated by a third physician (JHH) who had delirium expertise.

The primary outcome variables were six-month function and cognition adjusted for their respective baseline measures. Function was assessed for using the Older American Resources and Services Activities of Daily Living (OARS ADL) questionnaire to establish pre-illness (baseline) and six-month functional status. The OARS ADL consists of 14 items which include ratings for basic and instrumental ADLs, and has been validated for use in older ED patients (McCusker *et al.*, 1999). Scores range from 0 (completely dependent) to 28 (completely independent). The questionnaire was preferably completed by an informant who knew the patient well, but the patient completed the OARS ADL if no informant was available and if he/she was capable of providing informed consent which demonstrated capacity. Pre-illness (baseline) and six-month cognition were measured using the short-form Informant Questionnaire on Cognitive Decline in the Elderly score (IQCODE) (Jorm, 1994). This informant-based cognitive screen was used because global tests of cognition would not accurately reflect pre-illness cognition during a delirium episode. It has also been previously used to assess for cognitive decline (Serrano *et al.*, 2007; Inouye *et al.*, 2016; Han *et al.*, 2017b). The IQCODE was completed by informants who knew the patient for at least ten years; they were asked to answer 16 questions regarding the patient's cognition compared to ten years ago. The IQCODE ranged from 1 (markedly improved cognition) to 5 (markedly worse cognition, severe dementia), where a score of 3 represented no change in cognition. To establish pre-illness measures, OARS ADL and IQCODE were obtained in the ED at the time of enrollment; patients and/or their surrogates were asked to rate the patient's function and cognition two weeks prior to the ED visit. A trained research assistant who was blinded to the ED and hospital delirium assessments determined six-month functional status and cognition by administering the OARS ADL and IQCODE by phone. Every effort was made to contact the same person who completed the pre-illness OARS ADL and IQCODE assessments.

Medical record review was also performed to collect dementia status, comorbidity burden, and severity of illness. A patient was considered to have dementia if they had: (i) documented dementia in the medical record, (ii) a pre-illness IQCODE greater than a cut-off of 3.38 out of 5.00, which is 79% sensitive and 82% specific for dementia, (Jorm, 1994) or (iii) was on prescribed cholinesterase inhibitors prior to admission. The Charlson Comorbidity Index was used to quantify the patient's comorbidity burden (Murray *et al.*, 2006). The Acute Physiology Score (APS) of the Acute Physiology and Chronic Health Evaluation II (APACHE II) score was used to quantify severity of illness (Knaus *et al.*, 1985). Glasgow Coma Scale (GCS) was not incorporated in the APS because it is highly correlated with delirium which was our primary independent variable of interest. We performed double-data entry to ensure the accuracy of the data abstracted from the medical records.

Data analysis

Measures of central tendency and dispersion for continuous variables were reported as medians and interquartile ranges. Categorical variables were reported as frequency (percentage). κ statistics were reported to determine inter-rater reliability between the two physician raters. To determine if delirium etiologies were independently associated with six-month function and cognition, multiple linear regression models were performed, because our dependent variables were continuous in nature. Due to our sample size constraints, a multiple linear regression model was constructed for each delirium etiology. Therefore, patients with multiple delirium etiology subtypes were included in several regression models. Because of the limited degrees of freedom available, multiple linear regression was constructed for each delirium etiology subtype. For the six-month function outcome, the primary dependent variable was the six-month OARS ADL and the model was adjusted for pre-illness OARS ADL, dementia, comorbidity burden (Charlson Comorbidity Index), and severity of illness (APS). Two-factor interactions (delirium etiology subtype*pre-illness OARS) were incorporated to evaluate if the relationships between delirium etiology subtypes and 6-month function were modified by baseline function. For the 6-month cognition outcome, the primary dependent variable was the 6-month IQCODE and the model was adjusted for pre-illness IQCODE, pre-illness OARS ADL, comorbidity burden (Charlson Comorbidity Index), and severity of illness (APS). These covariates were chosen a priori based upon expert opinion, literature review, and our previous work. Two-factor interactions (delirium etiology subtype*pre-illness IQCODE) were incorporated to evaluate if the relationship between delirium etiology subtypes and six-month cognition was modified by baseline cognition. Because our analysis was exploratory in nature, interactions with p values <0.25 were retained in the multiple regression models; delirium etiology subtype β-coefficients were reported at the 25th and 75th percentile values of pre-illness OARS ADL and IQCODE for the function and cognition regression models, respectively. All statistical analyses were performed with SAS version 9.4 (SAS Institute, Carey, NC).

Results

Of the 3,383 older ED patients screened, 105 delirious and a random selection of 123 non-delirious older hospitalized patients admitted from the ED were enrolled. Details of the exclusions have been previously published (Han *et al.*, 2017b). In summary, a total of 3,383 older ED patients were screened, 1,282 were discharged home from the ED, 845 were non-delirious and were not randomly selected, 576 refused consent, and 452 met one of the exclusion criteria. Table 1 presents patient characteristics stratified by delirium status. Delirious patients were more likely to be female, non-white race, demented, functionally impaired, and have an ED chief complaint of "altered mental status." Delirium etiologies and inter-rater reliabilities can be seen in Table 2 for the 105 patients with delirium in the ED. Each delirious patient had a median (IQR) of 2 (1, 3) delirium etiology categories; 64 (61%) patients had two or more delirium etiology categories identified and 33 (31.4%) had three or more identified.

Of the 228 enrolled, all patients had a baseline OARS ADL, 42 (18.4%) patients died within six months, 13 (5.7%) patients opted out of the follow-up phone call, and 14 (6.1%) patients were lost to follow-up leaving 159 older patients available for delirium etiology and six-month function analysis (Table 3). Of these, 68 (42.8%) were noted to have delirium on ED presentation. Delirium secondary to metabolic disturbance and organ dysfunction were significantly associated with poorer six-month function after adjusting for pre-illness function, severity of illness, dementia, and comorbidity burden. The p values for the delirium secondary to metabolic disturbance*pre-illness function and delirium secondary to organ dysfunction*pre-illness function interactions were 0.0456 and 0.0144, respectively. The associations

Table 1. Patient characteristics and demographics

	NON-DELIRIOUS PATIENTS N= 123	DELIRIOUS PATIENTS N= 105
Median age (IQR)	73 (69, 80)	75 (68, 83)
Female gender	58 (47.2%)	68 (64.8%)
Non-white race	12 (9.8%)	18 (17.1%)
Nursing home residence	2 (1.6%)	5 (4.8%)
Dementia	31 (25.2%)	77 (73.3%)
Mechanically ventilated in ED	0 (0.0%)	0 (0.0%)
Median (IQR) OARS ADL	26 (21, 27)	16 (11, 23)
Median (IQR) IQCODE	3.19 (3.00, 3.56)	4.06 (3.28, 4.69)
Median Charlson (IQR)	3 (2, 5)	3 (2, 5)
Median APS (IQR)	4 (1, 6)	4 (2, 6)
ED chief complaint		
Abdominal pain	5 (4.1%)	7 (6.7%)
Altered mental status	4 (3.3%)	37 (35.2%)
Chest pain	23 (18.7%)	0 (0.0%)
Generalized weakness	7 (5.7%)	11 (10.5%)
Nausea/vomiting	8 (6.5%)	1 (1.0%)
Shortness of breath	20 (16.3%)	5 (4.7%)
Syncope	8 (7.3%)	0 (0%)
*Incident delirium	12 (9.8%)	6 (5.7%)

Abbreviations: IQR, interquartile range; APS, acute physiology score; ED, emergency department. *Incident delirium was delirium episodes that occurred after an episode of ED delirium resolved (two consecutive days with negative delirium assessments) or new onset delirium that occurred in those who were not delirious in the ED.

Table 2. Etiology frequency

ETIOLOGY	FREQUENCY (*N*)	PERCENT (%)	κ
Drug related	15	14.3	0.56
Metabolic disturbance	55	52.4	0.61
Infection	59	56.2	0.81
Organ dysfunction	44	41.9	0.69
CNS insult	23	21.9	0.78
Other	17	16.2	0.41

Etiology frequencies among 105 delirious emergency department patients. Two physician raters reviewed the medical record to determine delirium etiologies. Any disagreement was adjudicated by a third physician reviewer. κ between the two physician reviewers was measured to determine inter-rater reliability. CNS, central nervous system.

between these delirium etiology subtypes and six-month function were more prominent in patients with poorer pre-illness function. In patients with a pre-illness OARS ADL of 15 (poorer baseline function), the six-month OARS ADL was lowered by −2.9 points (95%CI: −0.3 to −5.6) and −4.3 points (95%CI: −4.4 to −8.5) in delirium secondary to metabolic disturbances and organ dysfunction, respectively. In patients with a pre-illness OARS ADL of 27 (excellent baseline function), no significant association between these delirium etiology subtypes and six-month function was observed.

Of the 228 enrolled, 198 (86.8%) patients had a baseline IQCODE, 41 (18.0%) died within six months, 10 (4.4%) opted out of follow-up, 16 (7.0%) were lost to follow-up, and 15 (6.6%) did not have a six-month IQCODE leaving 116 patients available for the ED delirium etiology and six-month cognition analysis (Table 4). Of these, 63 (54.3%) were noted to have delirium at ED presentation. Delirium secondary to CNS insult was the only subtype significantly associated with poorer six-month cognition after adjusting for pre-illness IQCODE, severity of illness, pre-illness function, and comorbidity burden. The p value for the delirium secondary to CNS insult*pre-illness cognition interaction was 0.0109. The association between delirium secondary to a CNS insult and six-month function was more prominent in patients with higher pre-illness cognition. In patients with delirium secondary to a CNS insult, the six-month IQCODE significantly increased by 0.69 (95%CI: 0.19 to 1.20) in patients with a pre-illness IQCODE score of 3.0625 (intact baseline cognition), but only 0.19 (95%CI: −0.33 to 0.71) points in patients with a pre-illness IQCODE of 4.1875 (poorer baseline cognition).

Discussion

Our data suggests that different delirium etiologies may have variable impact on six-month function

Table 3. Etiology and six-month function

DELIRIUM ETIOLOGY	β-COEFFICIENT (95%CI)	P VALUE FOR DELIRIUM ETIOLOGY*PRE-ILLNESS OARS ADL INTERACTION
Drug	−1.54 (−5.34 to 2.27)	0.3635
Metabolic		0.0456
Pre-illness OARS ADL = 15	−2.93 (−5.59 to −0.27)	
Pre-illness OARS ADL = 27	1.25 (−2.75 to 5.25)	
Infection	−0.27 (−2.62 to 2.09)	0.4314
Organ dysfunction		0.0144
Pre-illness OARS ADL = 15	−4.30 (−7.19 to −1.41)	
Pre-illness OARS ADL = 27	1.44 (−3.28 to 6.15)	
CNS insult		0.0536
Pre-illness OARS ADL = 15	2.17 (−1.50 to 5.84)	
Pre-illness OARS ADL = 27	−3.19 (−7.62 to 1.24)	
Other	−0.94 (−4.94 to 3.06)	0.4354

Etiology and six-month function as measured by the Older American and Services Activities of Daily Living (OARS ADL) questionnaire. The OARS ADL ranges from 0 (completely dependent) to 28 (completely independent). Each multiple linear regression was performed adjusted for pre-illness OARS ADL, severity of illness, dementia, and comorbidity burden. To determine if the effect of delirium etiology subtypes on six-month function was modified by pre-illness OARS ADL, two-factor interactions (delirium etiology subtype*pre-illness OARS ADL) were incorporated into the models. If the interaction term p value was < 0.25, then it was retained in the model. In regression models where the interaction terms were retained, the delirium etiology subtype β coefficients for the 25th and 75th percentile values of the pre-illness OARS ADL were reported. If the interaction term p value was ≥ 0.25, the interaction term was removed from the linear model and the β coefficients without the interaction were reported. CNS, central nervous system.

Table 4. Etiology and six-month cognition

DELIRIUM ETIOLOGY	β-COEFFICIENT (95%CI)	P VALUE FOR DELIRIUM ETIOLOGY*PRE-ILLNESS IQCODE INTERACTION
Drug	−0.23 (−0.67 to 0.20)	0.6978
Metabolic	0.15 (−0.14 to 0.44)	0.7880
Infection		0.0688
Pre-illness IQCODE 3.0625	0.29 (−0.04 to 0.63)	
Pre-illness IQCODE 4.1875	0.01 (−0.29 to 0.27)	
Organ dysfunction	0.12 (−0.22 to 0.45)	0.9344
CNS insult		0.0109
Pre-illness IQCODE 3.0625	0.58 (0.22 to 0.95)	
Pre-illness IQCODE 4.1875	0.07 (−0.30 to 0.44)	
Other	−0.03 (−0.47 to 0.42)	0.7671

Delirium etiology subtypes and six-month cognition as measured by the short form Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) which ranged from 1 to 5 (severe dementia). Each multiple linear regression was performed adjusted for pre-illness IQCODE, severity of illness, pre-illness function, and comorbidity burden. To determine if the effect of delirium etiology subtypes on six-month cognition was modified by pre-illness IQCODE, two-factor interactions (delirium etiology subtype*pre-illness IQCODE) were incorporated into the models. If the interaction term p value was < 0.25, then it was retained in the model. In regression models where the interaction terms were retained, the delirium etiology subtype β coefficients for the 25th and 75th percentile values of the pre-illness IQCODE were reported. If the interaction term p value was ≥ 0.25, the interaction term was removed from the linear model and the β coefficients without the interaction were reported. CNS, central nervous system.

and cognition, and that these relationships may be modified by pre-illness function and cognition, respectively. Specifically, delirium secondary to metabolic disturbances and organ dysfunction was the only delirium etiology subtypes significantly associated with poorer six-month function, and these associations were primarily observed in patients with poorer baseline function. Delirium secondary to CNS insult was the only etiology subtype significantly associated with poorer six-month cognition, but this association was more prominent in patients with intact cognition. Therefore, categorizing delirium as present or absent without taking into account patient pre-illness factors may be an oversimplification and have limited value in informing prognosis.

Delirium is a highly heterogeneous syndrome and this heterogeneity impacts long-term outcomes. To our knowledge, our study is the first to evaluate how delirium subtyped by etiology affects

outcomes. Delirium can also vary by psychomotor activity (hypoactive, hyperactive, mixed, or none) which is based upon the patient's motor activity, speech, and level of arousal (Meagher *et al.*, 2008). Hypoactive (decreased psychomotor activity) delirium is considered to carry the worst prognosis and is associated with higher short-term and long-term mortalities (Kiely *et al.*, 2007; Meagher *et al.*, 2011; Kim *et al.*, 2015; Jackson *et al.*, 2016). Delirium can also vary by level of arousal, which is a component of psychomotor activity, and is the patient's overall responsiveness to the environment. Level of arousal can be decreased, increased, or normal. In 1,084 older ED patients, delirium with normal arousal was the only arousal subtype associated with six-month mortality (Han *et al.*, 2017a). Delirium can vary by severity. Higher delirium severity is associated with prolonged hospital length of stays, increased 30-day re-admissions, death, functional impairment, and nursing home placement (Kelly *et al.*, 2001; Inouye *et al.*, 2014; Jackson *et al.*, 2016; Vasunilashorn *et al.*, 2016a, 2016b).

We also observed that the effect of delirium etiology subtypes on six-month function and cognition was modified by pre-existing function and cognition levels, respectively. In general, we observed delirious patients with metabolic disturbance and organ dysfunction etiologies were more susceptible to subsequent six-month functional decline if they had poorer pre-illness function. This is plausible mechanistically since patients with poorer pre-illness function have decreased physiological reserve, and are more vulnerable to developing functional decline after an episode of delirium. Surprisingly, delirious patients with better pre-illness cognition were more likely to have poorer six-month cognition if the etiologies were secondary to either a CNS insult or infection. The reason for this is unclear and further exploration into the mechanism of this relationship is needed. We used the IQCODE as our cognitive measure, and it is possible a floor effect may have been observed. IQCODE may not have been able to characterize additional cognitive decline in patients with poorer pre-illness function. Future studies should further evaluate this concept of patient vulnerability and use more robust neuropsychiatric evaluations to quantify long-term cognition.

Additional research is needed on multiple topics addressed in this paper. We assessed cognition at six months; future studies should evaluate if the associations between the delirium etiology subtypes and long-term outcomes persist beyond this time horizon. The mechanisms for the association between certain delirium etiology subtypes and long-term outcomes need to be elucidated. The poor prognosis may be related to the etiology itself or could reflect different underlying pathophysiological mechanisms, such as inflammation, which may be a prominent contributor of accelerated cognitive decline in delirious patients (Cunningham, 2011). The differential prognosis could be because different etiologies are more likely to present with certain psychomotor subtypes or higher severity. Future studies will need to investigate how delirium etiology, pathophysiology, psychomotor activity, and severity are inter-related. We also classified delirium etiology using a Delirium Etiology Checklist, retrospectively evaluating the electronic medical record. Future research should look at if delirium etiology can reliably and feasibly be determined in the ED or early in hospitalization. We also collapsed some of the Delirium Etiology Checklist's categories due to sample size constraints. It is possible that CNS infections may have different prognostic implications compared with cerebrovascular accidents. Future studies should enroll larger sample sizes to help address this uncertainty. Currently, there is no universally accepted treatment for delirium (AGS/NIA Delirium Conference Writing Group and Faculty, 2015). Most delirium interventions studied to date have been shown to have equivocal efficacy, (Abraha *et al.*, 2015) but their lack of efficacy may have been because they dichotomized delirium without taking into account its subtypes. Future studies should determine if performing these delirium interventions in delirious patients at higher risk for poorer six-month function or cognition would improve their efficacy.

Our study has several limitations. First, it is a single-center study performed at a tertiary center with a large volume of stroke, cardiac, and medically complex patients that may not be generalizable to the average community hospital. Second, inherent to most prospective cohort studies, unmeasured (e.g., drug exposure during hospitalization), and residual confounding may have still existed. A significant proportion of patients died prior to the six-month follow-up period; it is possible that these patients had significant cognitive and functional impairment, and this may have introduced additional residual confounding. Third, we created individual models for each delirium etiology subtype due to our relatively small sample. We did not incorporate all delirium etiology subtypes into one model to avoid over-fitting. Future studies with larger sample sizes should incorporate all the etiology subtypes into one model. Fourth, some delirium etiology categories, such as drug intoxication/withdrawal, had a small sample size. It is possible that a Type II (false negative) error may have occurred. Fifth, some delirium etiology categories

(i.e. drug withdrawal/intoxication and CNS) were collapsed because of small sample sizes. Due to pathophysiological differences, it is possible that these individual categories, such as CNS infection, may differentially impact long-term outcomes. Sixth, there were a significant proportion of patients who had missing six-month data due to death, loss to follow-up, or missing IQCODEs. These patients were probably more likely to be vulnerable, have higher severities of illness, have underlying dementia, and be more functionally dependent; their exclusion may have introduced selection bias. Seventh, 38 (16.7%) of pre-illness OARS ADLs were completed by the patient which may have biased our functional measurements. However, surrogates completed the OARS ADL in 104 (99.0%) delirious and 105 (96.3%) demented patients minimizing this source of bias. Finally, our study also did not enroll patients on weekends or between 6 pm and 4 am. This may have introduced selection bias as these patients may have been sicker.

Conclusion

Our findings are consistent with delirium as a heterogeneous syndrome and different delirium etiologies potentially may have an effect on six-month function and cognition, although further direct assessments will require larger samples. Further adding to delirium's complexity, the etiology subtypes' effect on these long-term outcomes was modified by pre-illness function and cognition, which reflects patient vulnerability. Delirium secondary to metabolic disturbances and organ dysfunction was the only delirium etiology subtypes significantly associated with poorer six-month function, but these associations were primarily observed in patients with poorer baseline function. Delirium secondary to CNS insult was the only delirium etiology subtype significantly associated with poorer six-month cognition, but this association was more prominent in patients with intact pre-illness cognition. Future studies are also needed to elucidate the pathophysiologic mechanisms for our findings, and how they are inter-related with delirium severity and duration. Such studies may provide information to assist clinicians in understanding more about targeting treatment, rehabilitation, prognosis, and follow-up in patients with delirium.

Conflict of interest

None.

Description of authors' roles

J. Cirbus collected the data, determined delirium etiology, and wrote the paper. A. MacLullich provided guidance and revision notes. C. Noel assisted with data collection, determining delirium etiology, and revisions. E. W. Ely provided guidance and revision notes. J. Han designed the study, supervised the data collection, adjudicated disagreements on delirium etiology, carried out statistical analysis, and assisted with writing the paper. R. Chandrasekhar reviewed and advised on biostatistical details.

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Supplementary material

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