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Long-Term Cognitive Impairment Associated With Delirium in Acute Neurological Injury

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Objectives: To characterize the risk of long-term cognitive impairment associated with delirium in acute neurologic injury patients.

Design: We analyzed a 10-year cohort of adult acute neurologic injury patients (stroke and traumatic brain injury) without preexisting mild cognitive impairment or dementia, utilizing administrative databases. Patients were followed for in-hospital delirium and mild cognitive impairment or dementia. We report incidence and adjusted hazard ratios for mild cognitive impairment or dementia associated with delirium. Subgroups analyzed include acute neurologic injury categories, dementia subtypes, repeated delirium exposure, and age strata.

Setting: We used state emergency department and state inpatient databases for New York, Florida, and California. All visits are included in the databases regardless of payer status.

Patients: We included adult patients with diagnosis of stroke and traumatic brain injury as acute neurologic injury. Patients with preexisting mild cognitive impairment or dementia were excluded.

Interventions: None.

Measurements and Main Results: Among 911,380 acute neurologic injury patients, 5.2% were diagnosed with delirium. Mild cognitive impairment or dementia incidence among delirium patients was approximately twice that of nondelirium patients. In adjusted models, risk of mild cognitive impairment or dementia was higher among patients with delirium (adjusted hazard ratio, 1.58). Increased risk was observed across all subgroups including patients less than or equal to 55 years old.

Conclusions: Identification, management, and prevention of in-hospital delirium could potentially improve long-term cognitive outcomes in acute neurologic injury patients.

Key Words: brain injuries, traumatic; cerebral hemorrhage; delirium; dementia; stroke

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Delirium is a clinical syndrome manifested as an acute and fluctuating change in concentration and attention. Reported in-hospital delirium prevalence is as high as 50% (1–3). Particularly susceptible are the elderly and those admitted to intensive care (4). Evidence of an independent link between delirium and poor outcomes is growing. Critical care patients experiencing delirium are at a higher risk for longer length of stay and worse cognitive outcomes (5, 6). Delirium has been independently associated with higher mortality, institutionalization, and dementia among elderly patients (7, 8). Although delirium has been studied in medical/surgical patients (4, 9), it has not been investigated in patients hospitalized for ischemic/hemorrhagic stroke or traumatic brain injury (TBI), defined as acute neurologic injury (ANI) in this study (10). Advanced age, prolonged intensive care, and underlying brain injury potentially expose ANI patients to risk factors and pathophysiological pathways for delirium development. The widely reported link between delirium and cognitive decline in non-ANI patients (4, 5, 11) and

cognitive impairment comorbidity burden among ANI patients (12–14) warrants assessment of the risk of long-term cognitive impairment associated with delirium among the neurocritically ill. Prior attempts to explore this relationship are limited by small sample size and short follow-up (15–17). Therefore, we compared the long-term incidence of mild cognitive impairment or dementia (MCID) between delirium and nondelirium ANI patients. We report the independent risk of delirium associated with MCID and dementia subtypes, quantify the "dose response" effect of repeated delirium exposure for the development of MCID in the setting of ANI, and investigate the risk of developing MCID associated with delirium across age categories.

MATERIALS AND METHODS

Study Design

We used a retrospective three state cohort of all hospital discharges over a 7–10 year time period. Patients were identified and included into the study cohort at the time of their first ANI event with or without in-hospital delirium. In-hospital delirium was identified using two published algorithms for administrative databases (18, 19). These algorithms use a combination of *International Classification of Diseases*, 9th Revision (ICD-9) codes and have high specificity (99% and 95%) and positive predictive value (PPV) (91% and 83%) when compared with clinically relevant and validated methods of diagnosis of delirium, such as the Confusion Assessment Method (CAM) or CAM-ICU. The cohort was followed for the duration of available data for incident diagnosis of MCID identified either during a subsequent emergency department (ED) visit or hospital admission. We further identified various dementia subtypes, such as vascular dementia, Alzheimer's disease, Lewy body dementia, frontotemporal dementia, and dementia not otherwise specified based on accepted ICD-9 codes (20).

Study Population

The overall study population of ANI patients comprised of four subpopulations. These were defined by patients having a validated primary discharge diagnosis ICD-9 code for either 1) acute ischemic stroke (AIS), 2) intracerebral hemorrhage (ICH), 3) subarachnoid hemorrhage (SAH) or 4) any diagnosis for TBI (21–27). ICD-9 codes for AIS include 433.01, 433.11, 433.21, 433.81, 433.91, 434.01, 434.11, 434.91, and 436 with sensitivity of 75% (21); specificity of 95% (21); and PPV of 85–94% (21–24). ICD-9 codes for ICH and SAH include 431 (sensitivity: 85% [21], specificity: 96% [21], PPV: 89–97% [21, 23, 25]) and 430 (sensitivity: 90% [21], specificity: 97% [21], PPV: 94–100% [21, 23, 25]), respectively. TBI was identified utilizing the Centers for Disease Control and Prevention criteria for identifying TBI from diagnostic codes and include ICD-9 codes 800.0–801.9, 803.0–804.9, 850.0–854.1, and 959.01 (26, 27). Patients less than 18 years old, those with missing age or linkage variables, those with MCID diagnosis prior to or within 90 days of ANI event, and those who died either during the initial hospitalization or within 90 days of discharge were excluded. Patients with a traumatic ICH or SAH, defined as a primary diagnosis of ICH or SAH with concurrent head trauma diagnosis, were not included in respective ICH or SAH subpopulations.

Study Outcomes

The outcome of MCID was defined using validated and previously reported ICD-9 codes. Mild cognitive impairment was defined using ICD-9 codes 331.83 and 780.93 as previously reported in the literature (28). Dementia ICD-9 codes were previously validated for the identification of dementia in the in-patient setting with 30–76% sensitivity, 95–100% specificity, and 60–96% PPV (29). These diagnosis codes were combined to define the primary outcome of MCID. We further identified mild cognitive impairment and various dementia subtypes and evaluated the association between delirium and each of these subcategories of MCID. Dementia subtypes were defined using previously reported classification of ICD-9 codes and include the following: Alzheimer's dementia (331.0), vascular dementia (290.40, 290.41, 290.42, 290.43), Lewy body dementia (331.82 or 331.0 and 332.0 concurrently), and frontotemporal dementia (331.1, 331.11, 331.19) (20). Validated dementia ICD-9 codes that did not meet prior dementia subtype classifications were categorized as dementia not otherwise specified and include the remaining validated ICD-9 codes (290.0–290.3, 290.8, 290.9, 331.2, 294.1–294.11).

Data Source

We used State Emergency Department (SEDD) and Inpatient (SID) administrative databases for New York (2006–2014), Florida (2005–2014), and California (2005–2011), maintained by the Agency for Healthcare Research and Quality (AHRQ) under its Healthcare Cost and Utilization Project (HCUP). The SEDD captures information on all patients across the state who present to a hospital-affiliated ED; whereas, the SID includes statewide records for all inpatient discharges. Unique linkage variables allow individual patients to be identified and followed for repeated ED visits and hospital admissions. These states were selected to represent the largest patient volumes across three distinct U.S. census regions and due to the availability of linkage variables across multiple years. Analysis time period was restricted to avoid coding inconsistencies across ICD-9 and *International Classification of Diseases*, 10th Revision. Study investigators completed training and signed data use agreement. Use of publicly available de-identified data did not warrant an institutional board review for this study.

Data Analysis

Descriptive methods were used to provide summary of various characteristics for the overall cohort and for patients who did and did not have delirium. We report unadjusted odds ratios (ORs) with respective 95% CIs for factors associated with in-hospital delirium and incidence rate of MCID among delirious and nondelirious ANI patients. We fit Cox proportional hazards model and report adjusted hazard ratios (aHRs) and 95% CI for comparison of MCID risk among ANI patients with and without delirium. In the adjusted model, we controlled for demographic, comorbidity, disease severity, treatment intensity factors, and in hospital complications such as sepsis, urinary tract infection, pneumonia,

seizures, and acute respiratory distress syndrome (ARDS) known to be associated with cognitive impairment (30, 31). For assessment of potential misclassification of delirium, we estimated the overall risk of MCID associated with delirium using two algorithmic definitions of delirium as described above (18, 19). Additionally, we present alternative risk estimates for MCID associated with delirium, generated using analyses conducted in a subcohort selected over a 2-year period. To assess a "dose response" effect of delirium, we compared the risk of MCID between patients with repeat delirium diagnoses and those with a single delirium diagnosis in the setting of ANI. We also conducted a stratified analysis to study the effect of age on risk of MCID among delirium and nondelirium patients. For these analyses, age was divided into five categories: 1) 18–54 years, 2) 55–64 years, 3) 65–74 years, 4) 75–84 years, and 5) greater than or equal to 85 years. In the overall sample, 49,186 patients had the outcome of interest (MCID), which provides more than 95% power to conduct fully adjusted analyses in multivariable models. Analyses were conducted by Drs. Bambhroliya and Vahidy.

Data Availability

Data used in this work is publicly available through the HCUP maintained by the AHRQ.

RESULTS

Study Population

Altogether, our "eligible population" comprised of 911,380 unique ANI patients, with the following four ANI subgroups: AIS (51.7%), ICH (6.3%), SAH (2.8%), and TBI (39.2%). With all four ANI subgroups combined, 47,752 (5.2%) patients were coded to have at least one event of in-hospital delirium. Differences in baseline characteristics between delirium and nondelirium patients are presented for the eligible population (**Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCX/A189). From within the eligible population, a total of 265,077 patients (29.1%, n = 911,380) had no subsequent ED visit or hospital admission and thus did not contribute person-time in the time-to-event analyses. The proportion of patients not contributing person-time were similar for the delirium and nondelirium groups (26.7% and 29.2%, respectively). The final "analysis population" comprised of 646,303 patients who contributed a total of 1,397,143 person-years with a median follow-up time of 587 days per person. **Figure 1** provides a Consolidated Standard for Reporting Trials style schematic for proportions and CI for excluded, eligible, and analysis populations.

Factors Associated With MCID

Females experiencing in-hospital delirium were at a significantly higher risk of developing MCID as compared with males (HR, 1.34; CI, 1.31–1.36). Older ANI patients with delirium were at a higher risk of developing MCID (HR, 1.06; CI, 1.06–1.06). An increased MCID risk was also associated with an overall higher burden of comorbidities, and in-hospital complications such as sepsis (HR, 1.27; CI, 1.19–1.36), seizures (HR, 1.26; CI, 1.21–1.32), and pneumonia (HR, 1.26; CI, 1.21–1.32). Supplemental Table 1 (Supplemental Digital Content 1, http://links.lww.com/CCX/A189) provides unadjusted HR (CI) for various demographic, comorbidity and treatment intensity factors, and in-hospital complications associated with development of MCID.

Incidence and Risk of MCID and Other Dementia Subtypes

Overall incidence (CI) of MCID among ANI patients per 1,000 person-years is 35.2 (34.9–35.5). The incidence of MCID among patients who had delirium was almost twice the incidence of those who did not have delirium (65.8 vs 33.8 per 1,000 person-years). After adjusting for multiple demographic, comorbidity, treatment intensity factors and in-hospital complications, exposure to in-hospital delirium remained significantly associated with the risk of developing MCID (aHR, 1.58; CI, 1.52–1.63). The risk of MCI without dementia and all dementia subtypes was also significantly higher for delirious patients. **Table 1** reports the proportions, incidence rates, crude, and adjusted HR (CI) for various MCI and dementia outcomes associated with delirium in ANI patients. **Figure 2** shows the cumulative survival function based on final multivariable Cox proportional hazards model for development of MCID among ANI patients with and without delirium. Independent association of delirium with MCID was also demonstrated individually across all ANI subgroups aHR (CI) AIS: 1.76 (1.68–1.85), ICH: 1.38 (1.22–1.55), SAH: 1.44 (1.15–1.81), and TBI: 1.31 (1.23–1.38) (**Supplemental Fig. 1*a–d***, Supplemental Digital Content 2, http://links.lww.com/CCX/A190; **legend**, Supplemental Digital Content 1, http://links.lww.com/CCX/A189). Furthermore, association between in-hospital delirium and risk of MCI and dementia subtypes was significant across all four categories of ANI patients (**Supplemental Table 2*a–d***, Supplemental Digital Content 1, http://links.lww.com/CCX/A189).

Subgroup Analyses

The risk of MCID associated with delirium among ANI patients was statistically significant and similar across all five age categories (**Fig. 3**). **Supplemental Figure 2*a–d*** (Supplemental Digital Content 3, http://links.lww.com/CCX/A191; legend, Supplemental Digital Content 1, http://links.lww.com/CCX/A189) includes age-stratified estimates for each ANI subgroup. Based on fully adjusted models the aHR (CI) for age 18–54: 1.52 (1.31–1.75); 55–64: 1.72 (1.54–1.93); 65–74: 1.67 (1.54–1.80); 75–84: 1.68 (1.59–1.78); and greater than or equal to 85: 1.39 (1.30–1.48). From among the ANI patients who have had a single episode of in-hospital delirium, patients experiencing repeated ANI with delirium events were at a greater risk of developing MCID as compared with those who only had a subsequent ANI event without delirium (aHR, 1.31; CI, 1.05–1.63).

Sensitivity Analyses

Our estimates based on the second algorithmic definition of delirium were similar to the main analysis utilizing the first algorithmic definition of delirium (aHR, 1.66; CI, 1.61–1.71). Likewise, the estimates of MCID risk among ANI patients obtained using an alternative 2-year closed-cohort design were similar in magnitude and direction (aHR, 1.37; CI, 1.28–1.46).

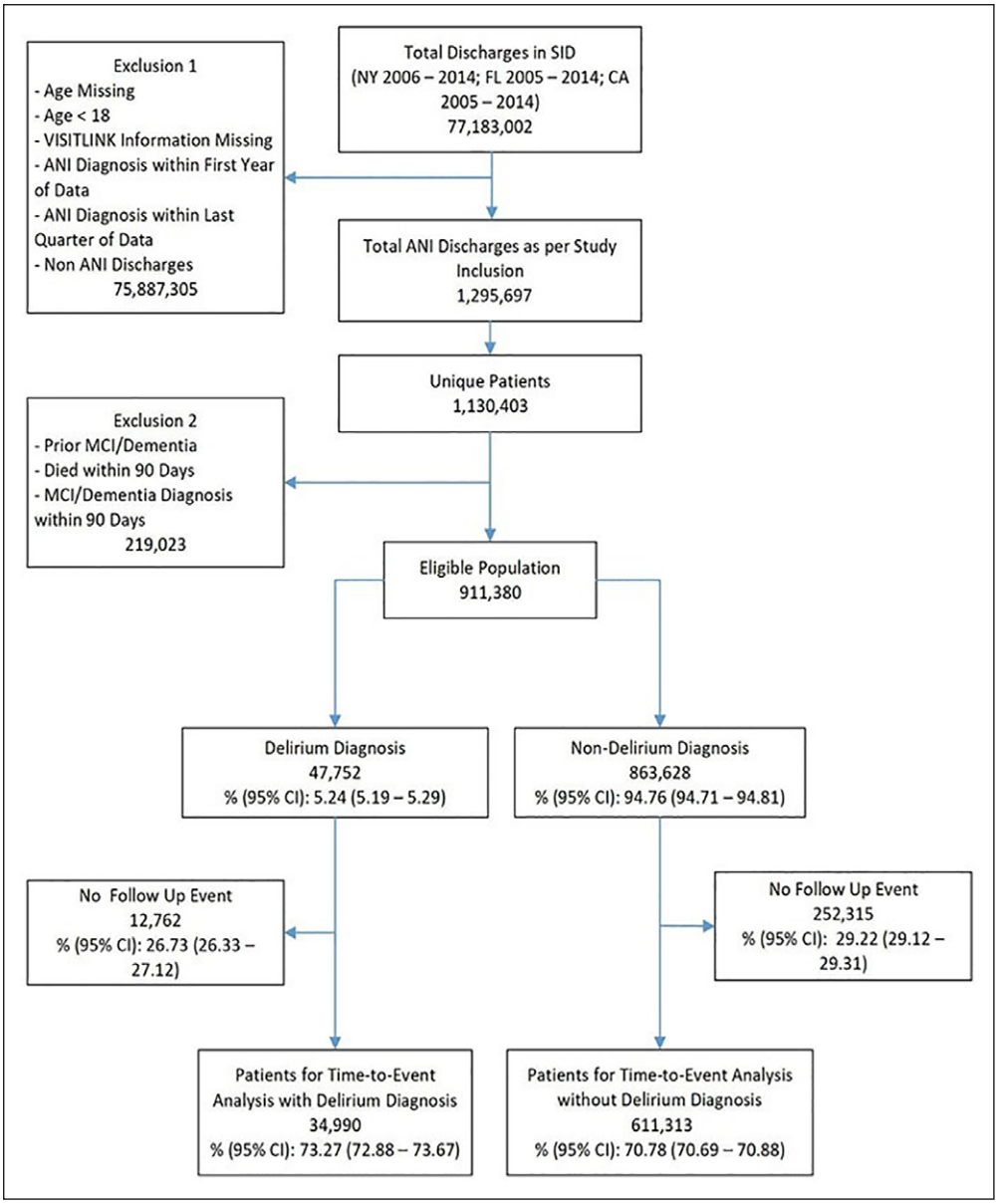

Figure 1. Consolidated Standard for Reporting Trials style diagram or proportions of excluded, eligible, and analysis population starting total discharges in New York, Florida, and California State Inpatient Databases (SID) for included years. Inpatient visits were excluded first for missing linkage information, age missing or less than 18 yr, visit without a diagnosis of acute neurologic injury (ANI), or a diagnosis of neurologic injury during the 1 yr "screening period" (to screen for a prior diagnosis of mild cognitive impairment [MCI]/dementia) or minimum 90-d follow-up period (to determine death or MCI/dementia diagnosis within 90 d of ANI discharge diagnosis). Remaining unique patients were screened for ineligibility due to prior MCI/dementia and/or death or MCI/dementia diagnosis within 90 d of ANI discharge diagnosis resulting in the eligible population. The eligible population was divided into those that were and were not diagnosed with delirium at the time of ANI inpatient stay and further divided into patients that did and did not have a follow-up visit for the duration of available data. VISITLINK = Visit Link variable uniquely identifying patient level data.

DISCUSSION

In-hospital delirium is a major risk factor for cognitive impairment (32). Neurocritically ill patients have generally been excluded from assessments of delirium and hence its impact on long-term cognitive outcomes is not well established among ANI patients. Despite the perceived restrictions in evaluation of delirium due to neurologic and functional deficits among ANI patients such as among patients with aphasia and neglect, it is important to recognize delirium as it has been reported that up to 30–40% of delirium is preventable (4), and that nonpharmacologic interventions are effective in ameliorating delirium (33). These simple, low-cost interventions such as routine spontaneous awakening trials, routine spontaneous breathing trials for ventilated patients, routine agitation and sedation monitoring, early patient mobilization, and associated care team coordination reduced the incidence of delirium by almost half in a recent effectiveness study (33). Identification of in-hospital delirium has been improved by development and application of validated diagnostic scales such as the CAM and CAM-ICU (34–37). Their feasibility for assessment of delirium among ANI patients has been reported (10). Given the well-established morbidity burden of cognitive impairment among ANI patients, it is important to identify and prevent potential triggers or accelerators of cognitive impairment among the neurocritically ill. We present our findings from analyses of a population-based cohort comprised of ED visits and in-hospital stays over a 10-year period in New York, Florida, and California. To our knowledge, this is the first population-based attempt to quantify the risk of long-term cognitive impairment associated with delirium among ANI patients.

In our cohort of over 900,000 ANI patients, the frequency of in-hospital delirium was 5.2%. This proportion is lower than a recently published review for neurocritically ill patients (12–43%) (10). Lower proportion in our analyses is most likely explained by evident differences in the study populations. The studies included in the review were conducted in a single or two-center setting, with relatively limited number of patients (average n = 168), who were probably managed in tertiary care ICUs with protocols in place for periodic delirium assessments. Although an underrepresentation of a true delirium prevalence, we believe that our estimates reflect a generalizable proportion of ANI patients among whom delirium is diagnosed and coded across varied hospital settings at a population level.

Our analyses demonstrate that ANI patients with in-hospital delirium are approximately 58% more likely to develop MCID

TABLE 1. Proportion, Incidence Rate, and Adjusted Hazard Ratios for Development of Mild Cognitive Impairment and Various Dementia Subtypes Among Acute Neurologic Injury Patients Who Did and Did Not Experience in Hospital Delirium

Outcomes	Total (*n* = 646,303)	No Delirium (*n* = 611,313)	Delirium (*n* = 34,990)
Mild cognitive impairment or dementia			
Patients with outcome, *n* (%)	49,186 (7.6)	45,165 (7.4)	4,021 (11.5)
Follow-up time (person-years)	1,397,143	1,336,102	61,041
Incidence rate[a]: % (95% CI)	35.2 (34.9–35.5)	33.8 (33.5–34.1)	65.8 (63.9–67.9)
Unadjusted HR (95% CI)		Reference	2.06 (1.99–2.12)
Adjusted[b] HR (95% CI)		Reference	**1.58 (1.52–1.63)**
Mild cognitive impairment			
Patients with outcome, *n* (%)	7,290 (1.1)	6,716 (1.0)	574 (1.6)
Follow-up time (person-years)	1,418,164	1,355,590	62,574
Incidence rate[a]: % (95% CI)	5.1 (5.0–5.3)	5.0 (4.8–5.1)	9.2 (8.5–10.0)
Unadjusted HR (95% CI)		Reference	1.93 (1.77–2.1)
Adjusted[b] HR (95% CI)		Reference	**1.49 (1.36–1.63)**
Alzheimer disease			
Patients with outcome, *n* (%)	19,817 (3.1)	18,243 (3.0)	1,574 (4.5)
Follow-up time (person-years)	1,415,026	1,352,584	62,441
Incidence rate[a]: % (95% CI)	14.0 (13.8–14.2)	13.5 (13.3–13.7)	25.2 (24.0–26.5)
Unadjusted HR (95% CI)		Reference	1.99 (1.89–2.10)
Adjusted[b] HR (95% CI)		Reference	**1.58 (1.50–1.67)**
Vascular dementia			
Patients with outcome, *n* (%)	14,284 (2.2)	13,042 (2.1)	1,242 (3.6)
Follow-up time (person-years)	1,415,578	1,353,236	62,342
Incidence rate[a]: % (95% CI)	10.1 (9.9–10.3)	9.6 (9.5–9.8)	19.9 (18.8–21.1)
Unadjusted HR (95% CI)		Reference	2.14 (2.02–2.27)
Adjusted[b] HR (95% CI)		Reference	**1.78 (1.67–1.89)**
Frontotemporal dementia			
Patients with outcome, *n* (%)	133 (0.02)	118 (0.02)	15 (0.04)
Follow-up time (person-years)	1,425,819	1,362,663	63,157
Incidence rate[a]: % (95% CI)	0.1 (0.08–0.11)	0.1 (0.07–0.1)	0.2 (0.14–0.39)
Unadjusted[c] HR (95% CI)		Reference	**2.82 (1.65–4.83)**
Lewy body dementia			
Patients with outcome, *n* (%)	4,404 (0.68)	4,011 (0.66)	393 (1.12)
Follow-up time (person-years)	1,423,842	1,360,843	62,999
Incidence rate[a]: % (95% CI)	3.1 (3.0–3.2)	2.9 (2.9–3.0)	6.2 (5.7–6.9)
Unadjusted HR (95% CI)		Reference	2.26 (2.04–2.51)
Adjusted[b] HR (95% CI)		Reference	**1.47 (1.32–1.64)**

(*Continued*)

TABLE 1. (*Continued*). Proportion, Incidence Rate, and Adjusted Hazard Ratios for Development of Mild Cognitive Impairment and Various Dementia Subtypes Among Acute Neurologic Injury Patients Who Did and Did Not Experience in Hospital Delirium

Outcomes	Total (*n* = 646,303)	No Delirium (*n* = 611,313)	Delirium (*n* = 34,990)
Dementia not otherwise specified			
Patients with outcome, *n* (%)	13,903 (2.2)	12,770 (2.1)	1,133 (3.2)
Follow-up time (person-years)	1,414,665	1,352,348	62,316
Incidence rate[a]: % (95% CI)	9.8 (9.7–10.0)	9.4 (9.3–9.6)	18.2 (17.2–19.3)
Unadjusted HR (95% CI)		Reference	1.99 (1.87–2.11)
Adjusted[b] HR (95% CI)		Reference	**1.46 (1.37–1.56)**

HR = hazard ratio.

[a]Incidence rate per 1,000 person-years.

[b]Adjusted for 1) Demographics: age, gender, race, insurance (primary payer), patient location (urban-rural), income quartile of patient ZIP code, and state; 2) Comorbidities including Agency for Healthcare Research and Quality comorbidity measures: Charlson Comorbidity Index, atrial fibrillation, alcohol abuse, deficiency anemias, rheumatoid arthritis/collagen vascular diseases, chronic blood loss anemia, congestive heart failure, chronic pulmonary disease, coagulopathy, depression, diabetes, uncomplicated, diabetes with chronic complications, drug abuse, hypertension (combine uncomplicated and complicated), hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, other neurologic disorders, obesity, paralysis, peripheral vascular disorders, psychoses, pulmonary circulation disorders, renal failure, solid tumor without metastasis, peptic ulcer disease excluding bleeding, valvular disease, weight loss, AIDS, hyperthyroidism, tobacco use, concurrent diagnosis of acute ischemic stroke, concurrent diagnosis of intracerebral hemorrhage, concurrent diagnosis of subarachnoid hemorrhage, and acute neurologic injury subtypes; 3) Treatment severity: IV tissue plasminogen activator, intra-arterial therapy, and ICU use (hemicraniectomy/craniotomy, extra ventricular drain placement, gastric tube, tracheostomy, ventilatory support); 4) In hospital complications: sepsis with organ failure, pneumonia, acute respiratory distress syndrome, urinary tract infection, and seizures; and 5) In hospital outcomes: length of stay and discharge disposition.

[c]Adjusted estimates not provided because of small number of patients and events.

Boldface values indicate fully adjusted HR and 95% CI.

as compared with nondelirious patients. The large sample size allowed adjustment for demographic, comorbidity, and disease severity factors as well as for other in-hospital complications previously reported to be associated with cognitive impairment (sepsis, ARDS, seizures, urinary tract infection, pneumonia). There are no prior directly comparable estimates for risk of long-term cognitive impairment associated with delirium among ANI patients. Our results, however, corroborate a small retrospective study that demonstrated similar association for patients with ischemic stroke (17). Given a small sample (n = 50), this report lacked precision (OR, 4.7; CI, 1.08–20.42). Another small study has also reported similar imprecise estimates (OR, 4.3; CI, 1.2–15.6) for association between delirium and dementia, albeit limited to 90-day poststroke dementia (15). In addition to the limitations of small sample size and short follow-up time, this study has an unspecified stroke patient population and included patients with preexisting cognitive dysfunction. We excluded patients with evidence of either preexisting MCID and those who were coded to have a MCID diagnosis within 90 days of hospital discharge to further minimize potential preexisting undiagnosed MCID in our analysis population. Furthermore, in our cohort of over 600,000 patients, the median follow-up time was 19.6 months per patient.

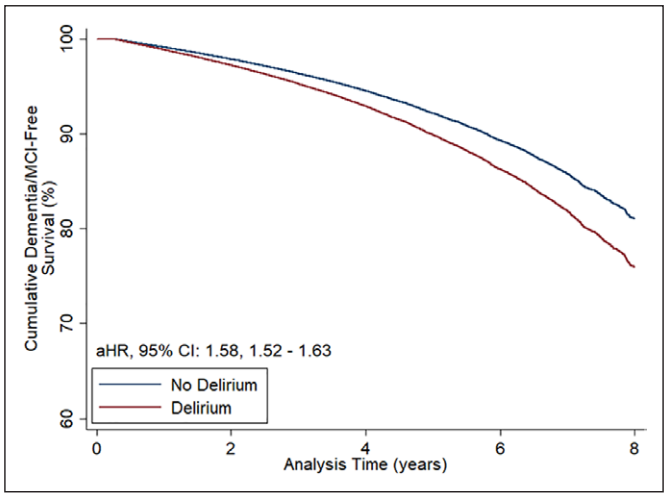

Figure 2. Multivariable Cox proportional hazard model showing percent of patients with combined acute neurologic injury that are free of mild cognitive impairment (MCI) or dementia (*y*-axis) for years of analysis (*x*-axis) for both those with (*red line*) and without (*blue line*) a delirium diagnosis during inpatient stay for acute neurologic injury. Included are the associated adjusted hazard ratio (aHR) and 95% CI. Model is adjusted for multiple demographic factors, comorbidities, and complications.

Findings from our main analyses are substantiated by the significant association observed between delirium and MCID independently across all ANI categories. It is possible that common pathologic pathways such as postinjury local and systematic inflammation and disruption of blood-brain barrier are responsible for this overlap. We also provide estimates for the risk of dementia subtypes across all categories of ANI patients. Most adjusted estimates in these subgroup analyses demonstrated a significant association between delirium and long-term cognitive impairment. Finally, our data show that repeated exposure to delirium was associated with even higher risk of MCID as compared with ANI patients who only had a single delirium episode.

We demonstrate that MCID risk associated with delirium was significantly increased across all age categories including ANI patients younger than 55 years. These data therefore support the hypothesis of an accelerated cognitive impairment associated with delirium among hospitalized ANI patients, a phenomenon reported in other patient populations (11).

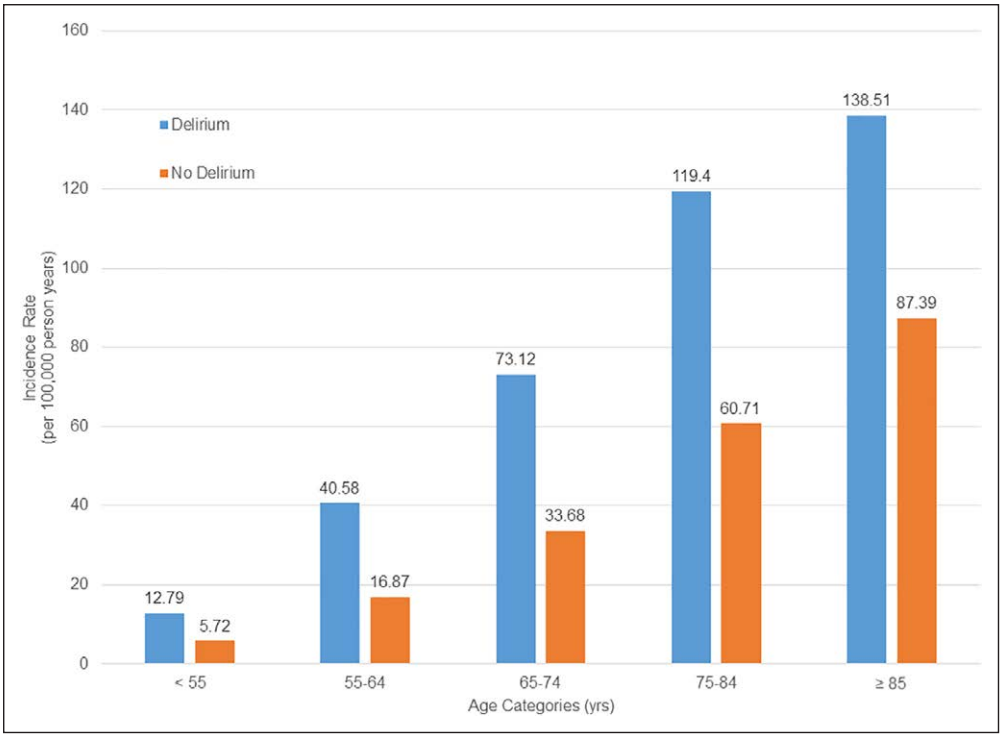

Figure 3. Age-stratified incidence rate of mild cognitive impairment or dementia among acute neurologic injury patients. Incidence is divided into patients that were diagnosed with delirium during initial hospitalization (*blue*) and those that were not (*orange*).

Findings of our study need to be interpreted considering the following limitations. First and foremost, our analyses based on administrative data underreport frequency of in-hospital delirium among patients with ANI. As indicated previously, a recent meta-analysis reported a pooled estimate of 12–43% based on data from 1,173 patients enrolled in seven prospective cohorts (10). We found a delirium episode to be documented in only 5.2% of our study population. This likely represents substantial under documentation of delirium in electronic medical records and/or coding omissions. Given this limitation, we cannot rule out a potential of selection bias in our analyses. However, our intent is not to provide a population-based prevalence estimate for delirium; instead, the primary aim is to evaluate the risk of incident dementia among patients who had in-hospital delirium. The high PPV (91%) and specificity (99%) (as compared to CAM score) of the algorithm, we used to identify delirium to a large extent preclude false positive delirium cases in our analyses. A differential rate of dementia among ANI patients who were delirious but were not coded to have delirium (false negatives) during hospitalization is however possible. We therefore conducted sensitivity analyses using a second delirium coding algorithm with higher sensitivity and found similar results. Likewise, the overall incidence of dementia may also be underreported in ED and in-hospital administrative databases. Therefore, our reported rates for dementia may not be regarded as valid population-based estimates of dementia incidence among ANI patients. Given the magnitude and consistency of results across all ANI subgroups for all dementia subtypes and a dose-response type relationship between delirium and risk of dementia, we believe that our data do provide evidence of delirium's independent association with risk of MCID among ANI patients. Second, approximately 30% of the initially identified cohort had no subsequent ED visits or in-hospital stays and hence may be regarded as lost to follow-up (LTF). There were no significant differences in age, sex, and comorbidity profiles between LTF and non-LTF patients. Although African American patients were more likely to be LTF, this was similar among patients with or without delirium. Also, among those with follow-up, the median follow-up time period was 1.5 years. This could potential under-estimate the risk of cognitive decline and dementia. However, cognitive decline and dementia incidence observed during an extended follow-up time period would be difficult to distinguish from age-related dementia and other exposures influencing the outcome. Third, our study design does not allow us to infer causality between delirium and MCID. Although we excluded patients with either preexisting or day 90 post-discharge MCID, the possibility of false negative cases of dementia in our baseline cohort cannot be eliminated. Also, given the predisposition to delirium in patients with dementia, a reverse causality relationship is possible (38). We also did not assess the association between delirium and dementia among non-ANI patients. Further studies are needed to compare these two population and assess the additive effect of ANI. Finally, use of an administrative database precludes adjustment for medication use, disease-specific severity, and brain lesion location for ANI patients.

CONCLUSIONS

In summary, we provide population-based evidence for increased risk of development of MCID and other dementia subtypes among various categories of ANI patients who experienced delirium during hospitalization. A higher risk was observed among ANI patients who had repeated delirium episodes, and the risk was consistent across all age categories including individuals less than 55 years old. With the large morbidity burden associated with cognitive decline in ANI patients and the association between delirium and MCID demonstrated even in young adults, identification, prevention, and low-cost, low-risk treatment of in-hospital delirium among ANI patients as well as potential enrollment in targeted programs to prevent cognitive decline is important, and further research is needed to identify potential biological targets linking delirium and cognitive impairment in patients with ANI.

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