Identifying Delirium Early after Stroke: A New Prediction Tool for the Intensive Care Unit

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Background: Delirium is common after stroke and associated with poor functional outcomes and mortality. It is unknown whether delirium is a modifiable risk factor, or simply an indicator of prognosis, but in order to intervene successfully, those at greatest risk must be identified early. We created a tool to predict the development of delirium in patients admitted to the intensive care unit for stroke, focusing on factors present on hospital admission. *Methods:* Charts of 102 patients admitted to the ICU or IMC after ischemic stroke or intracranial hemorrhage with symptom onset within 72 hours were reviewed. Delirium was identified using the Confusion Assessment Method for the ICU (CAM-ICU). Factors significantly associated with delirium were included in a multivariable logistic regression analysis to create a predictive model. The model was validated in a unique inpatient cohort. *Results:* In regression analyses, the variables present on admission most strongly associated with the development of delirium after stroke included: age greater than 64 years; intraventricular hemorrhage; intubation; presence of either cognitive dysfunction, aphasia, or neglect; and acute kidney injury. Using these variables in our predictive model, an ROC analysis resulted in an area under the curve of 0.90, and 0.82 in our validation cohort. *Conclusions:* Factors available on admission can be used to accurately predict risk of delirium following stroke. Our model can be used to implement more rigorous screening paradigms, allowing for earlier detection and timely treatment. Futures studies will focus on determining if prevention can mitigate the poor outcomes with which delirium is associated.

Key Words: Delirium—Intensive care—Outcomes—Recovery—Stroke

Introduction

Delirium is a significant problem in hospitalized patients and is associated with poor outcomes.[1–4] It is estimated that between 10% and 48% of patients admitted to the hospital after stroke develop delirium.[5] These patients are at increased risk for greater functional disability and level of dependence, cognitive impairment, longer hospitalization, discharge to a nursing home, and greater in-hospital and 1-year mortality.[6–9] It is not clear that delirium itself is the cause of these poor outcomes, and may instead be a marker for susceptibility to future cognitive decline. The details of how delirium impacts recovery and whether or not prevention can decrease the risk of poor outcome has yet to be determined.

The first step in preventing delirium is to predict it. Advanced age, pre-existing cognitive impairment, infarct volume, severity of initial deficits, metabolic disturbances, polypharmacy, and concomitant infections have all been identified as potential risk factors in previous studies.[9–14] While some of these risk factors are fixed, others are amenable to intervention, potentially allowing clinicians to lower a patient's likelihood of developing delirium. In 2014, Oldenbeuving et al. created a simple model that can be applied early in admission to predict delirium utilizing the patient's age, National Institutes of Health Stroke Scale (NIHSS) score, stroke subtype, and presence of infection with sensitivity of 76% and specificity of 81%.[13] As this model was created in the Netherlands, however, it may not be applicable to populations with a greater diversity of races and ethnicities, and thus may not reflect the risk factors of such groups.

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Past studies have shown that delirium is particularly common in ICUs, and that delirium tends to be diagnosed earlier in the hospitalization.[15–18] For this reason, we chose to study delirium in patients admitted to the ICU in the acute setting after stroke, with a tool that has been validated for this purpose, the Confusion Assessment Method for the ICU (CAM-ICU).[15,16]

In the present study, we develop a tool to predict delirium in patients from an urban United States population admitted to the intensive care unit (ICU) or intermediate care unit (IMC) after acute ischemic or hemorrhagic stroke, with emphasis on risk factors that can be identified on admission. In a subsequent analysis, we validate our model in a unique inpatient cohort.

Methods

Model cohort

The study population was recruited over a 10-month period, from July 2018 to April 2019. All patients admitted to the Neurosciences Intensive Care Unit at a large, urban, Comprehensive Stroke Center in Baltimore, Maryland with an acute cerebral infarct or primary intracranial hemorrhage within 72 h of admission were included in the analysis. Patients were excluded if they met any of the following criteria: age less than 18 years, primary subarachnoid hemorrhage or subdural hemorrhage, hemorrhage due to intracranial neoplasm, unresponsiveness or minimally responsive state without improvement throughout admission, or resolution of symptoms without evidence of stroke/hemorrhage on neuroimaging (e.g. transient ischemic attack, mimic such as migraine). Patients who were never admitted to the ICU or IMC were also excluded. This study was approved by our institutional review board, and given its observational nature, informed consent was not required.

Demographics and stroke characteristics**:** The following baseline data were collected: age, sex, race, medications taken at the time of admission, medical comorbidities, history of prior stroke, history of dementia, current alcohol use, illicit drug use, tobacco use. Premorbid functional status, classified as either independent in activities of daily living (ADLs) and instrumental ADLs or not, was determined by review of clinical documentation including providers' notes and physical/occupational therapy notes. On admission, all patients were evaluated by a neurology resident and underwent a clinical examination including scoring of the severity of clinical deficits using the NIHSS. All patients underwent non-contrast computed tomography (CT) scan of the head. The majority were also evaluated with magnetic resonance imaging (MRI) of the brain, and MR angiography (MRA) of the head and neck or CTA of the head and neck, and perfusion imaging with either MRI or CT. To determine the volume of ischemic or hemorrhagic lesions, volumetric analysis (automatic lesion segmentation, Carestream PACS) was performed on diffusion-weighted sequences of MRI, when available, or on non-contrast head CT. Stroke was classified as primary ischemic or hemorrhagic, and as involving either the anterior or posterior circulation (or both). Laterality was also recorded. Ischemic stroke etiology was categorized according to TOAST classification.[19] For intracranial hemorrhage, ICH score was recorded.

Medical risk factors: Charts were reviewed for presence of metabolic derangements including hypo- or hypernatremia (sodium < 135 or > 145 mmol/L), hypo- or hyperglycemia (glucose < 80 or > 200 mg/dL), hypo- and hypercalcemia (calcium < 8.4 or > 10.5 mg/dL), and hypoxia (capillary oxygen saturation < 90%). Infection was determined by patient symptoms, presence of a source, positive culture data, and treatment with antibiotics. Presence of leukocytosis (white blood cell (WBC) count > 12,000), erythrocyte sedimentation rate (ESR) elevation (> 35 mm/h), and fever (temperature > 37.9 °C) were also recorded. Minimum and maximum systolic blood pressures were recorded.

Delirium assessment: The CAM-ICU[15] was administered by nursing staff once per shift to the all patients admitted to the neurosciences ICU or IMC. Data on other markers of delirium were also collected, including requirement of restraints, medications used to treat delirium, and need for a patient safety attendant.

Outcomes**:** Short-term outcome data included hospital length of stay, discharge destination (e.g. home versus rehabilitation facility), discharge NIHSS score, and discharge modified Rankin scale (mRS) score. Post-discharge outcome data included NIHSS score, mRS score, and living situation at follow up (typically between 1 and 3 months). Outcomes associated with in-hospital delirium were identified using two-sample *t* tests for continuous variables and chi-squared analyses for categorical variables.

Creation of the prediction model

Univariable analyses, using two-sample *t* tests for continuous variables and chi-squared analysis for categorical variables, were performed to identify factors that were significantly associated with delirium, defined as positive CAM-ICU at any time during admission. Multivariable logistic regression was used to create our predictive model, with delirium as the dependent variable. Covariates that were significant in the univariable analysis were included in the stepwise regression analysis, and those that were most strongly associated with development of delirium were used in the predictive model. Because the goal was to predict delirium early in the hospital course, only variables that were measurable on admission were included. Coefficients generated by the multivariable analysis were used to create a predictive model, which was then evaluated using a receiver operating characteristics (ROC) analysis to calculate area under the curve (AUC). The results of the regression analysis yielded

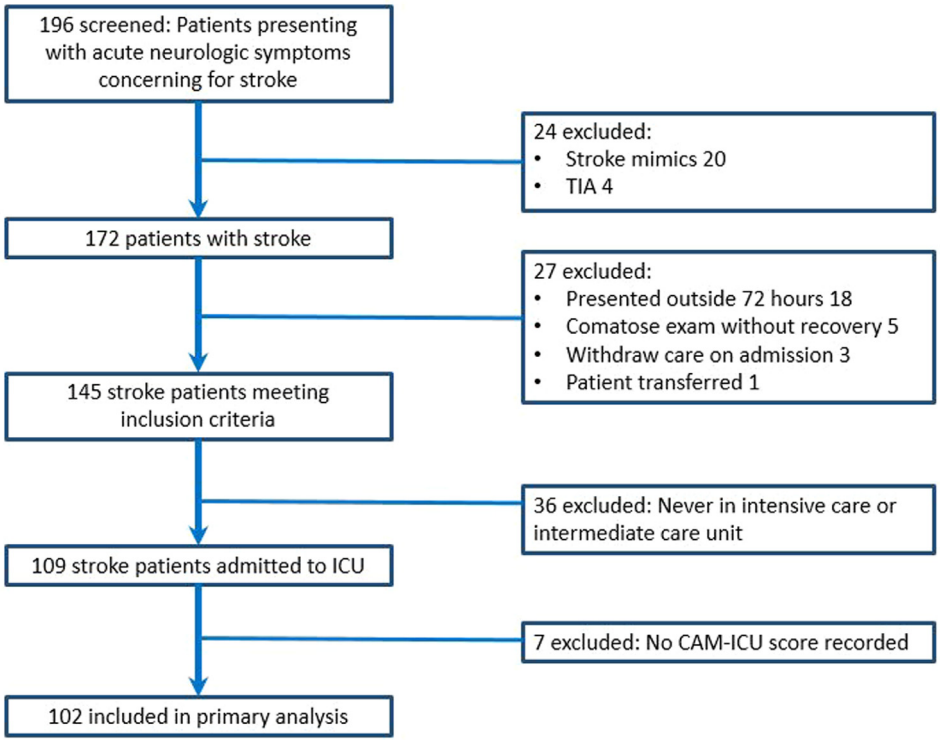

Fig. 1. *Study enrollment flow diagram.*

coefficients, which were used to create a formula with which the probability of developing delirium can be calculated.

Validation of the model

A unique population of 100 consecutive patients admitted with ischemic stroke or primary intracranial hemorrhage was recruited to test the validity of the model in predicting the development of delirium in the ICU. The validation cohort was recruited between May 2019 and December 2019. Inclusion and exclusion criteria were the same as for the initial population. Data collected included presence of delirium as defined by positive CAM-ICU at any point during admission, as well as data on demographics and stroke characteristics in order to compare to the model cohort. The relevant variables were inserted into the model in order to determine the sensitivity and specificity of correctly predicting delirium in this independent cohort. AUC was determined using a ROC analysis.

Results

Model cohort

The charts of 196 patients presenting with acute neurologic symptoms concerning for stroke were screened. One hundred and nine patients met all of the inclusion criteria, and 102 had CAM-ICU scores and were included in our primary analysis (Fig. 1).

Patient characteristics: Population characteristics are summarized in Table 1. There were 49 women (48%), and the mean age of the cohort was 65 years (range 26−97 years). Seventy-eight patients (76.5%) presented with ischemic stroke. The median NIHSS score on admission was 10 (range 0−34). Strokes most often involved the frontal lobe, and least frequently the thalamus, with a majority involving multiple brain regions (Table 2). Seven patients (6.9%) carried a diagnosis of dementia, and 21 patients (20.6%) were not fully independent at baseline. Twenty-seven percent of patients were treated with intravenous (IV) tissue plasminogen activator (TPA) and 21% underwent intraarterial mechanical thrombectomy (MT).

Delirium and association with stroke characteristics and in-hospital events: Of the 102 stroke patients admitted to the ICU with CAM-ICU data, 51 were diagnosed with delirium (50%) with a positive CAM-ICU at any point during their ICU stay. Twenty-eight of the patients (27.5%) had an initial positive CAM-ICU. Thirty-one patients (30.4%) required restraints, 12 (11.8%) received medications to treat delirium, and 9 (8.8%) required a patient safety attendant; the majority of these patients were CAM-ICU positive. Patients who developed delirium during their hospitalization were more likely to be older, have more medical comorbidities, and take more medications. They were more likely to have premorbid dementia and were less likely to be independent at baseline (Table 3). Delirium was associated with larger strokes and more severe deficits. Strokes involving the temporal or parietal lobes were also more likely to be

Table 1. *Population characteristics.*

	Variable	Model Cohort (n = 102)	Validation Cohort (n = 100)	p value
Patient characteristics				
	Age, mean (range)	65.0 (26−97)	66.6 (27−94)	0.4267
	Female sex, n (%)	49 (48.0)	44 (44)	0.565
	African American/black race, n (%)	31 (30.4)	38 (38)	0.015
	History of prior stroke, n (%)	21 (20.6)	29 (29)	0.154
	History of dementia, n (%)	7 (6.9)	3 (3)	0.212
	Independent at baseline, n (%)	81 (79.4)	77 (77)	0.670
Type of stroke				
	Ischemic stroke, n (%)	79 (77.5)*	73 (73)	0.763
	Intracranial hemorrhage, n (%)	24 (23.5)*	27 (27)	0.763
Stroke severity				
	Initial NIHSS score, mean	11.1	12.9	0.0951
	Initial NIHSS score, median (range)	10 (0-34)	13 (0−27)	
	Presence of IVH, n (%)	12 (11.8)	16 (16)	0.368
	ICH score, mean	1.4	1.6	0.5061
Stroke laterality				
	Right-sided, N (%)	44 (43.1)	60 (60)	0.032
	Left-sided, n (%)	51 (50)	32 (32)	0.032
	Bilateral, n (%)	7 (6.9)	8 (8)	0.032
Vascular territory				
	Anterior circulation, n (%)	78 (76.5)	68 (70.8)	0.306
	Posterior circulation, n (%)	27 (26.5)	24 (25)	0.781
	Multiple territories, n (%)	4 (3.9)	4 (4.2)	0.942
Type of deficit				
	Cognitive dysfunction, n (%)	20 (19.6)	28 (28)	0.161
	Aphasia, n (%)	31 (30.4)	41 (41)	0.116
	Neglect, n (%)	25 (24.5)	43 (43)	0.005
Ischemic stroke etiology				
	Large vessel, n (%)	17 (16.7)	22 (31.0)	0.202
	Cardioembolic, n (%)	31(30.4)	25 (35.2)	0.568
	Small vessel, n (%)	13 (12.7)	4 (5.6)	0.034
	Other, n (%)	7 (6.9)	7 (9.9)	0.853
	Unknown/incomplete, n (%)	10 (9.8)	13 (18.3)	0.354
Interventions				
	Received IV TPA, n (%)	27 (26.5)	24 (24)	0.686
	Mechanical thrombectomy, n (%)	21 (20.6)	24 (24)	0.560
	Intubation, n (%)	25 (24.5)	46 (46)	0.001
Medical complications				
	Infection, n (%)	43 (42.4)	39 (39)	0.648
	Acute kidney injury, n (%)	30 (29.4)	38 (38)	0.197

*percentage > 100%, one patient with both hemorrhage and ischemic stroke.

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; ICH, intracranial hemorrhage; IV, intravenous; TPA, tissue plasminogen activator.

Table 2. *Areas involved by ischemic or hemorrhagic stroke (regions are not mutually exclusive).*

	Frequency		
Brain region	Left	Right	Bilateral
Frontal lobe	25	22	5
Temporal lobe	20	13	4
Parietal lobe	14	13	3
Thalamus	5	5	2
Head of caudate	7	10	0
Multiple	23	17	4

associated with delirium; however, these associations were no longer significant when adjusting for stroke volume or initial NIHSS score. Patients who became delirious were more likely to have had procedures (with the exception of MT, which was not associated with the development of delirium), and were more likely to have other complications during hospitalization, such as infection, kidney injury, and seizures.

Outcomes: Development of delirium was associated with worse outcomes when compared to outcomes in patients who did not develop delirium, including

Table 3. *Patient and stroke characteristics, hospital events, and outcomes in relation to development of delirium.*

	Variable	Positive CAM-ICU ($n = 51$)	Negative CAM-ICU ($n = 51$)	p value
Baseline characteristics				
	Age, mean	70.73	59.29	< 0.001
	Age > 64 years, n (%)	36 (70.6)	21 (41.2)	0.0030
	Comorbidities, mean	5.24	4.098	0.0311
	Number of medications, mean	6.21	4.3	0.0176
	Independent at baseline, n (%)	32 (62.7)	49 (96.1)	< 0.001
	Premorbid mRS, mean	1.286	0.667	0.0177
	History of dementia, n (%)	7 (13.7)	0 (0)	0.0060
Stroke characteristics				
	NIHSS score initial, mean	15.4	6.8	< 0.001
	NIHSS score > 7, n (%)	40 (78.4)	21 (41.2)	< 0.001
	Stroke volume (cc), mean	73	16.8	< 0.001
	Cognitive dysfunction, n (%)	18 (35.3)	2 (3.9)	< 0.001
	Aphasia, n (%)	21 (41.2)	19 (37.3)	0.0180
	Neglect, n (%)	18 (35.3)	7 (13.7)	0.0110
	ICH score, mean	1.81	0.67	0.0078
	Presence of IVH, n (%)	11 (21.6)	1 (2.0)	0.0020
Interventions				
	Received IV TPA, n (%)	7 (13.7)	20 (39.2)	0.0040
	Mechanical thrombectomy, n (%)	13	8	0.2210
	Intubation, n (%)	20 (39.2)	5 (9.8)	0.0010
	Tracheostomy placed, n (%)	4 (7.8)	0 (0)	0.0410
	Gastrostomy tube placed, n (%)	17 (13.7)	1 (2.0)	< 0.001
Complications				
	Infection, n (%)	32 (62.7)	11 (21.6)	< 0.001
	Fever, n (%)	29 (56.9)	5 (9.8)	< 0.001
	Max WBC count, mean	14.9	11.6	0.0034
	Seizure, n (%)	6 (11.8)	1 (2.0)	0.0500
	AKI, n (%)	20 (39.2)	10 (19.6)	0.0300
	Max BUN, mean	34.6	21.4	< 0.001
Outcomes				
	Length of stay, mean	14.51	6.118	< 0.001
	Discharge to home, n (%)	7 (13.7)	29 (56.9)	< 0.001
	Discharge to acute rehab, n (%)	30 (58.8)	46 (90.2)	0.029
	NIHSS score on discharge, mean	9.878	3.1	< 0.001
	mRS score on discharge, mean	4.216	2.725	< 0.001

Abbreviations: mRS, modified Rankin scale; NIHSS = National Institutes of Health Stroke Scale; ICH, intracranial hemorrhage; IVH, intraventricular hemorrhage; IV, intravenous; TPA, tissue plasminogen activator; WBC, white blood cell, AKI, acute kidney injury; BUN, blood urea nitrogen.

longer length of stay, lower likelihood of discharge to home or to acute inpatient rehabilitation, higher NIHSS score on discharge, and higher mRS on discharge (Table 3). While post-discharge follow-up data was available for fewer than half the patients, those who were delirious in the hospital had higher mean NIHSS scores compared to patients who were never delirious (7 and 2 ($p < 0.001$), respectively) and higher mean mRS scores (3.8 and 1.7 ($p < 0.001$), respectively). In patients who were administered cognitive testing (the Montreal Cognitive Assessment, MOCA) at time of follow up ($n = 19$), delirium was associated with lower scores compared with no delirium (mean, 15 and 21 ($p = 0.0341$), respectively).

Creation of the prediction model

Variables associated with the development of delirium are displayed in Table 3. In multivariable analysis, age greater than 64 years, presence of intraventricular hemorrhage (IVH), intubation, presence of acute kidney injury (AKI), and stroke with either cognitive deficit, neglect, or aphasia remained significant and were most strongly associated with delirium (Table 4). These variables were included in the final model. In a ROC analysis, the AUC for the model including these five variables was 0.90.

The following formulas, which utilize the coefficients generated in the regression analysis, can be used to calculate the probability of delirium in a given patient:

Table 4. *Variables included in logistic regression analysis.*

Variable	Odds Ratio	*p*	95% Confidence Interval
Presence of IVH	37.31	0.006	2.88−482.72
Presence of cognitive dysfunction, aphasia, or neglect	16.18	< 0.001	4.07−64.27
Presence of AKI	6.31	0.014	1.45−27.38
Age greater than 64 years	3.94	0.018	1.26−12.30
Intubation	3.86	0.049	1.00−14.83

Log Odds of Delirium = −3.621 + (1.370)(**Age > 64 years**) + (2.784)*(**Cognitive deficit/aphasia/neglect**) + (1.842)*(**AKI**) + (1.350)*(**Intubation**) + (3.619)*(**Presence of IVH**)*

Odds of Delirium = exp(log odds)
Probability = odds/(1+odds)

Validation of the model

Characteristics of the validation cohort are displayed in Table 1. Patients were similar to the model cohort with the exception of there being fewer patients with lacunar infarcts in the validation cohort, as well as more patients who presented with neglect, and who required intubation. The incidence of delirium was higher than that of the model cohort, with 70% of patients scoring positive on the CAM-ICU at least once during admission. Patients in the validation cohort who developed delirium had poor outcomes, similar to the model cohort. Using data from this unique cohort of patients, ROC analysis resulted in an AUC of 0.82.

Discussion

Our findings indicate that age greater than 64 years, presence of IVH, intubation, stroke with cognitive dysfunction, aphasia, or neglect, and presence of AKI, are strongly associated with the development of delirium in patients presenting with acute stroke. Using these variables, we were able to create a model that allowed for precise calculation of a patient's probability of developing delirium with an AUC of 0.90. We then validated this tool in a unique cohort of patients, with an AUC of 0.82. The aim of this study was to create a novel prediction model based on risk factors seen in our patient population that would be more generalizable to a western urban population. Given that the Oldenbeuving model was created in the Netherlands, we hypothesized there would be different risk factors, general and stroke-specific, in an urban population in the United States. We chose to look at a population of patients admitted to the ICU or step-down unit, as prior studies have shown that these patients are at high risk for delirium.

The variables included in our predictive model are routinely identified at the time of admission for stroke, and so are readily available and do not require extra work on the part of the providers gathering the data. There were other factors that were found to be predictive, but not used because they were most often noted later during hospitalization and so are less useful for predicting delirium early: presence of infection, PEG placement, development of seizures, and history of dementia. Similarly, Oldenbeuving et al. found that infection and history of cognitive decline were predictive of delirium, and used them in versions of their proposed models. History of cognitive decline was ultimately not included in their final model, given need for extra investigation and similar performance of the model with its removal. We also found that presence of infection could be removed from our model without loss of predictive performance.

Many of the risk factors found to be associated with post-stroke delirium in this study were similar to those identified in the Oldenbeuving study, including older age, infection, and baseline cognitive impairment. Their study also found greater NIHSS score and involvement of the entire anterior circulation to be positively associated with delirium, both of which likely reflect the same process as stroke presenting with either cognitive dysfunction, aphasia, or neglect in our study. Interestingly, stroke presenting with cognitive dysfunction (defined as incorrect answers to orientation questions, not due to a language deficit or impaired consciousness), aphasia, or neglect, was highly predictive of delirium with AUC of 0.76 in ROC analysis. There are several possible explanations for this finding. First, these particular deficits may simply reflect a greater stroke volume, compared to infarcts resulting in only motor or sensory symptoms which can be seen with lacunar disease. Aphasia and neglect arise from cortical damage that is often seen in partial or entire-territory MCA strokes, and we have seen a correlation between larger strokes and the development of delirium. A second possibility is that aphasia and neglect may precipitate delirium, due to impairment in interacting with others and with the environment, which itself can lead to further disorientation in time and space.

It is also possible that injury to certain brain regions resulting in cortical deficits relates directly to the pathophysiology of delirium. Prior studies have shown that impaired cortical blood flow in these patients preferentially affects areas similar to those involved in stroke with aphasia or neglect such as the inferior frontal or temporoparietal regions.[20,21] Cerebral hypoperfusion in delirious

patients has also been demonstrated in diffuse areas of cortex, and subcortical regions including the thalamus and caudate.[22,23] Other studies suggest that disruption of more global neural networks, including the default mode network, is most closely associated with delirium.[24,25] It is possible that an injury to any of the aforementioned regions lowers the threshold for the development of delirium. In our model cohort, delirium was associated with strokes involving the temporal and/or parietal lobes. Interestingly, the default mode network involves the region of the temporal-parietal junction. However, given that these associations were no longer significant with inclusion of either stroke volume or initial NIHSS score in multivariable regression analyses, we believe it is more likely that involvement of these areas simply reflects larger strokes.

Ischemic or hemorrhagic stroke may contribute to the pathophysiology of delirium in ways other than by affecting specific structures and connections. These may include the induction of inflammation, or creation of neurotransmitter imbalances and neuroendocrine abnormalities.[5] In addition, different types of delirium, such as hypoactive versus hyperactive, may result from disruptions of differing brain regions or mechanisms.[24,25] We did not collect data on delirium subtype for our study cohorts, or data regarding potential serum or CSF biomarkers. These remain important questions for future study.

There were some notable differences between our model population and our validation population. Overall, patients in the validation cohort had more severe strokes; there tended to be fewer lacunar infarcts in this group, and patients were more likely to have presented with neglect (there were significantly more right-sided strokes in the validation group, which probably explains the higher rate of neglect). They did not develop more medical complications (AKI and infection), but were more likely to be intubated, which may also reflect large and more severe strokes in this group. The rate of delirium as measured by the CAM-ICU was significantly higher in the validation cohort than in the model cohort, 70% and 50%, respectively, which likely results from the tendency of this group to present with more severe brain injury.

Our study was not without limitations. Like previous studies, we were faced with the problem of how to best define delirium. The CAM-ICU was chosen, both because it has been well-validated and is easy to administer. Unfortunately, as it is only utilized in the ICU and IMC settings at our institution, it limits the most robust detection of delirium to the early stage of stroke management. Prior studies have shown, however, both that delirium is common in the ICU setting and that it tends to develop in the first few days of hospitalization.[15–18,26–29] A study by Mitasova et al. revealed that in stroke patients who were diagnosed with delirium, the CAM-ICU was positive in the first day of admission in a majority (67.3%), and within 5 days of admission for 100%.[16] Patients in this study were similar to ours in that they were admitted to a stroke unit that included both ICU and step-down/IMC level of care. For these reasons, it is reasonable to focus the effort of predicting delirium on the intensive care setting.

We did analyze data from the entire cohort of 145 patients, which included patients not admitted to the ICU or IMC (Fig. 1). In reviewing this group, we evaluated other potential markers of delirium: physician assessment, use of restraints or medications, need for a patient safety attendant. We found that these markers correlated strongly with positive CAM-ICU, and identified few patients (only 8) in addition to the 102 patients with positive ICU assessments. For this reason, we feel that our approach captured a majority of the patients who were at highest risk of developing delirium.

Despite the limitations, we believe that we have developed a simple and effective tool to predict delirium in patients presenting acutely with stroke that is generalizable to diverse populations. Further studies are needed to determine if identifying patients early and intervening can mitigate the poor outcomes with which delirium is associated. From there, it may be possible to determine if delirium is the cause of these outcomes, or if it is simply a marker of susceptible individuals.

Declaration of Competing Interest

None.

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