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Early Prediction of Prognosis in Elderly Acute Stroke Patients

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Objectives: Acute stroke has a high morbidity and mortality in elderly population. Baseline confounding illnesses, initial clinical examination, and basic laboratory tests may impact prognostics. In this study, we aimed to establish a model for predicting in-hospital mortality based on clinical data available within 12 hours of hospital admission in elderly (≥ 65 age) patients who experienced stroke.

Design: Retrospective observational cohort study.

Setting: Academic comprehensive stroke center.

Patients: Elderly acute stroke patients–2005–2009 (n = 462), 2010–2012 (n = 122), and 2016–2017 (n = 123).

Interventions: None.

Measurements and Main Results: After institutional review board approval, we retrospectively queried elderly stroke patients' data from 2005 to 2009 (training dataset) to build a model to predict mortality. We designed a multivariable logistic regression model as a function of baseline severity of illness and laboratory tests, developed a nomogram, and applied it to patients from 2010 to 2012. Due to updated guidelines in 2013, we revalidated our model (2016–2017). The final model included stroke type (intracerebral hemorrhage vs ischemic stroke: odds ratio [95% CI] of 0.92 [0.50–1.68] and subarachnoid hemorrhage vs ischemic stroke: 1.0 [0.40–2.49]), year (1.01 [0.66–1.53]), age (1.78 [1.20–2.65] per 10 yr), smoking (8.0 [2.4–26.7]), mean arterial pressure less than 60 mm Hg (3.08 [1.67–5.67]), Glasgow Coma Scale (0.73 [0.66–0.80] per 1 point increment), WBC less than 11 K (0.31 [0.16–0.60]), creatinine (1.76 [1.17–2.64] for 2 vs 1), congestive heart failure (2.49 [1.06–5.82]), and warfarin (2.29 [1.17–4.47]). In summary, age, smoking, congestive heart failure, warfarin use, Glasgow Coma Scale, mean arterial pressure less than 60 mm Hg, admission WBC, and creatinine levels were independently associated with mortality in our training cohort. The model had internal area under the curve of 0.83 (0.79–0.89) after adjustment for over-fitting, indicating excellent discrimination. When applied to the test data from 2010 to 2012, the nomogram accurately predicted mortality with area under the curve of 0.79 (0.71–0.87) and scaled Brier's score of 0.17. Revalidation of the same model in the recent dataset from 2016 to 2017 confirmed accurate prediction with area under the curve of 0.83 (0.75–0.91) and scaled Brier's score of 0.27.

Conclusions: Baseline medical problems, clinical severity, and basic laboratory tests available within the first 12 hours of admission provided strong independent predictors of in-hospital mortality in elderly acute stroke patients. Our nomogram may guide interventions to improve acute care of stroke.

Key Words: elderly; hypotension; intracerebral hemorrhage; ischemic stroke; mortality; subarachnoid hemorrhage

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Institutional Review Board Approval Status: This study was approved by the Human Studies Committee of University of Louisville (institutional review board number 13.0396). Due to the retrospective nature of the study and because there was no reason for reporting individual person's data, informed consent was not required.

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Elderly population is defined as 65 years old and older. Recent data showed that the size of this age group has reached at 13.2% of U.S. population and expected to surpass 20% in the year

2030 (1). Impact of acute and critical care admissions remain a major concern in elderly patients (2–5). Several recent studies focused on older age, elderly' baseline medical history, and admission primary diagnoses' contribution to mortality in the acute care setting (6–8). Being informed about severity status of elderly in acute care setting may enable tailored decision-making and prevent mortality.

Stroke affects about 800,000 people per year in the United States, accounting for 1.7% of national health expenditures, and it is the fifth leading cause of death in the United States (9). Within the stroke types, about 87% are ischemic strokes (ISs), 10% intracerebral hemorrhages (ICHs), and 3% subarachnoid hemorrhages (SAHs) (10). These ratios are likely different in the elderly population, and severe stroke as well as hypertensive ICH are more common (11–15).

Assessment of real-time physiologic variables and the impact of baseline confounding medical problems on existing organ functionality were shown to be the most effective ways to measure acute severity status and form management plans (16). Several severity and prognostic assessment scales and models have been developed (17–23), but their complexity and lack of validation limit their clinical use. Therefore, we aimed to build and validate a real-time prognostic tool, which would allow us to predict the prognosis and mortality of our elderly acute stroke patients as early as in the first 12 hours of admission.

METHODS

Patients

After obtaining approval from the Human Studies Committee (institutional review board number 13.0396), we included patients aging 65 years old and older, who were diagnosed with stroke, and admitted between the years 2005–2009 (training dataset). In this retrospective observational cohort study, a recently extended definition of stroke was used, which included IS, ICH, and nontraumatic SAH (24). Study data were prospectively collected and stored in our clinical neuroscience database. The main dependent variables examined were patient disposition and mortality.

Our criteria for stroke patients' ICU admission are as follows: 1) patients who received IV tissue plasminogen activator therapy, 2) patients with large hemispheric strokes, 3) strokes with posterior fossa involvement, 4) SAHs, 5) intracranial hemorrhages, 6) hemodynamically unstable patients, 7) Glasgow Coma Scale (GCS) of less than 9, 8) intubated patients, 9) patients with difficult to control seizures, 10) patients requiring beat-to-beat blood pressure monitoring (requiring arterial catheter management), and 11) patients with decompensated congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD) exacerbation.

In this study, we decided not to include patients who died within the first 48 hours of admission because of the following reasons: 1) Elderly patients who don't survive for more than initial 48 hours generally suffer from a serious primary or secondary injury namely "not survivable" and 2) In our setting, these elderly patients typically are either extremely medically sick or in very severe coma state, which requires goals of care discussions to be activated to address patients' will or a priori verbal guidance to their power of attorney. Additionally, in this analysis study, we did not include patients who eventually went although "withdrawal of life support."

Protocol

We extracted a wide variety of patient data from the clinical database including demographic information, comorbidities, home medications, baseline hemodynamic variables, established severity-injury assessment scales, baseline laboratory values, and patients' survival outcomes including disposition details. Clinical data from the years 2005 to 2009 were used as the training dataset to establish the prediction model. We first explored the univariable relationship between predictors and in-hospital mortality. Predictors were assessed with a backward variable selection for their independent contribution to in-hospital mortality. A selected best prediction model (converted to a nomogram) built from this initial dataset (training dataset) was used to predict mortality for validation purposes in a newer "test" dataset from the years 2010 to 2012. Because of the stroke guidelines recently were updated (2013) (9), we performed a second validation step by applying our prediction model to more recent patients from the years 2016 to 2017.

Measurements

We considered the following variables for predicting in-hospital mortality: age, gender, primary diagnoses (IS, ICH, SAH), concurrent cardiac diseases (coronary artery disease [CAD]), myocardial infarction, hypertension, and CHF, diabetes, COPD, smoking (current smokers), admission GCS, Acute Physiology and Chronic Health Evaluation (APACHE) III, Sequential Organ Failure Assessment (SOFA) scores, complete blood count, comprehensive metabolic panel, and the hemodynamic and oxygenation variables from the first 12 hours of admission. Within the range of clinically relevant cutoff thresholds, blood pressure and total WBC count data were converted to categorical variables in order to elevate their contributions to severity-mortality assessment. Hypotension is defined as mean arterial pressure (MAP) less than 60 mm Hg. Leukocytosis defined as WBC greater than or equal to 11,000/mm^3. Home medications, specifically aspirin, warfarin, statins, and beta-blockers were considered in the analyses.

APACHE III (25) and SOFA scores (26) were used to assess the severity of illness in the first 12 hours of admission. The presedation (when/if sedation was required) GCS scores were used to evaluate the consciousness level of the patients.

Statistical Methods

Model Fitting. Our training dataset contained baseline data (within the first 12 hours of ICU admission) on 462 patients from the years 2005 to 2009. We fit a multivariable logistic regression model predicting in-hospital mortality as a function of the following potential predictors: age, stroke type, CHF, COPD, smoking, WBC ($\geq$ 11 K vs < 11 K), MAP less than 60 mm Hg, aspirin, statin, beta-blocker, warfarin, external ventricular drain, craniotomy requirements, GCS, temperature, creatinine, and glucose. Both linear and nonlinear forms of the continuous variables were considered. Backward variable selection was used, and the model with the best

Bayesian information criterion (BIC) was chosen. The model with the lowest BIC was the best fit, regardless of whether variables were statistically significant (i.e., independent of *p* values). Due to their anatomic-pathologic and treatment approach differences as well as time-based changes in management, we forced stroke type and admission year into the final model regardless of statistical significance. We also tested the interaction between stroke type and MAP on mortality. Internal discrimination was assessed with an optimism-corrected (by 10-fold cross-validation) *C*-statistic (area under the curve [AUC]). Internal calibration was assessed with a plot of observed versus expected mortality. A nomogram was constructed to display the final model.

Model Validation. Variable estimates from the training set model were applied to the test data from 2010 to 2012 ($n = 122$) to assess the ability of the model to predict mortality in new patients. We also validated the model on a newer dataset from 2016 to 2017 ($n = 123$). Discrimination was assessed with the *C*-statistic (AUC). Calibration was assessed with a plot of the observed versus the nomogram-predicted mortality probability and with the Hosmer-Lemeshow goodness of fit test of predicted versus observed event rate. Overall prediction was assessed with a Scaled Brier's score. Brier's score represents the square of the difference of the predictive ability found using the model compared with perfect predictability. Therefore, when the Brier's score is "0," this is the best case, and when it's "1," it represents the worst case.

With *n* equals to 462 patients and 108 events in the training dataset, we had sufficient data to allow appropriate fitting of a multivariable logistic regression model containing roughly 10 variables, based on the traditional rule of thumb of 10-events per variable for a logistic regression model.

RESULTS

A total of 462 elderly patients who were admitted to our neuroscience service for acute stroke diagnosis between 2005 and 2009 were included as the "training dataset." The first "test dataset" included 122 patients from 2010 to 2012, and second "test data" included 123 patients from 2016 to 2017. Overall, length of stay was a median (interquartile range [IQR]) of 12 days (7–19 d) for patients who survived and 6 days (4–11 d) for patients who died.

Of 584 stroke patients from 2005 to 2012, the admission National Institute of Health stroke scale (NIHSS) data for our elderly IS population (mean ± SD: 14.7 ± 8.4). The three stroke types of ICH ($n = 175$), IS ($n = 332$), and SAH ($n = 77$) did not differ significantly on baseline variables except for the percent with MAP less than 60 and WBC (≥ 11 K vs < 11 K) (**Appendix Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCX/A10). Of 332 patients with acute IS in the training dataset, the initial NIHSS mean (SD) was 13.4 (6.8) and baseline mRS was 4.7 (0.55). No difference was found among three types of strokes on initial NIHSS and baseline modified Rankin scale.

For 2016–2017 testing data, NIHSS data for our elderly IS population (mean ± SD: 14±8), the Hunt-Hess scale for the SAH patients (median ± IQR: 2 [2–4.5]), and the ICH score for the ICH patients (median ± IQR: 2 [1–3]).

First, we assessed the univariable association between mortality and demographics, diagnoses, baseline laboratory results, and severity of illness scores (**Table 1**). Age was 76 ± 7 and 79 ± 7 years for survivors and nonsurvivors, respectively ($p = 0.012$). The majority of patients had hypertension, CAD, and diabetes. A higher current smoker population was noted in the nonsurvivor (14%) compared with survivor group (7%) ($p = 0.049$). Baseline use of aspirin, statins, beta-blockers, and craniotomy requirements were not different between the survivor and nonsurvivors. The use of warfarin was higher in nonsurvivors (15% vs 29%; $p = 0.0029$) (Table 1).

Reasons of mortality were reported in the majority of the cases. Neurologic problems were the cause 63% of the time, and medical problems 29% of the time. Within the neurologic reasons, most common ones were the primary diagnosis (35%) and hemorrhagic transformation (18%). In the mean time, cardiac complications (10%) and sepsis (10%) were the most common medical reasons. (**Appendix Table 3**, Supplemental Digital Content 1, http://links.lww.com/CCX/A10)

Severity Assessment Scales

Compared with the nonsurvivors, survivors had higher means of GCS (12 ± 3 vs 9 ± 4; $p < 0.001$), lower APACHE III (41 ±13 vs 51 ± 17; $p < 0.001$), and SOFA score values (3.3 ± 2 vs 5.5 ± 2; $p < 0.001$).

Laboratory Variables

WBC was lower in survivors, 13/mm^3 ± 5 in the survivor group versus 16 ± 14 in the nonsurvivors ($p < 0.001$). Higher maximum glucose levels were noted in the nonsurvivor group (168 ± 54 vs 147 ± 54; $p < 0.001$).

Training Data Versus Test Data

Compared with the "training data," patients in the 2010–2012 "test data" were slightly younger ($p = 0.03$), less likely to have ICH and more SAH ($p < 0.001$), to have more CHF ($p = 0.008$), COPD ($p = 0.02$), smoking ($p < 0.001$), and less hypotension ($p = 0.007$). GCS scores were lower in the test dataset, which possibly contributed to higher mortality in the "test dataset" ($p < 0.001$). Compared with the training dataset, patients in the 2016–2017 had higher rates of ICH and smoking history ($p < 0.001$), but lower rates of IS ($p < 0.001$), higher rate of WBC greater than or equal to 11 K/uL ($p < 0.001$) (**Table 2**).

Model Development and Validation

Our final multivariable model for predicting mortality from the "training set" included stroke type (ICH vs IS: odds ratio [95% CI] of 0.92 [0.50–1.68] and SAH vs IS: 1.0 [0.40–2.49]), hospital admission year (1.01 [0.66–1.53]), age (1.78 [1.20–2.65] per 10 yr), smoking (8.0 [2.39–26.7]), MAP less than 60 mm Hg (3.08 [1.67–5.67]), GCS (0.73 [0.66–0.80] per 1 point increment), WBC less than 11 K (0.31 [0.16–0.60]), creatinine (1.76 [1.17–2.64] comparing 2 vs 1), CHF (2.49 [1.06–5.82]), and warfarin use (2.29 [1.17–4.47]) (**Table 3** and **Fig. 1**; and **Appendix Table 2**, Supplemental Digital Content 1, http://links.lww.com/CCX/A10). The fitted model is acceptable with Hosmer-Lemeshow goodness of fit ($p = 0.99$).

TABLE 1. Baseline Characteristics of Training Data 2005–2009 Stratified by Primary Outcome of In-Hospital Survivor Status (*n* = 462)

Factor	Survivors (*n* = 354)	Nonsurvivor (*n* = 108)	*p*
Age, yr	76 ± 7[a]	79 ± 7[b]	0.0012
Male	180 (51)	56 (52)	0.86
Stroke type			0.71
Intracerebral hemorrhage	114 (32)	39 (36)	
Ischemic stroke	201 (57)	59 (55)	
Subarachnoid hemorrhage	39 (11)	10 (9)	
Admission year			0.90
2005	64 (18)	22 (20)	
2006	51 (14)	19 (18)	
2007	86 (24)	17 (16)	
2008	81 (23)	25 (23)	
2009	72 (20)	25 (23)	
Hypertension	154 (44)	47 (44)	0.99
Coronary artery disease with history of myocardial infarction	77 (22)	22 (20)	0.76
Congestive heart failure	59 (17)	15 (14)	0.039
Diabetes	29 (8)	10 (9)	0.49
Chronic obstructive pulmonary disease	15 (4)	10 (9)	0.73
Smoking history	26 (7)	15 (14)	0.049
Aspirin use	90 (25)	29 (27)	0.77
Statin use	83 (23)	21 (19)	0.38
Beta-blocker use	115 (32)	36 (33)	0.87
Warfarin	52 (15)[c]	31 (29)[d]	0.0029
External ventricular drain	32 (9)	14 (13)	0.32
Craniotomy	35 (10)	13 (12)	0.55
Glasgow Coma Scale	12 ± 3[e]	9 ± 4[f]	< 0.001
Acute Physiology and Chronic Health Evaluation III	41 ± 13	51 ± 17	< 0.001
Sequential Organ Failure Assessment score	3.3 ± 2	5.4 ± 2[g]	< 0.001
Maximum core temperature (°F)	99.4 ± 1	100.2 ± 2	< 0.001
Mean arterial pressure < 60 mm Hg	54 (15)[f]	45 (42)[g]	< 0.001
WBC (Thou/mm^3)	13 ± 5	16 ± 14	< 0.001
WBC (≥ 11 vs < 11)	195 (56)[c]	84 (78)	0.003
Creatinine (mg/dL)	1.1 ± 0.97[c]	1.3 ± 0.96[c]	0.13
Glucose (mg/dL)	147 ± 54[a]	168 ± 54[h]	< 0.001

[a]Missing data = 5.
[b]Missing data = 1.
[c]Missing data = 3.
[d]Missing data = 2.
[e]Missing data = 15.
[f]Missing data = 6.
[g]Missing data = 1.
[h]Missing data = 9.
p value is from the univariable logistic regression.
Data represented as mean ± SD or *n* (%).

TABLE 2. Baseline Patient Characteristics of Training and Test Datasets

Predictor	Training Set ($n = 462$)	2010–2012 Test Set ($n = 122$)	p[a]	2016–2017 Test Set ($n = 123$)[b]	p[a]
Age, yr	77 ± 7[c]	75 ± 8	0.03	76 ± 9	0.45
Stroke type			< 0.001		< 0.001
Intracerebral hemorrhage	153 (33)	22 (18)		76 (62)	
Ischemic stroke	260 (56)	72 (59)		33 (27)	
Subarachnoid hemorrhage	49 (11)	28 (23)		14 (11)	
Congestive heart failure	41 (9)	21 (17)	0.008	16 (13)	0.17
Chronic obstructive pulmonary disease	39 (8)	19 (16)	0.02		
Smoking history	25 (5)	27 (22)	< 0.001	28 (23)	< 0.001
WBC (≥ 11 vs < 11)	279 (61)	82 (67)	0.19	45 (37)	< 0.001
Mean arterial pressure < 60 mm Hg	99 (21)	13 (11)	0.007	27 (22)	0.90
Aspirin use	119 (26)	36 (30)	0.40		
Statin use	104 (23)	33 (27)	0.29		
Beta-blocker use	151 (33)	34 (28)	0.31		
Warfarin	83 (18)[d]	18 (15)	0.38	22 (18)	0.94
External ventricular drain	46 (10)[d]	17 (14)	0.22		
Craniotomy	48 (11)[d]	15 (12)	0.57		
Glasgow Coma Scale	11 ± 3[e]	10 ± 3	< 0.001	11 ± 4	0.97
Max core temperature (°F)	99.7 ± 1[f]	99.6 ± 1	0.47		
Creatinine (mg/dL)	1.2 ± 0.97[g]	1.0 ± 0.58	0.09		
Glucose (mg/dL)	152 ± 55[d]	149 ± 47[h]	0.56		
Mortality	108 (23)	50 (41)	< 0.001	38 (31)	0.09

[a]*t* test for continuous predictors and χ^2 test for categorical predictors.
[b]Only collected risk factors, which were included in the final fitted model.
[c]Missing data = 6.
[d]Missing data = 5.
[e]Missing data = 21.
[f]Missing data = 10.
[g]Missing data = 3.
[h]Missing data = 1.
Data represented as mean ± SD or *n* (%).

Nomogram

Based on the final prediction model, we constructed a nomogram. Each variable corresponds to a particular point system. The total added points across variables correspond to a predicted probability of mortality. Internal AUC (95% CI) in the "training set" was 0.83(0.78–0.89) after adjustment for over-fitting, indicating excellent discrimination.

In a sensitivity analysis, we replaced the five factors comprising the APACHE III score with the APACHE III score itself. The AUC decreased from 0.83 to 0.73, a substantial loss of discrimination. As well, when we replaced the three SOFA components with the SOFA score itself, the AUC was reduced from 0.83 to 0.79. This justifies our consideration of the components of these scores instead of only the scores.

When the model was applied to the 2010–2012 "test data," the AUC was 0.79 (0.71–0.87), still good discrimination, and the scaled Brier's score was 0.17 (**Fig. 2**). However, calibration on the "test data" was poor (over-prediction), especially for predicted probabilities less than 0.40 with Hosmer-Lemeshow goodness of fit ($p = 0.017$), rejecting the null hypothesis of a "good fit."

For the 2016–2017 "test data," the results were consistent with that of the 2010–2012 "test data," indicating the model was robust. The AUC was 0.83 (0.75–0.91) and scaled Brier's score was 0.27 (Fig. 2). Calibration on the 2016–2017 "test data" appeared better

TABLE 3. Odds Ratios From Final Model Based on Training data ($n = 462$)[a]

Predictor Variables	OR (95% CI)	*p*
Stroke type		0.96
Intracerebral hemorrhage	0.92 (0.50–1.68)	
Subarachnoid hemorrhage	1.0 (0.40–2.49)	
Ischemic stroke	Reference = 1	
Admission year (2-yr increment)	1.01 (0.66–1.53)	0.96
Age (10-yr increment)	1.78 (1.20–2.65)	0.0045
Glasgow Coma Scale (1-point increment)	0.73 (0.66–0.80)	< 0.001
Creatinine[b] (e.g., 2.0 vs 1.0)	1.76 (1.17–2.64)	0.0065
Congestive heart failure (yes vs no)	2.49 (1.06–5.82)	0.036
Current smoking (yes vs no)	8.0 (2.39–26.7)	< 0.001
Mean arterial pressure (< 60 vs ≥ 60 mm Hg)	3.08 (1.67–5.67)	< 0.001
Warfarin (yes vs no)	2.29 (1.17–4.47)	0.015
WBC (≤ 11 K vs > 11 K)	0.31 (0.16–0.60)	< 0.001

OR = odds ratio.

[a]Multivariable logistic regression model on $n = 462$ patients in learning dataset.

[b]Creatinine was modeled as log2 (creatinine), so this odds ratio refers to doubling in creatinine.

than the earlier data, showing observed values closer to predicted values (45-degree line), but with Hosmer-Lemeshow goodness of fit ($p = 0.015$) still suggests lack of "good fit."

DISCUSSION

The model built to assess in-hospital mortality of elderly acutely ill stroke patients provided a good to excellent discrimination in both the "training dataset" and the two "test validation datasets." Because the predictions are obtained from individual patient characteristics assessed/measured within the first 12 hours of hospital admission, model's prognostic importance and therapeutic potential for modifiable factors are noteworthy. Overall, the area under the receiver operating characteristic curve (0.79–0.83) showed acceptable to good discriminative ability, suggesting that the sensitivity and specificity of the model appear robust enough to be an aid in clinical judgment of acute stroke patients. The utility of this nomogram is to identify the sickest elderly stroke patients as early as within the few hours of admission. Implementing nomogram to the electronic medical record may provide additional severity trigger alerts to the stroke teams. Alerting stroke teams early to focus on potentially modifiable risk factors may help to prevent further progression of this high-risk patient population. Additionally, this prediction tool may further help providing patient-centered prognostics information to the surrogates.

Overall, the mortality rate of our patients was about 28%, which is comparable with other studies for the range and sickness levels (6). Mortality of IS is generally around ~10% (9), but in acutely ill IS patients, this rate may increase to 20–25% (27). For ICH, mortality is generally higher and ranges between 30% and 48% (28, 29). Mortality for SAH ranges between 27% and 44% (30). In a recent study, Rincon et al (31) reported expectedly high mortality rates for critically ill and ventilated IS (48%), ICH (59%), and SAH (44%) patients. In this cohort of elderly stroke patients, we did not find any statistically sound contribution of stroke type to the mortality. Possibly, major mortality reasons such as acute illness severity, coma, hypotension, decompensated CHF, and advanced age may have masked the specific contribution of different etiologies of stroke.

In our study, presence of hypotension, defined as MAP less than 60 mm Hg within the first 12-hour of admission, was associated with increased mortality. Such association is more evident in neurologically impaired elderly patients wherein the cerebral perfusion pressure altered by lowered MAP (32–35). Considering majority of IS patients are hypertensive at baseline, MAP less than 60 mm Hg is likely to compromise cerebral perfusion. Due to impaired cerebral autoregulation, penumbra tissue perfusion becomes directly pressure dependent, and hypotension may drastically compromise blood flow, which may result in larger strokes (32–34). Significant portion of ICH and SAH patients are also hypertensive at baseline, and relative decreases in blood pressure may compromise perfusion of other vital organs such as heart and kidneys. Poor physiologic adaptation during stress may further risk elderly patients' chances to prevent secondary injuries (36). Cardiac issues and sepsis were the two most common medical mortality reasons of our patient population, and possibly hypotension may have contributed to both. However, it should be noted that our low-frequency blood pressure data sampling might have resulted an exaggerated contribution of hypotension to our prediction model.

Persistent leukocytosis correlates with poor functional outcomes especially for IS and SAH patients (37, 38). Although more prominent in SAH, stroke patient is prone to develop systemic inflammatory response due to progressing injury. WBC count is an important component of the severity assessment scores including APACHE and SAPS (25, 39). Although WBC alone can neither serve as the sole diagnostic step for infections nor trigger empiric antibiotic treatment, they do serve as a critical step in various infection diagnostic tools such as clinical pulmonary infection score and Centers for Disease Control and Prevention pneumonia criteria (40, 41).

Heart failure can predispose patients to cardiac thromboembolism. Additionally, low ejection fraction per se may result in chronic cerebral hypoperfusion (42, 43). American College of Cardiology/American Heart Association recommends evidence-based therapy for CHF to be individualized for elderly patients (43). Because elderly stroke patients are more vulnerable to CHF, immediate management according to the current guidelines may further decrease mortality (42).

Some factors in the nomogram, which contributed to patient mortality, were not modifiable upon admission such as GCS. Although each stroke type has its own established neurologic assessment score (e.g., NIHSS for IS) (44), GCS is universally one of the most commonly used neurologic assessment tools and takes an important part in severity assessment tools like

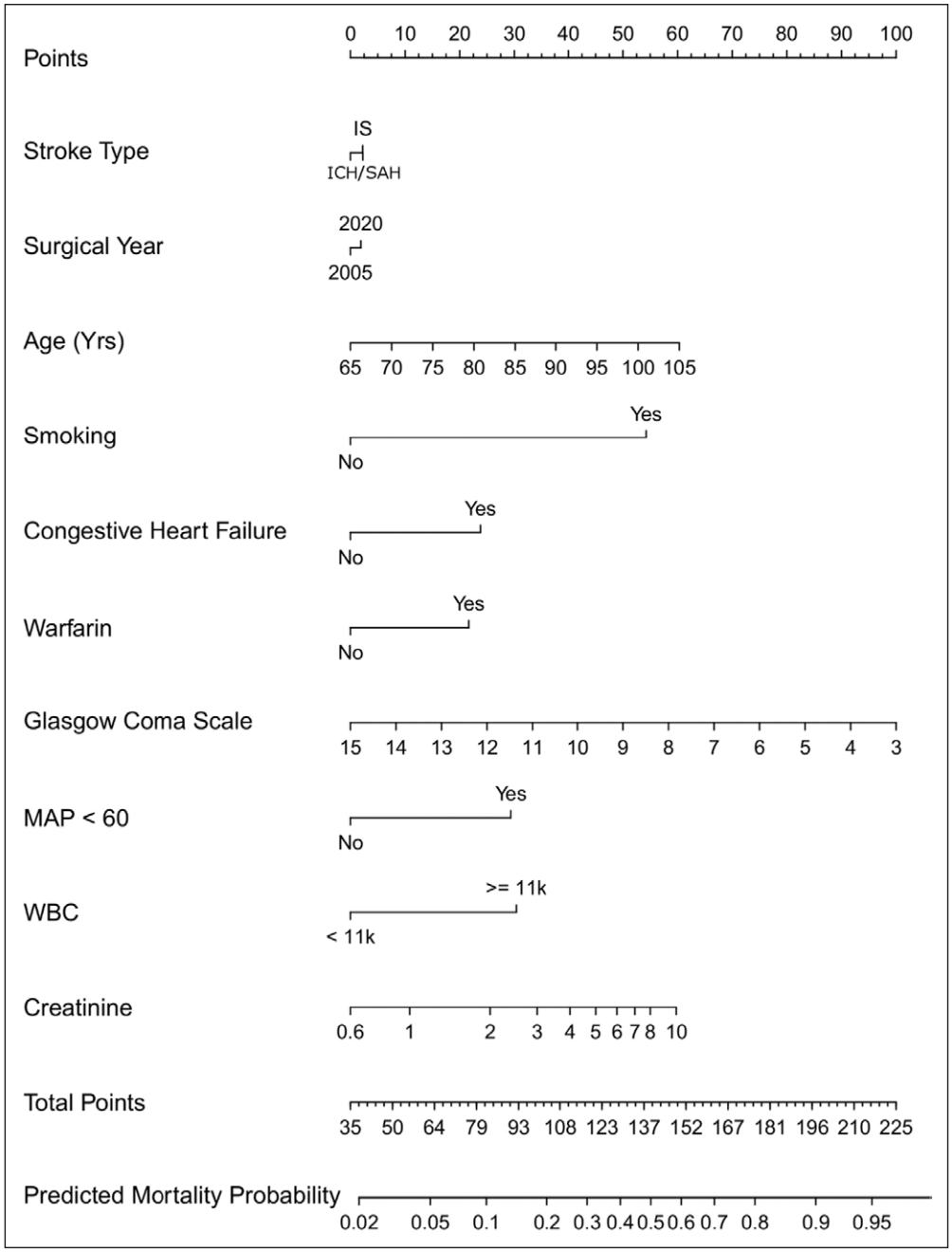

Figure 1. Nomogram for predicting in-hospital mortality. This nomogram tool is a direct representation of our multivariable model given in Table 3 and meant for clinician use for predicting in-hospital mortality for individual patients. The concordance index for the model from evaluation on the external validation dataset is 0.79. (Instructions on how to use the nomogram: For a given patient profile, each predictor value is first used to locate the position on the predictor scale. Each scale position has a corresponding prognostic point (0–100) on the top "Points" scale. The prognostic points from each predictor are summed to obtain a total point value. The total points are then located at the Total Points scale (second from the bottom). Finally, the corresponding predicted mortality probability is determined by drawing a vertical line down from the total points scale to the Predicted Mortality Probability scale [the bottom scale]). ICH = intracerebral hemorrhage, IS = ischemic stroke, MAP = mean arterial pressure, SAH = subarachnoid hemorrhage.

APACHE and SOFA (25, 26). Although emphasizing GCS' role in poor prognostics, it needs to be noted that interpretation of this scale is limited when patients are intubated and sedated, or intoxicated (23, 45).

Creatinine levels in elderly patients are associated with increased mortality (26, 46). Interesting finding of our study is creatinine levels' association with mortality appears to start even within clinically established normal range. Therefore, renal functions need to be closely watched in elderly stroke population. One needs to avoid under hydration, hypotension, contrast requiring radiological assessments, and use of nonsteroidal anti-inflammatory agents (47).

Warfarin use at baseline was found to be associated with mortality. Such association was likely related to the bleeding risk due to warfarin. Similarly, active smoking's contribution to mortality is also through many indirect mechanisms. Although the association found between active smoking and mortality in elderly acutely ill stroke patients is unsurprising, it is likely that this contribution depends on organ-system damage caused by years of exposure. Notably, neither warfarin nor smoking status is immediately modifiable to influence hard outcomes.

Although we did not find an association between stroke type and mortality, inclusion of all stroke types in the same pool of analysis, and disregarding their different pathology is a limitation of this study. Management of ICH and SAH have many differences compared with acute IS including details in blood pressure management (48–50). Management of acute hypertension is possibly the most important treatment of the ICH (51). Also, there are different blood pressure management recommendations within the acute IS patients depending on whether they are treated with fibrinolytic therapy or they have large-vessel occlusion (9, 52).

Overall, there are important limitations of this study as follows: 1) retrospective design, 2) being a single-center study, 3) having no a priori sample-size estimate, 4) using low-frequency data collection for some variables (e.g., MAP), and finally 5) using short-term outcomes (i.e., in-hospital mortality). Additionally, the number of modifiable risk factors may appear as a limitation.

Although the fitted model from the training dataset was acceptable (the Hosmer-Lemeshow test $p = 0.99$), the Hosmer-Lemeshow

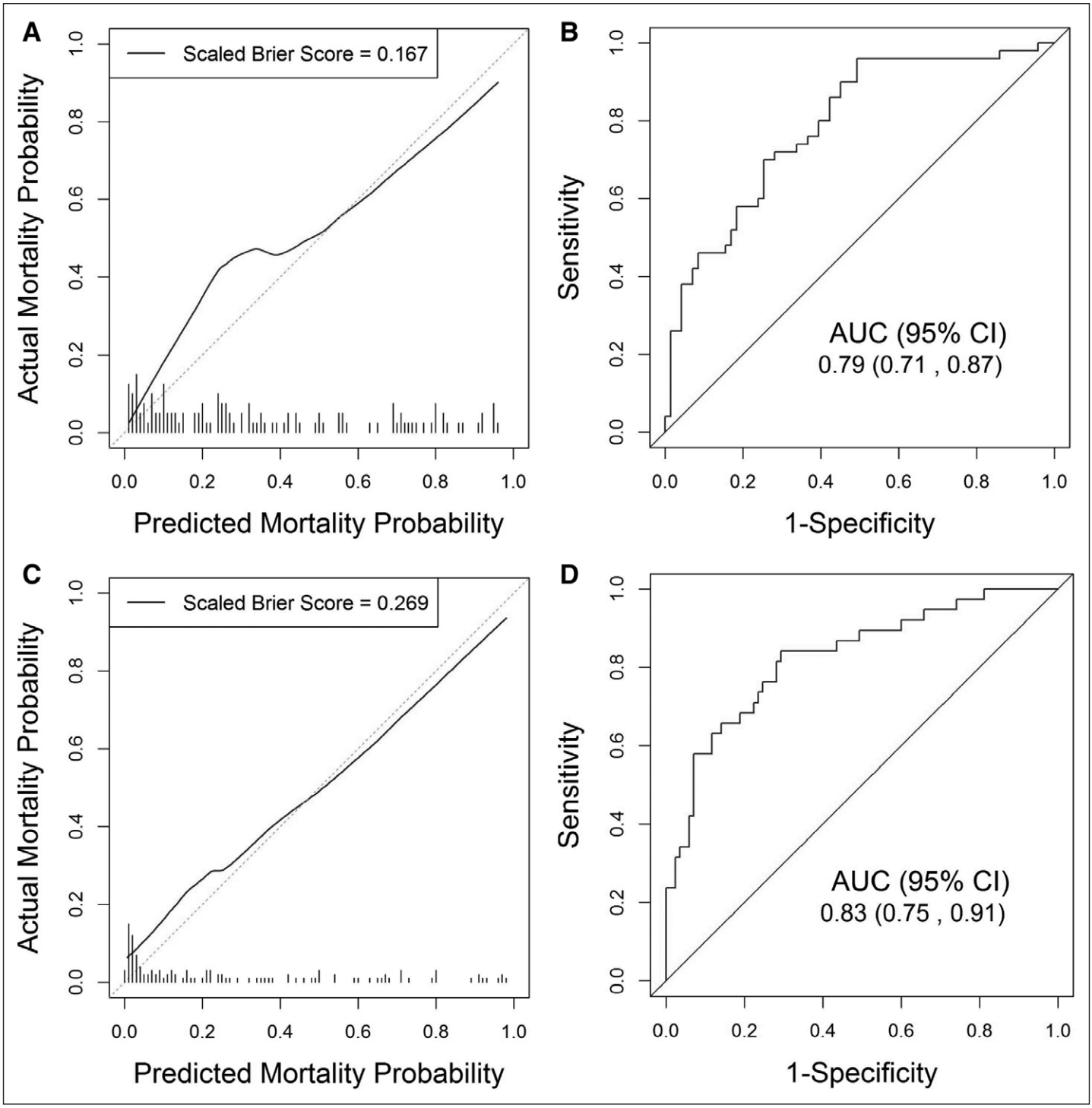

Figure 2. Calibration and receiver operating characteristic (ROC) curves. **A**, Calibration curve on 2010–2012 test data based on final model (Table 3). Models show moderate to good calibration, with smoothed curve of observed data fairly close to predicted values (45-degree line), and with Brier score of 0.17. **B**, ROC curve analysis on 2010–2012 test data based on final model (Table 3). Plot shows very good discriminant ability of the model, with area under the curve (AUC) of 0.79 on the test data. Internal AUC (95% CI) in the training set was 0.83 (0.78–0.89) after adjustment for over-fitting, indicating excellent discrimination. **C**, Calibration curve on 2016–2017 test data based on final model (Table 3). Model shows moderate to good calibration, with smoothed curve of observed data fairly close to predicted values (45-degree line), and with Brier score of 0.27. **D**, ROC curve analysis on 2016–2017 test data based on final model (Table 3). Plot shows excellent discriminant ability of the model, with AUC of 0.83 (95% CI, 0.75–0.91) on the test data.

test for both testing datasets suggested poor fit. Possible reasons include small testing datasets, and the population changing over time compared with the training dataset. In spite of its shortcomings, our model maintained very good discrimination in repeated validation cohorts over time. The variables in the nomogram can be readily obtained, even as short as in the first hour of hospital admission. Therefore, the availability of such tool would help identification of high-risk population and enhance preventive strategies.

Our early prediction model for in-hospital mortality of elderly, acutely ill stroke patients resulted in a very good discrimination and calibration when applied to more recent data. Further validation of our prediction model in different stroke types at different medical centers and finding timely applicable acute care protocols to modify treatable medical conditions are our goals for future research.

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