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A prediction model of brain edema after endovascular treatment in patients with acute ischemic stroke

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ABSTRACT

Background: Clinical tools predicting brain edema after reperfusion therapy in acute ischemic stroke are scarce. We aim to develop a nomogram model to predict brain edema within the first 24 h after endovascular treatment (EVT) in the anterior cerebral circulation.

Methods: A total of 199 patients were retrospectively identified in a single-center stroke registry. Brain edema was measured by midline shift (MLS). The associations between MLS and early neurologic outcomes were described. A nomogram predicting MLS was developed and internally validated. The nomogram was also compared with an available model using the area under the receiver operating characteristic curve (AUC) and decision curve analyses.

Results: Overall, 87 patients (43.7%) had MLS. The patients with MLS ≥ 6 mm showed progressive neurological deterioration according to repeated measures analysis of variance. Each millimeter increase in MLS was strongly correlated with the presence of in-hospital death or forgoing treatment (Spearman's rho = 0.429, $P < .001$). Patients with brain edema were less likely to have functional independence at 3 months (19.5% vs. 46.8%, $P < .001$). A nomogram model including 24-h CT ASPECT scores and cisternal effacement, hypertension and complete recanalization showed a C-index of 0.874. This tool exhibited a higher AUC and higher net benefit than the available model.

Conclusions: This study showed a profound association between MLS and early neurologic outcomes. A nomogram model was developed to predict patients at risk of brain edema after EVT in the anterior cerebral circulation.

1. Introduction

Brain edema is a well-described complication following large vessel occlusion in ischemic stroke. Brain edema peaks 2 to 5 days after stroke onset and can be particularly devastating, leading to secondary neurological deterioration and death. Although endovascular treatment (EVT) for proximal vessel occlusion in the anterior cerebral circulation has shown overwhelming efficacy in selected patients, subsequent brain edema is still a common complication [1,2].

Recent post hoc analyses of the EPITHET and MR RESCUE cohorts have indicated that modest improvement in reperfusion may reduce mass effects [3]. Despite this demonstrated benefit, brain edema has still been present in approximately half of EVT cases, neutralizing the beneficial effect of EVT on functional outcome [4]. Therefore, identifying the risk factors that mediate postoperative brain edema is critical, and may help refine the appropriate perioperative management.

Known risk factors for the development of brain edema after EVT include admission stroke severity as measured by the National Institutes of Health Stroke Scale (NIHSS), baseline Alberta Stroke Programme Early CT (ASPECT) score, recanalization status, collateral score and extent of contrast enhancement on postoperative noncontrast CT scans [4–6]. However, individual variables have limited predictive accuracy, and a multivariate risk prediction tool based on demographic, clinical and neuroimaging features can be more practical [7]. A prediction model named the TURN score has been used to predict 24-h cerebral edema after IV thrombolysis with an AUC value of 0.69 [8], but to our knowledge, at present, there has been no such model put forth that can aid in the prompt early identification of patients at risk for brain edema after EVT.

The purpose of this study was to develop a nomogram based on clinical and neuroimaging features that can aid in triaging brain edema patients within the first 24 h after EVT in acute anterior-circulation

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ischemic stroke.

2. Methods

2.1. Participants

Consecutive subjects who underwent EVT in the anterior cerebral circulation according to a prospective Nanjing First Hospital Stroke (NFHS) Registry were identified [9]. This single-center NFHS Registry is affiliated with the Chinese Stroke Association, and it includes consecutive patients with acute ischemic stroke who had undergone reperfusion therapy since 2015. Participants were patients with at least a 24-h follow-up noncontrast computed tomography (NCCT) scan after EVT from May 2015 to June 2018. Patients who progressed to hemicraniectomy were not excluded because this procedure was performed after the 24-h scan. In these cases, brain edema was measured with an early NCCT scan before the surgical procedure. The institutional review board at Nanjing First Hospital approved this study.

2.2. Medical history

Data on demographics and clinical factors regarding the index event were extracted from the NFHS registry database. Basic information of age, sex, and comorbidities was recorded. In addition, the prestroke modified Rankin scale and stroke severity (National Institutes of Health Stroke Scale, NIHSS score) scores were measured on admission, and after 24 h, 72 h and 7 days.

2.3. EVT procedure

The EVT procedure included mechanical thrombectomy as well as emergent carotid/middle cerebral artery stenting. This procedure was performed within 6 h of witnessed stroke onset, and in the unwitnessed stroke patients, those who showed perfusion-diffusion mismatch would be considered for EVT. The exact number of retrieval attempts was recorded. The door-to-puncture time (DPT), the intervals between the time of last known normal and puncture, and between the first observation of symptoms and puncture were calculated. The recanalization status was assessed after EVT by H.S. who was blinded to the clinical information. This assessment was based on the modified Thrombolysis in Cerebral Infarction (mTICI), and complete recanalization was defined as mTICI-3.

2.4. Neuroimaging examination

Whole-brain NCCT scans (5-mm slice thickness, field of view 218 × 218 mm, 120 kV, and 320 mA) were acquired on a 16-multi-detector CT scanner (Siemens, Erlangen, Germany). Scans were performed immediately after the EVT procedure, at 24 h, and at any time when neurological deterioration occurred after EVT. All neuroimaging measurements were generated by readers blinded to the clinical data.

Brain edema was measured by midline shift (MLS) as the horizontal septum pellucidum displacement on the follow-up CT scans [10]. By using the built-in software, a straight midline was drawn between the anterior and posterior attachment of the falx cerebri. The presence of MLS was defined as any deviation of midline structures. It was determined by 2 readers (X.C. and Q.H.) with an interrater reliability (κ value) of 0.876. In addition, MLS was also quantified as the maximal deviation of the septum pellucidum from the midline by X.C. (the intrarater agreement measured by intraclass correlation coefficient was 0.891, tested by 10% randomly selected scans read by the same rater who was blinded to the previous rating scores).

We assessed the ASPECT score, cisternal effacement and any hyperdensity on the 24-h follow-up NCCT. ASPECT is a 10-point semi-quantitative system used to estimate the infarct size after an anterior circulation ischemic stroke, with one point subtracted for one area of

Table 1
Comparison of characteristics in patients with and without midline shift.

Characteristics	Patients without MLS (*n* = 112)	Patients with MLS (*n* = 87)	*P* value
Demography			
Age (years)	70.3 ± 13.0	73.7 ± 10.3	0.047
Sex (female)	42 (37.5%)	34 (39.1%)	0.820
Comorbidities			
Hypertension	76 (67.9%)	72 (82.8%)	0.017
Diabetes mellitus	26 (23.2%)	14 (16.1%)	0.214
Atrial fibrillation	43 (38.4%)	46 (52.9%)	0.042
Previous stroke/TIA	23 (56.1%)	18 (43.9%)	0.979
Prestroke mRS score ≤ 2	105 (94.6%)	81 (95.3%)	0.548
Admission NIHSS score	13.7 ± 5.9	17.3 ± 5.8	< 0.001
Blood test			
FBG (mmol/l)	6.2 (5.0–7.6)	7.2 (6.1–8.5)	0.001
TC (mmol/l)	3.8 (3.4–4.5)	4.1 (3.4–4.8)	0.308
LDL-c (mmol/l)	2.4 ± 0.8	2.5 ± 0.8	0.577
Hs-CRP (ug/ml)	6.1 (3.0–10.5)	8.4 (3.4–13.6)	0.091
Lp-PLA2 (ng/ml)	208.3 (135.5–386.5)	308.8 (163.7–412.0)	0.066
Use of intravenous alteplase	58 (51.8%)	47 (54.0%)	0.754
Evaluation of baseline noncontrast CT			
ASPECT score	9 (8–10)	9 (7–10)	0.004
Effacement	6 (5.4%)	21 (24.1%)	< 0.001
Occlusion site			0.310
Intracranial ICA	41 (36.6%)	40 (46.0%)	
The first segment of MCA	65 (58.0%)	41 (47.1%)	
The second segment of MCA	6 (5.4%)	6 (6.9%)	
Endovascular treatment procedure			
Emergent stenting	17 (15.9%)	3 (3.7%)	0.007
Number of retrieval attempts	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.041
Complete recanalization	77 (68.8%)	34 (39.1%)	< 0.001
Time interval before puncture			
Last known normal	258.5 (197.8–398.3)	240.0 (169.0–366.5)	0.159
First observation of symptoms	233.5 (185.0–327.3)	225.0 (162.5–290.0)	0.231
Door-to-puncture time	119.0 (89.0–142.0)	110.0 (85.0–148.0)	0.694
Evaluation of 24-h noncontrast CT			
ASPECT score	8 (8–9)	5 (3–7)	< 0.001
Effacement	18 (16.1%)	62 (71.3%)	< 0.001
Type of hyperdensity[c]			< 0.001
Contrast enhancement	34 (30.4%)	14 (16.1%)	
HI1	21 (18.8%)	19 (21.8%)	
HI2	14 (12.5%)	13 (14.9%)	
PH1	3 (2.7%)	10 (11.5%)	
PH2	0	15 (17.2%)	
Hemicraniectomy	1 (0.9%)	8 (9.5%)	0.005
Door-to-MLS days	4.0 (1.0–9.8)	2.0 (1.0–4.0)	0.032
TURN score	−3.2 ± 0.7	−2.8 ± 0.7	< 0.001
mRS 0–2 at 90 days	51 (46.8%)[a]	16 (19.5%)[b]	< 0.001

Data are expressed as the number, number (%), mean (SD), or median (IQR). Abbreviations: TIA = transient ischemic stroke; mRS = modified Rankin scale; NIHSS = National Institute of Health Stroke scale; FBG = fasting blood glucose; HbA1c = hemoglobin A1c; TC = total cholesterol; LDL-c = low-density lipoprotein cholesterol; Hs-CRP = hypersensitive C-reactive protein; Lp-PLA2 = lipoprotein-associated phospholipase A2; ICA = internal carotid artery; MCA = middle cerebral artery; ASPECT = Alberta Stroke Programme Early CT; mRS = modified Rankin scale.

[a] 3 patients were lost to follow-up.
[b] 5 patients were lost to follow-up.
[c] Hemorrhage classification according to ECASS-2 criteria.

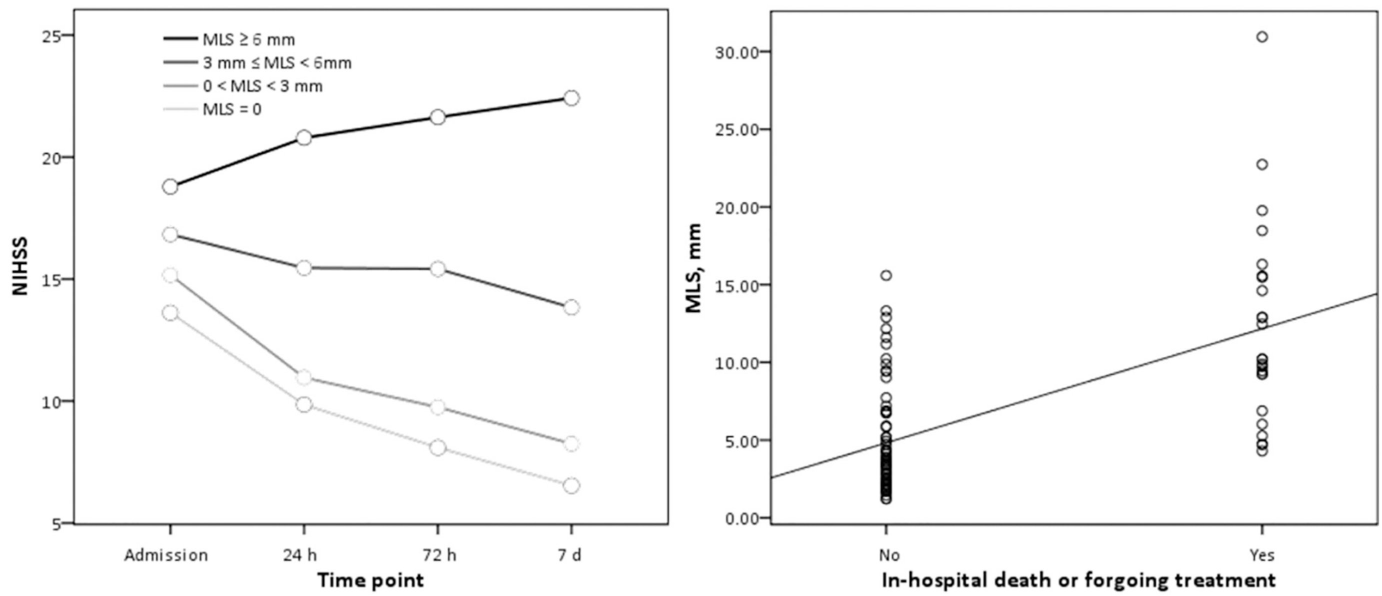

Fig. 1. Midline shift and short-term effects.

Table 2
Predictors associated with midline shift according to multivariate logistic regression (model adjusted for age, sex, atrial fibrillation, admission NIHSS score, fasting blood glucose, hypersensitive C-reactive protein, lipoprotein-associated phospholipase A2, emergent stenting, number of retrieval attempts, ASPECT score, effacement on the baseline noncontrast CT, and type of hyperdensity on 24-h noncontrast CT).

Risk factors	Odds ratio	95% Confidence interval	*P* value
ASPECT score	0.448	0.299–0.671	< 0.001
Effacement	4.372	1.291–14.809	0.018
Hypertension	3.585	1.007–12.758	0.049
Recanalization	0.180	0.059–0.552	0.003

early ischemic change [11]. Cisternal effacement was recorded according to the presence of narrowing of the basal cisterns [12]. The type of hyperdensity was classified as contrast enhancement, HI1, HI2, PH1, and PH2 according to the ECASS-2 criteria.

2.5. Statistical analysis

Descriptive statistics were calculated in patients with and without MLS. Repeated measures analysis of variance was employed to detect the NIHSS changes based on MLS. Spearman's rho was used to describe the association of MLS with in-hospital death or forgoing treatment. Factors that were < 0.2 on the univariate analyses, except those that were highly correlated, were introduced as independent variables in the multivariate stepwise logistic regression analysis. Significant variables were selected by the forward stepwise method and were used to construct a nomogram. The discrimination of the nomogram was assessed by Harrell's C-index. Calibration was performed using a calibration plot. The area under the receiver operating characteristic curve (AUC) and the decision curve analysis were used to compare the discriminative ability and clinical net benefit associated with the previous prediction model of TURN score, calculated as $\text{TURN} = -4.65 + (\text{mRS} * 0.27) + (\text{NIHSS} * 0.10)$. All analyses were performed using the R software, version 3.5.2, and the SPSS Statistics for Windows, version 17.0. A two-sided $P < .05$ indicated statistical significance.

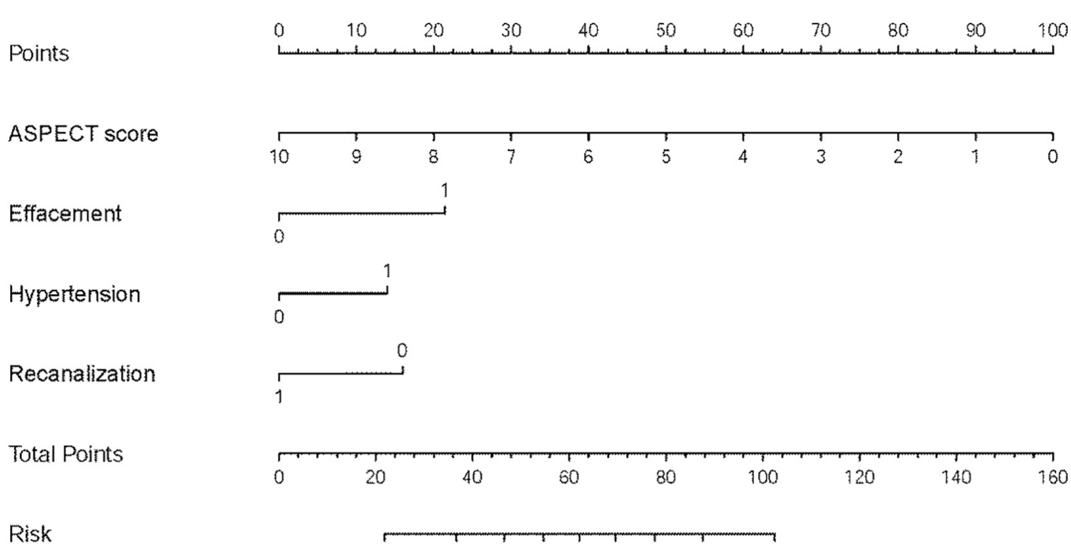

Fig. 2. The nomogram predicting the risk of midline shift.

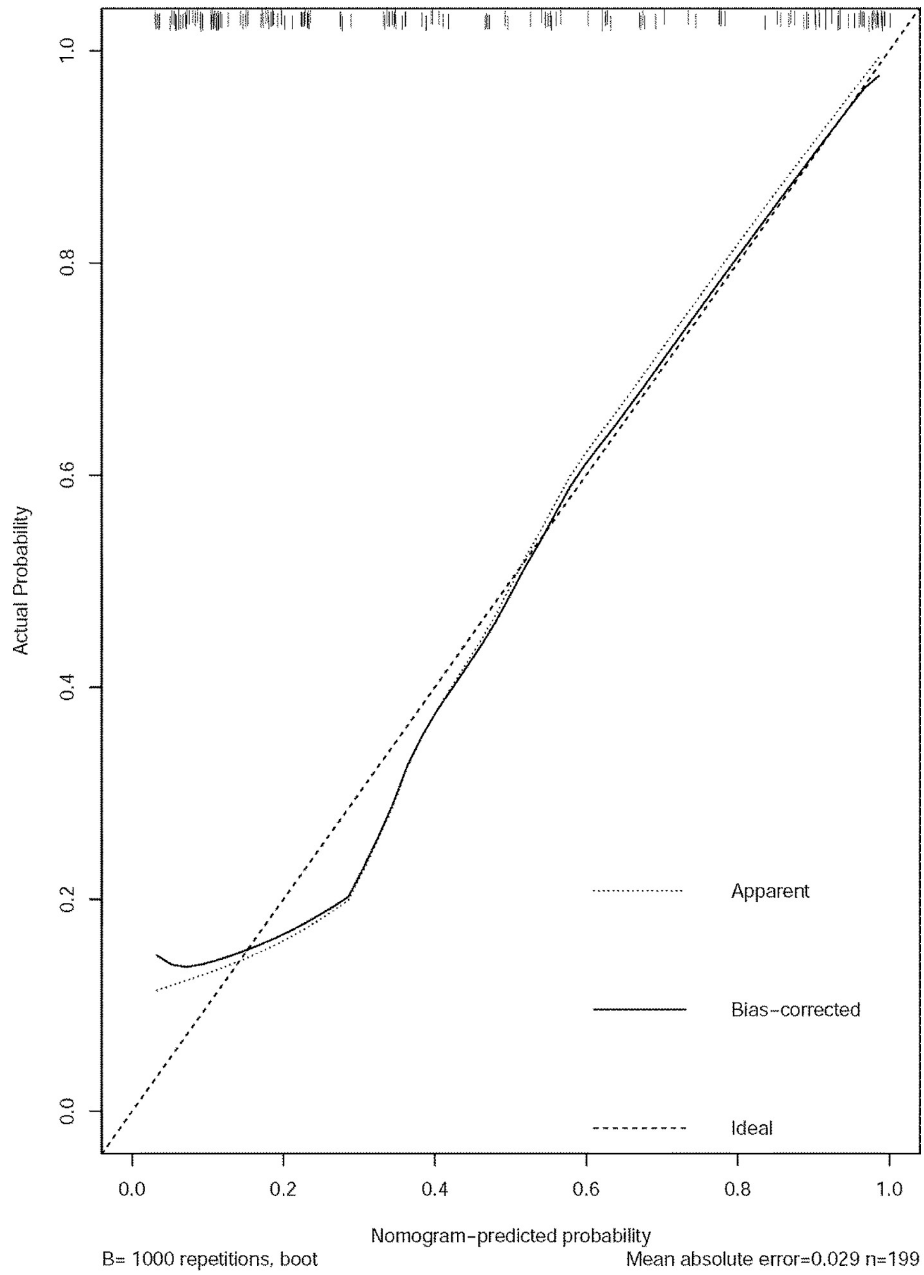

Fig. 3. The calibration plot for the nomogram.

3. Results

3.1. Characteristics of patients with and without MLS

A total of 199 patients were included in this study, of which 43.7% (n = 87) had MLS present on any of the follow-up NCCT scans. The clinical characteristics comparing patients with and without MLS are shown in Table 1. Patients with MLS were older and more likely to have a history of hypertension and atrial fibrillation, and had a higher baseline NIHSS score, a higher level of fasting serum glucose, and a lower rate of complete recanalization. These patients exhibited worse ASPECT scores, a higher proportion of effacement, and more hemorrhage on the 24-h NCCT. There was also a greater tendency for them to undergo decompressive hemicraniectomy.

3.2. Midline shift and early neurologic outcomes

Early neurologic outcomes concerning changes in stroke severity and rapid deterioration (in-hospital death or forgoing treatment) are presented in Fig. 1. The NIHSS score at baseline and after 24 h, 72 h and 7 days showed a significant difference based on MLS levels through repeated measures analysis of variance (F value = 9.467, $P < .001$). Overall, patients with MLS ≥ 6 mm showed progressive neurological deterioration, while those with MLS ≤ 3 mm had a similar progression of neurologic deficits compared to patients without MLS (P = .252). The presence of in-hospital death or forgoing treatment was strongly correlated with each millimeter increase in MLS (Spearman's rho = 0.429, $P < .001$). Furthermore, the patients without MLS were more likely to have functional independence at 3 months (46.8% vs. 19.5%, P < .001).

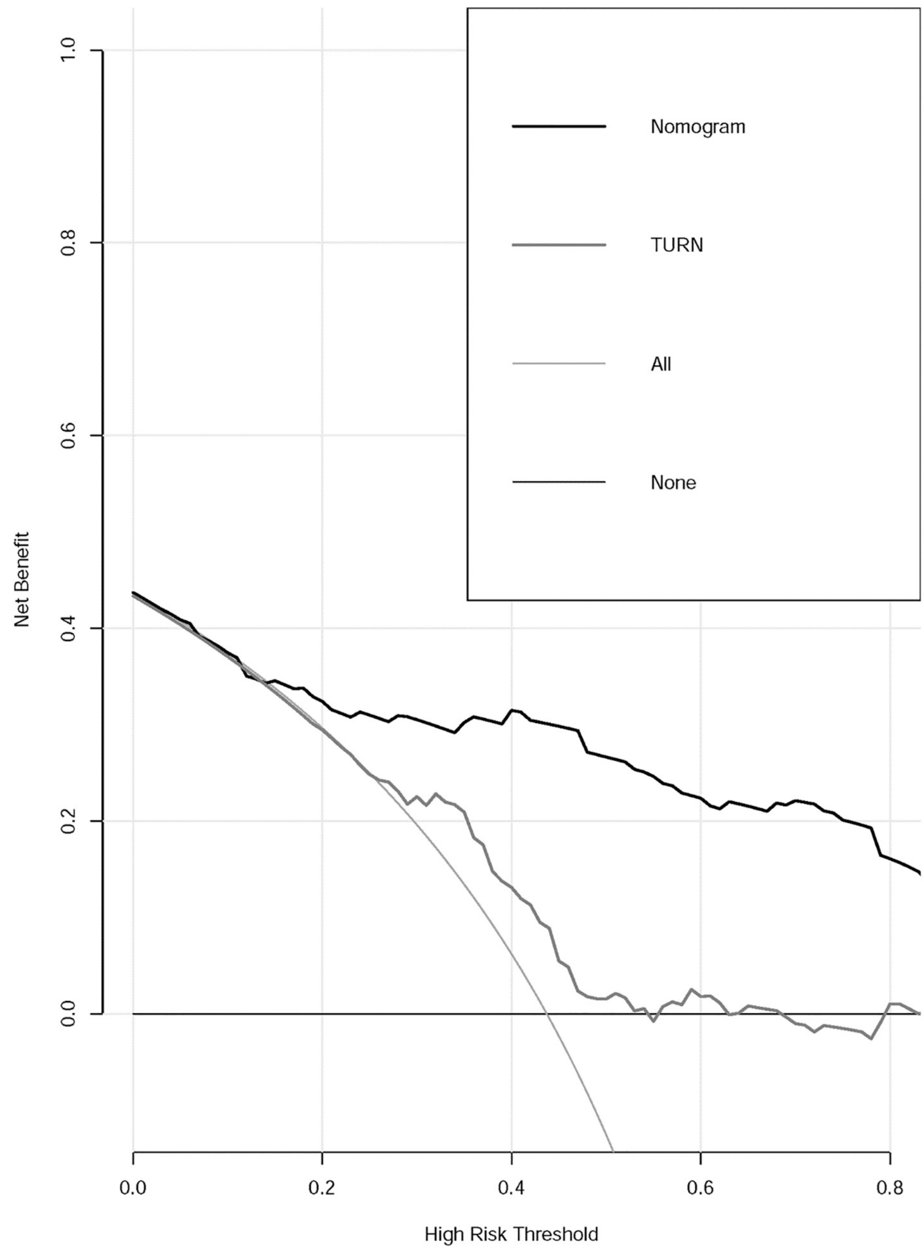

Fig. 4. Decision curve analysis demonstrating the net benefit of the nomogram in compared to the TURN score for the early detection of brain edema.

3.3. Predictors of midline shift identified by multivariable logistic regression analysis

According to the multivariate stepwise logistic regression model, which included those filtered factors that were < 0.2 based on the univariate analyses, four predictors were independently correlated with MLS (Table 2):ASPECT score on the 24-h NCCT (odds ratio [OR] 0.448, 95% confidence interval [CI], 0.299–0.671; $P < .001$); effacement on the same NCCT (OR 4.372, 95% CI, 1.291–14.809, $P = .018$); hypertension (OR 3.585, 95% CI, 1.007–12.758, $P = .049$); and total recanalization (OR 0.180, 95% CI, 0.059–0.552, $P = .003$). The Hosmer-Lemeshow goodness-of-fit test indicated that the model fit the data well ($P = .414$).

3.4. Development of a nomogram predicting midline shift

The results from the multivariable regression analyses were used to construct a nomogram. Fig. 2 illustrates the nomogram established for predicting the probability of MLS based on these selected parameters. The observed value of each parameter was designated a certain point by drawing a perpendicular line towards the first row. A total point was then calculated, which corresponded to the individual risk of developing MLS. The C-index of the nomogram was 0.874. Internal validation was performed by a bootstrap method with 1000 resamples. A calibration plot was generated to validate the similarities between the probability of MLS predicted by the nomogram and the actual MLS rate (Fig. 3).

3.5. Comparison of the nomogram and the TURN score

In our series, the TURN score demonstrated an AUC of 66.3% (95% CI, 59.2% - 72.8%), and the nomogram exhibited high discriminative value (AUC 87.6%, 95% CI, 82.2% - 91.8%, $P < .001$). The nomogram also displayed a higher net benefit than the TURN score (Fig. 4).

4. Discussion

This study established a nomogram model to predict the risk of brain edema after EVT in acute anterior circulation stroke. The nomogram exhibited excellent predictive ability with a C-index of 0.874. Lower ASPECTS and cisternal effacement at the 24-h NCCT, a history of hypertension and incomplete recanalization were independently associated with the presence of MLS.

Thirty percent of the patients (34/111) who achieved complete recanalization developed MLS, limiting the benefits of reperfusion. However, there are limited data to assist clinicians in identifying patients at risk of brain edema after early reperfusion treatment [8]. Given this paucity of data, we developed this nomogram specifically focused on patients who underwent EVT in the anterior circulation. The use of this nomogram achieved excellent discrimination in terms of internal validation, and compared to the TURN score, the nomogram also showed a higher net benefit.

Our nomogram has several novel elements compared to previously published predictors. First, it is based on the 24-h follow-up NCCT after EVT and considers both the ASPECT score and the presence of cisternal effacement. Although the ASPECT score on pretreatment NCCT is often emphasized when stratifying patients for EVT, the posttreatment ASPECT score could also have a prognostic impact. Consistently, a previous report showed that patients with a favorable outcome at 3 months had a markedly higher ASPECT score in the 24-h NCCT [13]. This may be due to a smaller infarct size on posttreatment NCCT to indicate better reperfusion, which can lead to a smaller swelling volume and greater preservation of neurological functions [3]. Likewise, the clinical significance of sulcal effacement has been widely investigated and was demonstrated to be independently associated with collateral status in proximal occlusion strokes [14]. Moreover, perisylvian sulcal effacement in conjunction with recanalization status can predict clinical outcomes in patients with acute middle cerebral artery stroke. Those effacement-negative patients who underwent early recanalization were more likely to experience favorable clinical outcomes [15]. Finally, patients were less likely to develop brain edema when they achieved mTICI-3 recanalization, which supports the recent findings that the recanalization status of mTICI-3 was associated with greater neurological improvement and better 3-month functional outcomes [16,17]. Interestingly, a higher rate of emergent stenting was observed in the non-MLS group, possibly yielding a higher recanalization rate [18]. Therefore, more aggressive brain edema preventive strategies may be needed in patients with cisternal effacement and low ASPECT scores after incomplete recanalization.

After early reperfusion therapy, the secondary goal of stroke clinical care is the treatment of acute complications that may exacerbate further neurological deterioration. From this clinical standpoint, our findings enable the triage of patients who are at high risk for complicating brain edema. Apart from the close monitoring of these patients, a multidisciplinary approach to reduce the space-occupying effects is required. Recommended measures include elevation of the head of the bed to 30°, osmotic therapy, use of brief moderate hyperventilation, and decompressive hemicraniectomy [19,20]. A recent novel pharmacological therapy involving IV glyburide was associated with improvements in midline shift and a reduced proportion of deaths attributed to cerebral edema [21]. In contrast, routine intracranial pressure monitoring, hypothermia, barbiturates, corticosteroids or high-dose albumin are not recommended in these patients [19,20].

Nevertheless, our findings should be interpreted with caution due to their limitations. First, the excellent discrimination of our nomogram might be related to the use of internal validation. Therefore, formal external validation is needed before the implementation of this model in clinical practice. Second, the relatively small sample size and the number of events might limit the generalizability of the results. Third, brain edema was assessed by measuring MLS, which is an indirect measure of mass effects. Therefore, this nomogram is possibly insensitive and underpowered for detecting the clinically meaningful event of reperfusion edema. Quantitative measures, such as the difference in lesion net water uptake [22] or the subtraction of the infarct growth volume and parenchymal hemorrhage volume from the change in lesion volume between baseline and follow-up DWI [23], as well as other advanced imaging parameters, will probably be soon incorporated into more personalized predictive tools. Nevertheless, clinical tools including this presented nomogram will still be facilitative in daily routine until these techniques become universal.

5. Conclusions

There is a profound association between MLS and early neurologic outcomes in acute ischemic stroke, and available prediction tools are lacking. We built a predictive nomogram for predicting brain edema after EVT in the anterior cerebral circulation.

Declaration of Competing Interest

None.

Acknowledgments

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