Early identification of Malignant Brain edema in laRge Artery oCclusive stroke after Endovascular therapy (EMBRACE study)

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Background

Stroke is a significant global cause of death and disability. Endovascular thrombectomy (EVT) is currently the best treatment for acute large vessel occlusion stroke (ALVOS), as it can greatly reduce mortality and improve patient outcomes. However, only half of patients who undergo EVT achieve functional independence, and malignant brain edema (MBE), a severe complication, can occur after the procedure, leading to a poor prognosis. Previous studies have confirmed the effectiveness of early decompressive hemicraniectomy in reducing morbidity and mortality in patients with malignant brain edema. Therefore, identifying high-risk patients for MBE can help clinicians make appropriate triage and early intervention decisions, potentially saving patients' lives.

Predictive factors for post-ischemic stroke brain edema have been widely discussed, and reliable early predictive indicators have been identified, such as age, early consciousness disorders, baseline National Institutes of Health Stroke Scale (NIHSS), atrial fibrillation, hypertension, baseline blood glucose, and the level of reperfusion after EVT. Radiological factors, such as the Alberta Stroke Program Early CT Score (ASPECTS), collateral circulation rating of arteries, venous outflow status, CT perfusion core infarct volume, perfusion-based collateral status, and clot burden, are closely associated with the occurrence of MBE post-EVT. However, due to individual differences and multiple factors affecting MBE, a single factor cannot effectively predict MBE. Establishing a clinical risk prediction model can effectively identify high-risk populations for MBE at an early stage.

Aim

To design and validate a predictive model for MBE after EVT.

Design

Study Type: Observational [Patient Registry]

Time Perspective: Prospective

Study population

The study is a multicenter, prospective, observational clinical registry study, commenced on April 1, 2024, and is expected to end in June 2027. Participants were ALVOS patients undergoing EVT treatment in neurology departments from multiple stroke centers. The data from Zhejiang Provincial People's Hospital compose the model training cohort, while data from other centers serve as an independent external validation cohort. The protocol of the study has been approved by the human Ethics Committee of Zhejiang Provincial People's Hospital (KY2024058). All clinical investigations will be conducted according to the principles set in the Declaration of the Helsinki.

Inclusion Criteria:

(1) Age > 18 years old;

(2) Onset of stroke to hospital admission < 24 hours;

(3) Admission with a head CT scan ruling out hemorrhage;

(4) Patients undergoing CT perfusion scan before treatment;

(5) Confirmation of internal carotid artery (ICA) or middle cerebral artery (MCA) occlusion or tandem occlusion by Digital Subtraction Angiography (DSA) and subsequent EVT;

(6) complete 3-months follow-up.

Exclusion Criteria:

(1) Poor quality of preoperative CT perfusion imaging;

(2) Posterior circulation occlusion or isolated anterior cerebral artery occlusion;

(3) Presence of other severe diseases such as malignant tumors, severe organ failure, or other life-threatening conditions with an expected survival period of less than 90 days;

(4) Incomplete imaging and clinical data.

Procedures

All ALVOS patients will undergo comprehensive evaluation by neurologists at admission to the stroke center to obtain baseline data from clinical and laboratory examinations. Multimodality CT, including head non-contrast CT (NCCT), CT perfusion (CTP) and CTP-derived multiphase CT angiography (CTA), will be performed to assess whether patients are eligible for EVT. After EVT, all patients will be transferred to the neuro-intensive care unit for close perioperative and postoperative care to ensure stability of vital signs and implementation of comprehensive monitoring and management. This includes daily neurological assessments, monitoring of vital signs and oxygenation, and management of endotracheal intubation. Once the patient's vital signs stabilize or after the patient is extubated, they will be transferred to the neurology stroke care unit for further treatment. In principle, this trial does not involve the selection and intervention of therapeutic drugs. Within 24 hours post-EVT, patients will undergo repeat head NCCT to exclude hemorrhage and evaluate surgical outcomes. Antiplatelet therapy may be considered based on the patient's specific condition but should be cautiously selected in clinical practice and closely monitored to prevent bleeding complications. In case of signs of hemorrhagic transformation, physicians may adjust the antiplatelet therapy regimen at their discretion, potentially reducing the dose or delaying antiplatelet treatment. Additionally, regular in-hospital follow-up head NCCT scans will be performed on patients at day 3, to monitor disease progression and adjust treatment plans promptly.

Imaging protocol

Head NCCT is performed on a Toshiba Aquilion 320-slice CT scanner (Toshiba Medical Systems) using the following acquisition parameters: 120 kV, 128 mAs, scan coverage of 240 mm, and scan width of 5 mm. Simultaneously, 4-dimensional time-resolved whole-brain CTA and whole-brain CTP can be acquired. Lohexol (45 mL) (Medrad Stellant D SCT-212; Bayer Healthcare) is injected at a rate of 5

mL/second, followed by a 30 mL saline flush at an injection rate of 4 mL/second. All perfusion parameters are analyzed using post-processing software.

Radiological assessments

The imaging variables collected in this study involve arterial, venous and perfusion status variables, including NCCT-ASPECTS, ischemic core volume, the penumbra volume, collateral status based on CTP and multiphase CTA, clot burden score, and venous outflow status. Imaging evaluations will be performed by imaging physicians who are blind to the clinical information.

CT perfusion assessment

Areas with relative cerebral blood flow (rCBF) <30% is defined as the ischemic core. The penumbra volume is calculated by subtracting the ischemic core volume (lesions with rCBF <30%) from the perfusion lesion volume (delay time threshold >3 seconds). The collateral index is defined as the volume of tissue with delay time (DT) >6 s divided by the volume with DT >2 s.

Clot burden score

We use a CBS for the anterior circulation to quantify the extent of ipsilateral intracranial thrombus, allotting major arteries 10 points for the presence of contrast opacification on CTA. Two points each is subtracted for the absence of contrast opacification in the complete cross-section of any part of the proximal M1 segment, distal M1 segment, or supraclinoid ICA, and 1 point each for M2 branches, A1 segment, and infraclinoid ICA. Partial filling defects suggesting stenosis or non-occlusive thrombus are rated as patent. A score of 10 indicates the absence of a visible occlusion on CTA, while a score of 0 indicates occlusion of all major intracranial anterior circulation arteries.

Venous outflow assessment

The outflow status of the sphenoparietal sinus, superficial middle cerebral veins, and intracerebral veins will be evaluated. Venous opacification will be graded per vein using a three-point scale based on baseline CT angiography:
0: Complete absence of cortical vein opacification
1: Moderate opacification (attenuation of one of the target veins on the contralateral side)
2: Full opacification.

Clinical assessments

We will record the demographic data (gender, age, hypertension, diabetes, history of atrial fibrillation), site of occlusion, baseline systolic and diastolic blood pressure, prior IVT administration, baseline NIHSS score, NIHSS score at discharge, modified Rankin Score (mRS) at discharge, and TOAST stroke etiology (Trial of ORG 10172 in Acute Stroke Treatment) of each participant. Hematological laboratory results will include baseline glucose, baseline white blood cell count, baseline neutrophil count, baseline hemoglobin, and platelet count. The EVT operator will record the time from stroke onset to puncture (OTP), time from puncture to recanalization (PTR), and degree of blood flow restoration. The occluded vessel will be determined based on intraoperative angiography results, and reperfusion level will be graded using the modified Thrombolysis in Cerebral Infarction (mTICI) score, with complete reperfusion defined as mTICI 2b-3. Clinical assessments will be conducted by neurologists unaware of the clinical diagnosis.

Study groups

- training set

To determine potential predictive factors, imaging and clinical parameters will be enrolled into LASSO regression analysis, which effectively eliminated several irrelevant or multicollinearity independent variables to reduce high-dimensional data. The multivariable logistic regression analysis will be applied to determine the

variables predicting MBE, and the results will be used to create a predictive model based on the training set.

- validation set

The predictive model will be further validated in the validation set.

Outcome assessment

Primary Outcome Measures:

The occurrence of MBE: Patients developed MBE within 3 days post-EVT

Secondary Outcome Measures:

1. The follow-up mRS scores of enrolled patients at 90 days since stroke onset.
2. Evidence of parenchymal hemorrhage (PH type) on cranial imaging during hospitalization.

Sample size

In this study, predictive model will be constructed using the EVT database from Zhejiang Provincial People's Hospital as a training cohort, and prospective data from other centers will be used to validate the performance of predictive model. We will randomly select 70% of the patients from the Stroke Center EVT database at Zhejiang Provincial People's Hospital as the training cohort, while the remaining 30% will constitute the internal validation cohort. Within the training cohort, our aim will be to analyze imaging and clinical parameters when constructing the predictive model. Given the requirement of at least 10 events per candidate variable for model establishment, a minimum of 200 MBE patients is necessary in the training cohort to ensure stable model estimation. Based on a study design with a sample ratio of 7:3 for the training and internal validation sets, at least 290 MBE patients will be required in this study at Zhejiang Provincial People's Hospital. The external validation set will require 100-200 positive samples; considering an approximate 20% incidence rate of MBE in anterior circulation EVT patients, this study will need to include at least 1950 EVT patients.

Statistical analysis

Compare baseline clinical and imaging data of EVT patients with and without MBE across the training, internal validation, and external validation sets. Continuous variables conforming to a normal distribution will be described using means and standard deviations, while those not conforming will be described using medians and quartiles. Categorical variables will be expressed as percentages.

In the training set, factors influencing MBE will be analyzed. Continuous variables will be analyzed using Student's *t*-test or Mann-Whitney U test, while categorical variables will be analyzed using chi-square test and Fisher's exact test. Collinearity among variables will be assessed using Variance Inflation Factors (VIFs), where VIF <10 and Tolerance >0.1 indicate no significant collinearity. Variables with a significance level of P <0.1 in univariate analysis will be incorporated into logistic regression analysis using forward stepwise selection method, and odds ratios (ORs) and 95% confidence intervals (CIs) will be calculated. Factors with $P < 0.05$ will be included as independent predictors of MBE in the model. After constructing the predictive model, it will be converted into a dynamic nomogram and deployed on a webpage, generating a dynamic nomogram URL.

The dynamic nomogram URL will be used to externally validate EVT data from other stroke centers and will collect data. The area under the receiver operating characteristic (ROC) curve (AUC) will be used to evaluate the ability of the predictive model to identify high-risk MBE patients after EVT in the training, internal and external validation sets, and corresponding 95% CIs will be calculated. Calibration plots and the Hosmer-Lemeshow goodness-of-fit test will assess the consistency between actual MBE occurrence and predicted MBE risk probability in EVT patients. Decision curve analysis (DCA) will determine the clinical net benefit of the model at different risk threshold probabilities in the three sets.

Statistical analyses will be performed using IBM SPSS Statistics software (version

26.0; IBM Corporation, Armonk, NY, USA) and R software (version 4.3.1, R Development Core Team, Vienna, Austria).