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Factors associated with unfavorable outcome of anterior circulation ischemic stroke following emergency endovascular therapy after complete recanalization

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Abstract

Objective: Endovascular thrombectomy (EVT) improves long-term patients outcomes and decreases mortality among ischemic stroke patients. However, not all patients can benefit from EVT recanalization. The present study aims to evaluate the predictors of unfavorable outcomes associated with emergency endovascular therapy despite complete recanalization. *Methods:* We investigated 74 eligible patients receiving EVT from January 2019 to January 2022 at a comprehensive stroke center. Demographics, clinical, radiological and treatment characteristics, safety, and functional outcomes were collected. Modified Rankin scale (mRS) score ≤ 2 at 90 days was defined as a good functional outcome. *Results:* A total of 111 patients were initially eligible for the study, of which 37 were excluded, resulting in 74 patients in the final study. The mean age was 69.08±12.12 years old, 67.57% patients were male, 44.59% patients with atrial fibrillation, 64.86% with hypertension, 21.62% patients with diabetes mellitus, 16.22% patients with coronary artery diseases, 6.76% with parenchymal hematoma. Median pre-EVT NIHSS (IQR) was 15.5 (12.0, 19.25). Median door-to-recanalization time (DRT) (IQR) was 208.0 (160.0,278.5) minutes and median last known norma to puncture time (LKNPT) (IQR), was 362.0 (280, 452.5) minutes. Individuals with a poorer outcome were older [73.56±9.29 vs. 65.28±13.02 years old, P=0.002], had a higher prevalence of atrial fibrillation (AF) [58.82 vs. 13%, P=0.023] and a higher National Institute of Health Stroke Scale (NIHSS) [median 16 (IQR 12.0-22.3) vs median 15 (IQR 10.0-18.0), P=0.143]. Female sex, hypertension, diabetes mellitus, coronary artery disease, and a slightly longer door-to-recanalization time were more prevalent in the unfavorable prognosis group; however, statistical analysis did not show any significant differences. Logistics binary regression model showed that older age [OR: 0.1.160 (1.011 to 1.112, P=0.031)] and AF [OR: 3.190 (1.111 to 9.164, P=0.031)] were associated with an unfavorable outcome.
Conclusion: Older age, and atrial fibrillation were factors associated with the unfavorable outcome despite complete recanalization after emergency EVT of ischemic stroke.

Keywords: Recanalization, unfavorable, ischemic stroke, endovascular therapy, thrombectomy

INTRODUCTION

According to the Global Burden of Disease Study in 2019, stroke remained the second-leading cause of death (11.6% of total deaths) and the third-leading cause of death and disability combined accounting for 5.7% of total disability-adjusted

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life-years.[1] There were 12.2 million incident cases of stroke, 101 million prevalent cases of stroke, 143 million disability-adjusted life-years due to stroke, and 6.55 million deaths from stroke in 2019.[1] Several factors contribute to mortality among stroke patients, which can be related to in-hospital stays, such as pneumonia, urinary tract infection, pressure ulcer, falls, deep venous thrombosis, pulmonary embolism, severe constipation, or caused by the natural progression of the stroke, recurrence of stroke, malignant edema, and hemorrhagic transformation.[2,3]

Data from clinical trials in the past decade has shown improved functional outcomes at 90 days in patients submitted to endovascular thrombectomy (EVT) compared to pharmacological therapy.[2-5] In this context, EVT has been proven as a standard treatment of large vessel ischemic strokes within 24 hours after onset.[2,4,5] In addition, a meta-analysis of five randomized clinical trials (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA) with 1,287 patients, comprised of 634 patients assigned to EVT and 653 patients assigned to control, showed no significant differences in mortality rates at 90 days in EVT patients.[6] Therefore, an increasing body of evidence shows positive outcomes from the EVT in large vessel occlusion, further reinforcing the benefit of thrombectomy in acute ischemic stroke (AIS).[6]

With the widespread implementation of EVT, concerns have also been raised regarding early and late outcomes associated with this procedure.[7,8] A retrospective analysis of 245 EVT patients with AIS investigating death occurring during hospitalization after EVT or within seven days following hospital discharge from the stroke event showed that mortality occurred in 22.8% of cases.[2] The study found that recanalization status, National Institute of Health Stroke Scale (NIHSS) 24 hours after EVT, and symptomatic intracerebral hemorrhage (sICH) were predictors of early mortality in AIS patients treated with EVT.[2] Furthermore, a retrospective analysis of the North American Solitaire Stent Retriever Acute Stroke (NASA) registry showed that 116 (49.6%) had poor outcomes among 234 successfully recanalized patients evaluated for 90-day modified Rankin scale (mRS) score.[5] Therefore, more studies are needed to evaluate EVT outcomes in AIS and predictors of mortality and prognostic factors associated with recanalization.[9] In this context, the present study aims to evaluate the predictors of unfavorable outcomes associated with emergency EVT despite complete recanalization.

METHODS

Study participants

We performed a retrospective analysis of prospectively collected data on patients who underwent EVT for ischemic stroke within 24 hours at a university comprehensive stroke center in China. The patients' data were retrieved from a nationwide database, the Big Data Observatory Platform for stroke in China, as well as the hospital data platform. The study data collection was approved by the Ethical Board of the hospital in China.

Inclusion criteria were as follows: 1) patients who underwent emergency EVT, 2) age ≥18 years old, 3) signs and symptoms within 24 hours from the onset, and 4) anterior circulation ischemic stroke. Exclusion criteria were as follows: 1) missing follow-up data, 2) pre-EVT Alberta stroke program early CT score (ASPECTS < 6), 3) pre-EVT NIHSS < 6, 4) posterior circulation stroke, 5) patients post emergency EVT with modified thrombolysis in cerebral infarction (mTICI) without complete recanalization.

Data collection

We assessed baseline demographic characteristics (age, sex), risk factors of cerebrovascular disease (hypertension, diabetes mellitus type 2, coronary heart diseases, atrial fibrillation (AF), history of stroke, smoking status, dyslipidemia), initial premorbid mRS, door-to-puncture time (time between first hospital admission and arterial access, DPT), last know normal to puncture time (LKNPT), door-to-recanalization time (DRT), NIHSS pre-EVT, ASPECTS pre-treatment, mTICI after emergency EVT. Complete recanalization was defined as post-EVT mTICI of 3. Patients' outcomes were evaluated by mRS three months after EVT. Functional outcome was defined as mRS of 0-2 after three months. Unfavorable outcome was defined as mRS of 3-6 after three months.

The decision to perform EVT was made by a team of vascular neurologists and treating neuroradiologists. Board-certified interventional neuroradiologists performed the EVT procedure. In eligible patients, EVT was performed according to previous guidelines.[10] Mechanical thrombectomy was performed from femoral puncture using a guiding sheath, an intermediate catheter, and a stent retriever. Substantial reperfusion was defined as mTICI 2b or three after the procedure.[2] Patients were admitted to the

stroke unit for close monitoring and observation for at least 24 hours postoperatively.

Statistical analysis

Double data entry and standardized procedures were performed for quality assessment. The data was then trasnferred to the IBM Statistical Package for the Social Sciences (SPSS) software version 26 (IBM Corp., Armonk, NY) for statistical analysis. Categorical variables were represented as proportions, and continuous variables were represented as means and standard deviations. A *P*-value <0.05 was considered statistically significant in all of the analyses. Kolmogorov-Smirnov statistics were used for normality assessment. A non-parametric Mann-Whitney U test was performed to analyze non-normally distributed continuous data, reported as medians along with the interquartile range (IQR). Normally distributed data are reported as means with corresponding standard deviations (SD) and compared using the student's t-test. We used multilevel linear modelling in our data analysis. An unfavorable outcome was defined as mRS ≥3, while a favorable outcome was defined as mRS (0–2) at three months. We considered the covariates that were more associated with an unfavorable outcome in the multivariate analysis. Restricted maximum likelihood was used to fit the model, and nonsignificant variables were excluded until only significant variables (P<0.05) were left.

RESULTS

In total, 111 patients were initially eligible for the study, of whom 37 were excluded. 74 patients were included in the final study. Table 1 summarizes the baseline patient characteristics. For overall patients, the mean age was 69.08±12.12 years old. 67.57% patients were male, 44.59% patients with atrial fibrillation, 64.86% with hypertension, 21.62% patients with diabetes mellitus, 16.22% patients with coronary artery diseases, 6.76% with parenchymal hematoma. Median Pre-EVT NIHSS (IQR) was 15.5 (12.0, 19.25). Median DRT (IQR) was 208.0 (160.0,278.5) minutes and Median LKNPT (IQR), was 362.0 (280, 452.5) minutes.

Comparing the unfavorable outcome group with the favorable outcome group, individuals with a poorer prognosis were older [73.56±9.29 vs. 65.28±13.02 years old, P=0.002] and had a higher prevalence of AF [58.82 vs. 13%, P=0.023]. Female sex, hypertension, diabetes mellitus, coronary artery disease, and a slightly longer door-to-recanalization time were more prevalent

Table 1: Baseline characteristics of study participants

Variable	Overall patients	Unfavorable outcome *n*=34	Favorable outcome *n*=40	X2/t/z	p
Age (years) (mean±SD)	69.08±12.12	73.56 ± 9.29	65.28 ± 13.02	3.182	0.002**
Male (n, %)	50 (67.57)	20 (58.82)	30 (75.00)	2.195	0.138
Hypertension (n, %)	48 (64.86)	25 (73.53)	23 (57.50)	2.072	0.150
Diabetes mellitus (n, %)	16 (21.62)	10 (29.41)	6 (15.00)	2.252	0.133
Coronary artery diseases (n, %)	12 (16.22)	7 (20.59)	5 (12.50)	0.885	0.347
Atrial fibrillation (n, %)	33 (44.59)	20 (58.82)	13 (32.50)	5.154	0.023*
Stroke history (n, %)	9 (12.16)	3 (8.82)	6 (15.00)	0.205	0.650
Pre-EVT NIHSS (IQR)	15.5 (12.0, 19.25)	16.0 (12.0, 22.3)	15.0 (10.0, 18.0)	-1.464	0.143
DRT (IQR, min)	208.0 (160.0,278.5)	205.0 (160.0, 253.5)	209.5 (158.0, 283.8)	-0.363	0.716
LKNPT (IQR), min	362.0 (280, 452.5)	352.000 (265.8, 432.5)	389.000 (282.5, 482.5)	-0.792	0.428
PH1 and PH2, n (%)	5 (6.76)	3 (8.82)	2 (5.00)	0.035	0.851

DRT, Door-to-recanalization time; LKNPT, Last-known normal-to-puncture time; PH1, Parenchymal hematoma type 1; PH2, Parenchymal hematoma type 2. *Denotes significance.

Table 2: Multivariate logistics regression analysis of factors associated with unfavorable outcome of ischemic stroke following emergency endovascular therapy after complete recanalization

						95% C.I. for EXP(B)	
	B	S.E.	Wald	Sig.	OR	Lower	Upper
Age	.058	.024	5.722	.017	1.060	1.011	1.112
AF	1.160	.538	4.644	.031	3.190	1.111	9.164

AF, atrial fibrillation; EVT, endovascular thrombectomy; NIHSS, National Institute of Health Stroke Scale

in the unfavorable prognosis group; however, statistical analysis did not show any significant differences.

Older age [OR: 0.1.160 (1.011 to 1.112, *P*=0.031)] and AF [OR: 3.190 (1.111 to 9.164, *P*=0.031)] were associated with an unfavorable outcome in the logistics binary regression model (Table 2).

DISCUSSION

Our study demonstrated that comparing the unfavorable outcome group with the favorable outcome group, individuals with a poorer prognosis were older and had a higher prevalence of AF; Older age and AF were also associated with an unfavorable outcome in the logistics binary regression model.

The documentation of unfavorable outcomes after successful recanalization is infrequent in the literature. Complications after EVT are associated with multiple complex factors associated with patient characteristics and comorbidities, the time elapsed since the beginning of symptoms, the technology available, logistics, and surgical technique.[11-14] Data on the implications of AF on the outcome of patients with acute ischemic stroke treated with mechanical thrombectomy is scarce and controversial. In a previous retrospective study of 221 eligible patients receiving EVT from January 2019 to January 2022 from three comprehensive stroke centers, AF patients achieved similar outcomes compared to non-AF patients with anterior circulation occlusion treated with EVT.[15] However, AF was associated with unfavorable outcome of ischemic stroke following emergency endovascular therapy after complete recanalization in the multivariate regression analysis in our study.

In another retrospective cohort study of 705 patients (314 AF and 391 non-AF), functional outcomes were better with bridging IVT in the non-AF (adjusted odds ratio (aOR) 2.28, 95% CI 1.06 to 4.91, *P*=0.035), compared with the AF subgroups (aOR 1.89, 95% CI 0.89 to 4.01, *P*=0.097).[17] However, reperfusion, sICH, and mortality were similar between bridging IVT and EVT for both AF and non-AF patients, and there was no significant effect modification by the presence of AF on bridging IVT (interaction aOR 0.12, 95% CI –1.94 to 2.18, *P*=0.455).[17] Thus, AF did not modify the outcome of bridging IVT.[16] Most specifically, regarding complications following successful EVT in patients with AIS, a recent meta-analysis showed that about 5% of patients might experience reocclusion within one week after successful recanalization.[17] The risk factors associated with this complication are not fully elucidated, but large artery atherosclerosis was associated with a higher risk of reocclusion.[18]

A high NIHSS score pre-EVT was unpredictive of poor outcomes despite recanalization in our study. This may be attributed to a small sample size and limitation to a single centre study. However, another study in a large retrospective analysis from the NASA registry showed that NIHSS score predicted poor outcome.[9] Such data demonstrate that severe neurological deficits pre-EVT are reliable prognostic factors of poor outcomes. Interestingly, in other studies, age ≥80 years, occlusion site other than M1/M2, NIHSS score ≥18, diabetes mellitus, absence of pretreatment with intravenous tissue-type plasminogen activator (IV t-PA) ≥3 passes with the Solitaire device, and use of rescue therapy were independent predictors of poor 90-day outcome.[9] The strongest effects were NIHSS score and rescue therapy, which increased the risk of a poor outcome approximately four times.[9] Future controlled trials and meta-analyses are needed to elucidate further the risk factor associated with unfavorable outcomes despite complete recanalization after EVT of ischemic stroke.

Another fact that should be considered is the futile recanalization, characterized by early recanalization of an occluded artery failing to improve neurological outcomes. The predictors of futile recanalization are worth studying due to the economic burden of no improvement in the patient's symptoms, even with high

investments.[19,20] Two recent systematic reviews with metanalysis revealed that age (standardized mean difference [SMD] 0.49, 95% CI 0.42 0.56; *P*<0.0001) and baseline NIHSS (SMD 0.75, 95% CI: 0.65 0.86; *P*<0.001) are important for recanalization outcomes.[19,20] Noteworthy, age is not a factor for worsening outcomes, but it is a factor for futile recanalization. Therefore, data from the current study can be used to improve patients outcome and provide a better care for AIS patients.[21-23]

In line with previous studies[24,25], older age could be a strong predictor of futile recanalization. Advanced age is constantly associated with undesirable neurological outcomes after stroke, which may be due to more comorbidities, higher occurrence of complications, higher rate of cardioembolic strokes, and less rehabilitation potential.[26] Nevertheless, setting a strict upper limit of age for EVT seems unreasonable. In this study too, older age [OR: 0.1.160 (1.011 to 1.112, *P*=0.031)] was associated with an unfavorable outcome in the logistics binary regression model. However, it can be regarded as a factor for futile recanalization.

There are several limitations in the present study. First, the sample was relatively small, which can prevent generalizations. Second, the present cohort was hospital-based, leading to possible biased results. Third, the retrospective data extraction can decrease the number of individuals enrolled in the study or not provide sufficient data for specific analysis. Fourth, studies involving procedures regarding small differences among interventionalists can have a significant effect. Despite such limitations, unfavorable outcomes were statistically associated with higher scores of NIHSS, especially in the multilevel linear regression, and disseminating such data can help other stroke centers across the globe to implement measures to improve patients outcomes.

In conclusion, older age, atrial fibrillation, were factors associated with the unfavorable outcome of complete recanalization after emergency EVT of ischemic stroke. Future large-scale prospective studies are required to expand and validate these findings.

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DISCLOSURE

Ethics: The Central People's Hospital of Zhanjiang Ethics Committee approved the study stroke center data collection.

Availability of data: Availability of data and materials were available by contacting corresponding authors on reasonable request.

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Conflict of interest: None

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