Outcome prediction for patients with anterior circulation acute ischemic stroke following endovascular treatment: A single-center study

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Abstract. Previous studies have identified various factors associated with the outcomes of acute ischemic stroke (AIS) but considered only 1 or 2 predictive factors. The present study aimed to use outcome-related factors derived from biochemical, imaging and clinical data to establish a logistic regression model that can predict the outcome of patients with AIS following endovascular treatment (EVT). The data of 118 patients with anterior circulation AIS (ACAIS) who underwent EVT between October 2014 and August 2018 were retrospectively analyzed. The patients were divided into 2 groups based on the modified Rankin Scale score at three months after surgery, where 0-2 points were considered to indicate a favorable outcome and 3-6 points were considered a poor outcome. Non-conditional logistic stepwise regression was used to identify independent variables that were significantly associated with patient outcome, which were subsequently used to establish a predictive statistical model, receiver operating characteristic (ROC) curve was used to show the performance of statistical model and analyze the specific association between each factor and outcome. Among the 118 patients, 47 (39.83%) exhibited a good and 71 (60.17%) exhibited a poor outcome. Multivariate analysis revealed that the predictive model was statistically significant ($\chi^2$=78.92; $P<0.001$), and that the predictive accuracy of the model was 83.1%, which was higher compared with that obtained using only a single factor. ROC curve analysis shows the area under curve of the statistical model was 0.823, the analysis of diagnostic threshold for prognostic factors indicated that age, diffusion-weighted imaging lesion volume, glucose on admission, National Institutes of Health Stroke Scale score on admission and hypersensitive C-reactive protein were valuable predictive factors for the outcome of EVT ($P<0.05$). In conclusion, a predictive model based on non-conditional logistic stepwise regression analysis was able to predict the outcome of EVT for patients with ACAIS.

Introduction

Acute ischemic stroke (AIS) is the leading cause of death in China and one of the primary mortality-associated factors worldwide (1). At present, intravenous thrombolysis and endovascular treatment (EVT) are the only methods available for the treatment of AIS. As intravenous thrombolysis must be administered within a strict 4.5-h time-window and has a relatively low recanalization rate, it is only beneficial in a proportion of patients (2). However, EVT has a longer time-window that was extended to 24 h in 2018 (3), and has markedly improved the application scope of EVT. Once contraindications have been excluded, the majority of AIS patients may be subjected to EVT within the 24-h time frame (3). However, despite advances in surgical instruments in the last 10 years, the overall probability of post-operative complications and ineffectiveness of treatment for EVT remains relatively high (4,5). Therefore, there is an urgent requirement for novel predictive indicators of patient outcome following EVT for AIS.
A number of biochemical, clinical and imaging factors have been identified to be associated with the prognosis of patients with AIS. In terms of biochemical factors, the levels of glucose on admission (AG), high-sensitivity C-reactive protein (hs-CRP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) on admission all associated with the outcome of patients with AIS (6-8). However, these biochemical indicators reflect only a limited number of the aspects associated with AIS (and are not used in combination with symptomatic and medical imaging data); thus, their predictive accuracy is relatively low.

Of the imaging characteristics, diffusion-weighted imaging (DWI) lesion volume, cerebral blood flow, cerebral blood volume and mean transit time have been associated with patient outcome (9-11). Due to the requirement for prompt recanalization and the lack of medical resources in certain locations, most patients do not undergo a pre-operative perfusion scan and only receive a conventional magnetic resonance imaging (MRI) sequence scan, which has limited the popularization of most MRI modal features. In terms of clinical factors, the National Institutes of Health Stroke Scale (NIHSS) score, modified Rankin Scale (mRS) score, age and onset-to-reperfusion time (ORT) have been indicated to be associated with the outcome of patients with AIS (12-14). Clinical factors also only reflect the functional state of the central nervous system and partially reflect the mechanisms of AIS; therefore, on their own, they are unable to accurately predict the outcome of patients with AIS.

At present, the number of studies predicting the outcome of EVT for AIS is relatively low, and the outcomes for patients who received EVT have only been predicted using single factors belonging to a single category; they have not been comprehensively predicted using a combination of biochemical, imaging features and clinical indicators. The present study aimed to use widely recognized prognostic indicators, including biochemical, imaging and clinical factors to predict the outcome of EVT, and to provide a reference for the establishment of personalized treatment plans.

Patients and methods

Patients. A retrospective analysis was performed using the clinical and imaging data of 169 patients with anterior circulation acute ischemic stroke (ACAIS) who received EVT between October 2014 and August 2018 at the Second Clinical College of Guangzhou University of Chinese Medicine (Guangzhou, China). All patients accepted mechanical thrombectomy using a solitaire stent retriever; if the vessel remained narrow or the distal circulation remained poor following thrombectomy, angioplasty was subsequently performed. A total of 10 patients with malignant tumors or neurological diseases were excluded, 12 patients were excluded due to a history of stroke, 6 due to having received unknown pre-treatment at another hospital and 23 patients dropped out during the follow-up period. Ultimately, 118 patients were included in the present study. The clinicopathological and demographic data of all patients were obtained from the hospital information management system and image examination center, and included age, sex, risk factors, DWI images, AG, hs-CRP, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and total cholesterol (TC) levels, in addition to systolic blood pressure (SBP), diastolic blood pressure (DBP), ORT, NIHSS score on admission and clinical outcome (Tables I and II). The patients were followed up for three months following EVT, and the NIHSS and mRS scores were used to assess each patient’s state on admission and three months after EVT. The NIHSS and mRS scores were independently evaluated by two experienced neurosurgeons; discrepancies were resolved through discussion or determined by more senior neurosurgeons.

All patients met the following inclusion criteria: i) Diagnosed with AIS according to the 2018 Guidelines for the Early Management of Patients with Acute Ischemic Stroke (15); ii) for patients with ACAIS, the occlusions were located in the intracranial internal carotid or middle cerebral artery; iii) an ORT at <24 h; and iv) an imaging examination performed no more than 1.5 h prior to surgery. The exclusion criteria included the following: i) The occurrence of intracranial diseases, including tumors, infection or any neurological or psychiatric disorders that may have affected neurological function; ii) an NIHSS score <7 on admission; and iii) patients with posterior circulation AIS. The present study was approved by the Ethics Committee of The Second Clinical College of Guangzhou University of Chinese Medicine (Guangzhou, China).

Clinical evaluation. The baseline assessments were performed within 1.5 h of admission and included evaluations of the NIHSS score, AG, blood pressure, demographic data, history of smoking or drinking and history of diabetes mellitus or hypertension. A history of smoking and drinking was defined as the patient admitting that they had previously smoked or consumed alcohol. A history of high blood pressure was defined as a systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg at any point prior to admission. Diabetes was defined as a blood glucose level >11.1 mmol/l. A fasting venous blood sample was used to detect blood lipids and hs-CRP levels were determined in the early morning and within 24 h of admission. Neurological assessments were performed by evaluating the NIHSS and mRS scores at admission and during the follow-up examination (3 months after surgery). The 3-month mRS score was used to assess patient outcome; a score of 0-2 was considered as a favorable outcome and a score of 3-6 was considered to indicate a poor outcome (16,17).

Image acquisition and DWI lesion volume calculation. MRI was performed using a MAGNETOM Verio 3.0T scanner (Siemens AG). The MRI protocol included DWI, apparent diffusion coefficient, T1-weighted imaging, T2-weighted imaging, fluid-attenuated inversion recovery imaging and MR angiography. The DWI scan parameters were as follows: B value, 0 and 1,000; echo time, 100 msec; repetition time, 6,600 msec; phrase encoding direction, AàP; field of view (FOV) read, 220 mm; FOV phase, 100%; slice thickness, 5.0 mm; slice spacing, 1.0 mm; slices, 20; bandwidth, 1,002 Hz/Pixel; echo spacing, 1.08 msec; fat saturation mode, weak; concatenation, 1; and scan time, 74 sec. Within the DWI images, the lesions were manually delineated using ImageJ Software (version 1.8.0; National Institutes of Health) by three associate chief physicians (initials, BL, GL and WZ).
the area occupied by the lesion on each slice was then measured and the total of these areas was multiplied by the slice thickness.

Statistical analysis. Continuous or numerical variables were expressed as the mean ± standard deviation and median (interquartile range). Shapiro-Wilk test was used to test the normality of variances and Levene test was used to test the homogeneity of variances. Normally distributed variables with assumed homogeneity of variance were compared using the independent-samples t-test, and non-normally distributed variables or those without homogeneity of variance were

Table I. Demographic and baseline data of the patients (categorical variables).

| Item           | Poor outcome<sup>a</sup> | Favorable outcome<sup>a</sup> | Sum     | <sup>χ</sup><sup>2</sup> | P-value |
|----------------|--------------------------|-------------------------------|---------|--------------------------|---------|
| Sex            | Males                    | 37 (52.1)                    | 35 (74.5)| 72                       | 5.94    | 0.02    |
|                | Females                  | 34 (47.9)                    | 12 (25.5)| 46                       |         |         |
| Smoking        | Yes                      | 20 (28.2)                    | 19 (40.4)| 39                       | 1.92    | 0.23    |
|                | No                       | 51 (71.8)                    | 28 (59.6)| 79                       |         |         |
| Drinking       | Yes                      | 7 (9.9)                      | 9 (19.1) | 16                       | 2.08    | 0.18    |
|                | No                       | 64 (90.1)                    | 38 (80.9)| 102                      |         |         |
| Hypertension   | Yes                      | 45 (63.4)                    | 29 (61.7)| 74                       | 0.03    | 1.00    |
|                | No                       | 26 (36.6)                    | 18 (38.3)| 44                       |         |         |
| Diabetes       | Yes                      | 18 (25.4)                    | 7 (14.9) | 25                       | 1.85    | 0.25    |
|                | No                       | 53 (74.6)                    | 40 (85.1)| 93                       |         |         |

<sup>a</sup>The mRS score at 3 months after EVT was used as the efficacy criterion, in which 0-2 was considered as a favorable outcome and 3-6 was considered as poor outcome.

Table II. Patient data in association with the outcome.

| Item                        | Poor outcome (n=71)<sup>b</sup> | Favorable outcome (n=47)<sup>b</sup> | t/Z   | P-value |
|-----------------------------|----------------------------------|--------------------------------------|-------|---------|
| Age (years)                 | 70.5 (10.2)                      | 63.49 (11.21)                       | 3.53  | <0.01   |
| DWI lesion volume (mm³)     | 30,914.6 (41489.7)               | 7,724.8 (7606.2)                    | 3.60  | <0.01   |
| AG (mmol/l)                 | 9.6 (4.6)                        | 7.1 (1.9)                           | 3.93  | <0.01   |
| NIHSS score                 | 15.0 (5.8)                       | 9.4 (3.4)                           | 5.40  | <0.01   |
| ORT (min)                   | 376.4 (232.2)                    | 301.4 (141.4)                       | 1.61  | 0.11    |
| hs-CRP (mg/l)               | 52.0 (36.3)                      | 39.0 (25.8)                         | 2.13  | 0.03    |
| Operation time (min)        | 142.1 (56.4)                     | 133.6 (56.3)                        | 0.82  | 0.41    |
| SBP (mmHg)                  | 152.4 (25.1)                     | 153.7 (24.9)                        | 0.07  | 0.94    |
| DBP (mmHg)                  | 84.9 (15.0)                      | 88.8 (15.7)                         | 1.33  | 0.18    |
| HDL (mmol/l)                | 1.2 (0.3)                        | 1.1 (0.3)                           | 1.04  | 0.30    |
| LDL (mmol/l)                | 2.9 (1.0)                        | 2.9 (1.1)                           | 0.26  | 0.79    |
| TC (mmol/l)                 | 4.6 (1.1)                        | 4.3 (0.8)                           | 1.31  | 0.19    |

<sup>b</sup>The mRS score at 3 months after EVT was used as the efficacy criterion, which 0-2 was considered as a favorable outcome and 3-6 was considered as poor outcome.

<sup>a</sup>The mRS score at 3 months after EVT was used as the efficacy criterion, in which 0-2 was considered as a favorable outcome and 3-6 was considered as poor outcome (16,17).<br>
<sup>b</sup>Rank-Sum test. DWI, diffusion-weighted imaging; AG, glucose on admission; NIHSS, National Institutes of Health Stroke Scale; ORT, onset-to-reperfusion time; hs-CRP, high-sensitivity C-reactive protein; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol.
compared using the Mann-Whitney U-test. Categorical variables were expressed as the composition ratio or rate and comparisons were performed using Pearson's $\chi^2$ or Fisher's exact test. Non-conditional logistic stepwise regression was used to identify factors that were significantly associated with patient outcome, which can establish the optimal statistical model. The specificity and sensitivity of the threshold value for each predictive factor were analyzed by receiver operating characteristic (ROC) curve analysis. Statistical analyses were performed using SPSS 19.0 for Windows (IBM Corp.) and $P<0.05$ was considered to indicate a statistically significant difference.

Results

Predictors of patient outcome at 3 months post-surgery. Patient outcome was predicted using non-conditional logistic stepwise regression analysis, and the follow-up result at 3 months after EVT was used as the dependent variable (Favorable outcome, $Y=0$; Poor outcome, $Y=1$). The results indicated that the model was able to effectively predict patient outcome ($\chi^2=78.916; P<0.001$) and that the coincidence rate (accuracy) of the model was calculated to be 83.1% (Tables III and IV), which was higher compared with that obtained using only 1 or 2 factors. Factors affecting patient outcome were sex, age, DWI lesion volume, AG, NIHSS score and ORT. The results also suggested that female patients exhibited a poorer outcome compared with male patients (odds ratio=3.39; 95% confidence interval, 1.022-11.24; Table V).

ROC curve analysis of the predictors of patient outcome. ROC curve analyses showed that the Area Under the ROC Curve (AUC) of the statistical model was calculated to be 0.823 (Table VI). In addition, age, lesion volume, AG, NIHSS score on admission and hs-CRP were all found to be associated with the outcome of patients following EVT ($P<0.05$); however, the AUC calculated for each of the aforementioned single factors was not large (Fig. 2), ranging from 0.616 to 0.794 (Table VII). After taking specificity and sensitivity into account, the cut-off value of each factor is presented in Table VII. The specificity of the significant factors ranged from 60.6 to 76.1%, and the sensitivity ranged from 61.7 to 70.2%. No significant influence on patient outcome was determined for ORT, HDL, LDL, TC, SBP and DBP ($P>0.05$). Regarding the predictive value of each factor, the order was NIHSS score, AG, lesion volume, age and hs-CRP.

Discussion

EVT is one of the main methods to treating AIS at present. In order to determine the treatment plan after EVT, clinicians need to predict the outcome of patients with AIS.
who underwent EVT. However, as the outcome of AIS is under the influence of a variety of factors, the accuracy of predicting the outcome of EVT by using only one or two factors is relatively low. In the present study, non-conditional logistic stepwise regression was used to identify the factors significantly associated with patient outcome, including biochemical, clinical and imaging parameters, which were then applied to establish an optimal predictive statistical model. In addition, multivariate logistic regression model is convenient and stable, and is commonly applied in many outcome prediction models of some diseases (18,19). The ROC curve also showed that the statistical model in the present study exhibited higher AUC and verified sex, age, DWI lesion volume, AG, hs-CRP and NIHSS score on admission to be significantly associated with patient outcome.

Previous studies have predicted the outcome of AIS patients using only one or two factors, particularly the NIHSS score and age, which have been recognized as the most direct contributors to patient outcome (20). The NIHSS score indicates the degree of neurological function damage and is frequently used to determine the severity of the patient's condition on admission (21). The majority of studies have used the NIHSS score as an important predictive factor for patient outcome following AIS; however, the outcome threshold frequently differed among these studies (21). The present study also indicated that the NIHSS score on admission was the strongest factor associated with patient outcome, which was consistent with the conclusions of previous studies.

Age is a clinical indicator of the aging of cells of the nervous system. Aging results in molecular damage, organelle dysfunction and cellular injury within the neurovascular unit, which leads to structural and functional impairments (22). Furthermore, the acceleration of aging may contribute to an increased risk of cerebrovascular pathologies and limit the recovery capacity or neuroplasticity of the nervous system. It has been indicated that older patients are more prone to stroke and exhibit more severe post-stroke neurological and behavioral deficits compared with younger patients (23). The present study supported the association between age and outcome of patients with AIS. In previous studies on outcome prediction, age was frequently combined with other factors to predict patient outcome; a study by Möbius et al (24) achieved an accuracy of 73% using the NIH Stroke Scale index, the SPAN-100 index, which relied primarily on age and NIHSS score to predict the outcome of intravenous thrombolysis following AIS.

Since brain tissues have strict requirements regarding recanalization time, the outcome of patients with AIS has been indicated to correlate with the ORT (25). Todo et al (26) revealed that ORT combined with the NIHSS score was able to predict the outcome of patients with AIS with an accuracy of 77.1%. The ROC curve in the present study did not indicate significant correlation between ORT and patient outcome, which was in line with a study by Koizumi et al (27), which suggested that the ORT was not an important outcome predictor of mechanical thrombectomy in elderly patients. It was speculated that this may have been due to the short ORT of all patients (within the 24-h time window, with most patients treated within 12 h).

In addition, the present study indicated that males had a more favorable outcome compared with females; this supported the results of a study by White et al (28), which predicted more severe strokes and poorer outcomes in females. This may have been caused by the between-sex differences in androgen levels. Indeed, further studies indicated that decreased testosterone levels were associated with insulin resistance, blood lipid metabolism and mortality following
lesion volume and the outcome of EVT. The present study also indicated a relatively strong correlation between age and outcome of EVT was 82%. The present study mined that the predictive accuracy of the DWI infarct volume of >10 cm^3 for outcome of patients with AIS and may serve as an independent predictor of damaged brain tissue. Numerous studies have indicated that females have better outcomes compared with males following AIS. This expression, this further explains why males may have better outcomes compared with females following AIS. In addition, various studies have indicated that LDL and blood pressure between patients with good or poor outcomes. However, no previous study has used these factors to directly predict the outcome of AIS and achieve high accuracy. The present study did not reveal any significant differences in LDL and blood pressure between patients with good or poor outcomes. It may be hypothesized that this is due to these factors.

Table VII. Receiver operating characteristic curve analysis of predictive factors for the outcome of patients with anterior circulation acute ischemic stroke.

| Outcome measure          | AUC  | Cut-off value | P-value | Lower limit | Upper limit | Specificity (%) | Sensitivity (%) |
|--------------------------|------|---------------|---------|-------------|-------------|----------------|----------------|
| Age                      | 0.677| 68.5          | 0.001   | 0.578       | 0.776       | 63.4           | 61.7           |
| DWI lesion volume        | 0.696| 6494.5        | <0.001  | 0.603       | 0.790       | 70.4           | 61.7           |
| AG                       | 0.714| 7.2           | <0.001  | 0.620       | 0.809       | 73.2           | 61.7           |
| NIHSS score              | 0.794| 11.5          | <0.001  | 0.713       | 0.874       | 76.1           | 70.2           |
| hs-CRP                   | 0.616| 39.5          | 0.034   | 0.512       | 0.720       | 60.6           | 63.8           |
| ORT                      | 0.588| 272.5         | 0.108   | 0.483       | 0.692       | 53.5           | 55.3           |

DWI, diffusion-weighted imaging; AG, glucose on admission; NIHSS, National Institutes of Health Stroke Scale; hs-CRP, high-sensitivity C-reactive protein; ORT, onset-to-reperfusion time; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; CI, confidence interval; AUC, Area Under the ROC Curve.

Among the biochemical factors used to predict patient outcome, AG is the most representative. It is generally accepted that AG represents an independent predictor of patient outcome following AIS (33). Abnormalities in the endocrine system caused by stress after a stroke lead to an increase in cortisol, adrenaline and glucagon expression levels, which subsequently leads to a rise in blood glucose levels. Not only does hyperglycemia have a toxic effect on the nervous system, but it may also inhibit the fibrinolytic system and further aggravate the patient’s condition (34). The present study verified the correlation between AG and the outcome following EVT. hs-CRP is a marker of cardiovascular or cerebrovascular inflammatory responses, which is involved in cerebrovascular injury and pathological alterations, and indicates the severity of inflammation in brain tissue (35). hs-CRP may activate the complement system, increase the production of plasminogen inhibitors that damage vascular endothelial cells, and ultimately promote multiple-organ and microcirculatory dysfunction (33). Cai et al (7) revealed that hs-CRP predicted the outcome of patients with AIS, and in the present study, ROC curve analysis only indicated a weak correlation between hs-CRP and patient outcome, with the AUC calculated to be 0.616. In contrast, non-conditional logistic stepwise regression analysis disregarded hs-CRP as a predictor of patient outcome, which may have been due to the non-conditional logistic stepwise regression comprehensively considered the relationship between multiple variables and outcomes, whilst ROC curve analysis only consider the association between hs-CRP and outcome. In addition, ROC analysis also showed the lesser effect of hs-CRP on the outcome of AIS, since the AUC, specificity and sensitivity of hs-CRP were relatively lower compared with other significant factors.

In addition, various studies have indicated that LDL and blood pressure may be considered to be risk factors for AIS, which may be associated with the prognosis of AIS (36,37). However, no previous study has used these factors to directly predict the outcome of AIS and achieve high accuracy. The present study did not reveal any significant differences in LDL and blood pressure between patients with good or poor outcomes. It may be hypothesized that this is due to these factors.
factors not being associated with the stress reaction after AIS, and that patients may have received anti-hypertensive and/or hypolipidemic therapy prior to or after the onset of AIS.

As clinical, imaging and biochemical factors indicate the severity of AIS from different aspects (and the abnormalities of these factors may occur at different times), the accuracy of predicting the outcome of AIS by combining three different types of factor may be higher than that achieved with single factors alone. Regarding the prediction of the outcome of EVT using a combination of clinical, biochemical and imaging factors, the present study achieved an accuracy of 83.1%, which is higher than that obtained with any single factor alone (as determined by ROC curve analysis) in the present and in previous studies (26,32). Furthermore, unlike the texture features of the medical image (used in radiomics) that are easily affected by variations in instrument model or manufacturer, the factors selected in the present study have universally applicable standard values, increasing the research practicability. Future studies will encompass the collection and integration of additional factors associated with the outcome of patients with AIS and establish more accurate predictive models for the generation of more precise auxiliary information.

The present study had several limitations. First, due to the limitation of the condition, not all of the indicators associated with patient outcome were investigated (e.g., homocysteine and NT-proBNP levels) and abnormal alterations to these variables may still cause injury to the brain. Investigation of additional factors in future studies may further enhance the predictive accuracy. Furthermore, the present study had a relatively small sample size and was a single-center study lacking the validation of multicenter results.

In conclusion, a predictive model based on non-conditional logistic stepwise regression analysis was able to predict the outcome of EVT following AIS. Patients belonging to different outcome groups displayed significant differences in sex, age, DWI lesion volume, hs-CRP, NIHSS score on admission and/or AG. The present study provided novel insight into the predictive capacity of these factors for patients with AIS.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

BL and XW conceived and designed the study. XW, XL, YW, SZ and WL collected and organized the data. BL, GL and WZ manually delineated the DWI infarct lesion data. XW and AO analyzed and interpreted the data, and XW wrote the manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of The Second Clinical College of Guangzhou University of Chinese Medicine (Guangzhou, China). The present study is a retrospective clinical analysis without any additional intervention for the patients. The requirement for informed consent was waived due to the retrospective nature of this analysis.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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