Derivation of a Prediction Rule for Unfavourable Outcome after Ischemic Stroke in the Chinese Population

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Abstract

Background: Efficient assessment of patients after ischemic stroke has important reference value for doctors to choose appropriate treatment and rehabilitation method for patients. Our study aimed to develop a new prognostic model for predicting outcomes three months after ischemic stroke among Chinese Population.

Methods: A prospective observational cohort study among ischemic stroke patients presenting to Emergency Department in the Second Affiliated Hospital of Guangzhou Medical University was conducted from May 2012 to June 2013. Demographic data of ischemic stroke patients, assessment of NIHSS and laboratory results were collected. Based on three-month modified Rankin Scale (mRS) ischemic stroke patients were divided into either favorable outcome (mRS: 0-2) or unfavorable outcome groups (mRS: 3-6). The variables closely associated with prognosis of ischemic stroke were selected to develop the new prognostic model consisted of four parameters: NIHSS, age, atrial fibrillation (AF), prealbumin (PA). The prognostic value of the modified prognostic model (NAAP: NIHSS+Age+AF+PA) was then compared with NIHSS alone.

Results: A total of 454 patients with suspected stroke were recruited. 186 patients with ischemic stroke were included in the final analysis. There were 105 (56.5%) cases of ischemic stroke with favorable outcome, and 81 (43.5%) cases of ischemic stroke with unfavorable outcome. A new prognostic model, NAAP was developed. The area under curve (AUC) of NAAP was 0.861 (95%CI: 0.803-0.907), whilst the AUC of NIHSS was 0.783 (95%CI: 0.717-0.840), (P=0.0048). Decision curve analysis (DCA) showed that NAAP had a higher net benefit for threshold probabilities of 65% for predictive risk of poor outcomes.

Conclusion: The modified prognostic model, NAAP may be a better prognostic tool for predicting 3-month unfavorable outcomes for ischemic stroke than NIHSS alone.

Keywords: prognosis, ischemic stroke, NIHSS, emergency department, decision curve analysis.

Background

Ischemic stroke is a common disease in China and worldwide [1]. Although the mortality of ischemic stroke has been declining in recent years, the disability rate of ischemic stroke is still high [2]. In the United States about 800,000 people could not take care of their daily life by themselves due to ischemic stroke every year [3]. In China, stroke causes a heavy burden on society in the past 30 years [4]. Efficient assessment of patients after ischemic stroke is important as it allows doctors to choose appropriate early treatment and rehabilitation methods.

The National Institutes of Health Stroke Scale (NIHSS) can reflect severity of neurological impairment and is recommended for prognosis of patients with ischemic stroke [5, 6]. However, many other factors are associated with the prognosis of patients with ischemic stroke, including age, gender, medical history, infarct size, location of ischemic stroke and complication, and biomarkers such as total bilirubin, uric acid and prealbumin [7-13]. Many prognostic models for ischemic stroke, including additional predictors to NIHSS have been published from the west but there are few studies from developing countries [7].

The objective of this study was to develop a emergency department-based prognostic model for ischemic stroke in the Chinese population. We applied a regression analysis to demographic data, medical history and clinical blood biomarkers of patients with ischemic stroke, and investigated which of these variables could improve the prognostic power of NIHSS alone in predicting 3-month post-stroke modified Rankin Scale.

Methods

Study design

This study was a prospective observational study. Patients with ischemic stroke were recruited consecutively and followed up from May 2012 to June 2013. Ethical approval was obtained from the Clinical Research Ethics Committee of the Second Affiliated Hospital of Guangzhou Medical University (AHGZMU).

Study setting

This study was conducted in the Emergency Department (ED) of AHGZMU, which serves a population of approximately 1.56 million people in the Hai Zhu district, Guangzhou. It is an academic hospital with 2500 beds affiliated with the Guangzhou Medical University. The ED receives more than 150 000 new patients per annum and serves a local population of approximately 3030 000 people.

Inclusion and exclusion criteria

Suspected stroke patients ≥ 18 years old presenting to the ED with symptoms or signs onset within 72 hours were recruited. Patients were excluded if they were <18 years old or had traumatic brain injury.

Data collection

Demographic data of ischemic stroke patients including gender, age, medical history, clinical manifestations, the assessment of NIHSS and laboratory results were collected. Ischemic stroke patients were divided into favorable outcome or unfavorable outcome groups based on the three-month modified Rankin Scale (mRS). All the doctors in this study have obtained the certification of NIHSS. Blood samples were drawn from patients with symptoms or signs onset within 72 hours. Laboratory

results were collected from the Central Laboratory of AHGZMU. The modified Rankin Scale at 3 months (3month mRS) after ED diagnosis were recorded by phone interview.

Statistical analyses

Categorical variables were compared using Chi-square analysis, whilst continuous variables were compared using independent t-tests. Firstly, univariate logistic regression analysis was used on all variables, and results were presented as odds ratios (ORs) with 95%CI. Significant variables ($p<0.05$) were further analyzed using backward stepwise multivariate logistic regression and used to develop the prognostic model for ischemic stroke. mRS was used to distinguish between ischemic stroke patients with favorable (mRS: 0-2) and unfavorable (mRS: 3-6) outcomes. Prognostic performances of the new model and NIHSS were compared using receiver operating characteristic curve (ROC) analysis. Decision curve analysis (DCA) was used to compare the clinical usefulness of the new model and NIHSS the full range of threshold mortality risk probabilities [14]. All analyses were performed using SPSS v18.0 (SPSS Inc, IL, USA), MedCalc v12.7.0 (MedCalc Software, Mariakerke, Belgium) and the R statistical package (https://www.r-project.org, https://github.com/mdbrown/rmda).

Results

Demographic and clinical characteristics

A total of 454 patients were recruited between May 2012 and June 2013. After 268 exclusions, 186 cases with ischemic stroke were included in the final analysis. There

were 105 (56.5%) cases of ischemic stroke with favorable outcome, and 81 (43.5%) cases of ischemic stroke with unfavorable outcome (Figure1). Compared with favorable outcome group, patients with unfavorable outcome were older, and had higher percentage of female, coronary heart disease, atrial fibrillation (AF). NIHSS score and concentrations of total bilirubin (TBIL) and monocyte counts (MON) in unfavorable group were higher than those in favorable outcome group. On the contrary, concentrations of uric acid (UA) and prealbumin (PA) in favorable group were higher than those in unfavorable group (Table 1).

Logistic regression analysis of NIHSS and other variables

Firstly, as shown in Table 2, univariate logistic regression was applied to analyze variables including gender, age, medical record, NIHSS, laboratory results for favorable outcome and unfavorable outcome groups. Variables showing statistical significance between two groups included male, age, coronary heart disease, AF, NIHSS, MON, TBIL, UA, PA . Secondly, those above variables were further analyzed by multivariate logistic regression. Only NIHSS, age, AF and PA showed statistical significance between the two groups. As shown in Table 3, the optimal cut-off values and the area under curve (AUC) included NIHSS (cut-off: >6, AUC: 0.783, 95%CI: 0.717-0.840), age (cut-off: >79, AUC: 0.705, 95%CI: 0.634-0.770), AF (cut-off: Yes, AUC:0.587, 95%CI: 0.513-0.659), PA (cut-off: ≤180 mg/L, AUC: 0.661, 95%CI: 0.588-0.729).

Prognostic performances of NAAP **and NIHSS**

Comparison of NAAP and NIHSS was undertaken using ROC analysis (Figure 2). The area under curve (AUC) for NAAP was 0.861 (95%CI 0.803-0.907), whilst the AUC

for NIHSS was 0.783(95%CI 0.717-0.840). Discrimination of the prognostic scores for 90-day unfavorable outcome showed that the modified NIHSS was superior to the original NIHSS (P=0.0048). As shown in Figure 3, the net benefit for the modified and original NIHSS scores surpassed the strategies of treat all and treat none between threshold probabilities of 20% and 80%. Above a threshold probability of 65%, the two scores had a similar net benefit. Below a threshold probability of 65%, the NAAP became superior to the original NIHSS.

Discussion

In this study, the common predictors of prognosis of ischemic stroke were analyzed comprehensively and the modified prognostic model, NAAP was firstly developed based on NIHSS in Chinese population.

Ischemic stroke is a common disease in Emergency Departments and prognosis of ischemic stroke is one of the most concerned problems to doctors, patients and family members. NIHSS is a 15-item scale which can reflect severity of neurological impairment of cerebral infarction. It is associated with infarct size and 3-month prognosis of cerebral infarction [15-17]. Our results showed that the NIHSS score of favorable outcome group was lower than that of the unfavorable outcome group (6.1±5.69 vs14.01±9.07, $p<0.001$) and the OR of NIHSS score was 1.16 in the regression model. NIHSS was associated with unfavorable outcome after three months of cerebral infarction when the NIHSS score was >6 by ROC analysis, which was consistent with the results of an earlier research [5]. However, in our study, the AUC of NIHSS for predicting favorable outcome of ischemic stroke is 0.783, which suggested that the predictive effectiveness of NIHSS requires further improvement.

In order to investigate factors that could improve the predictive effectiveness of NIHSS, our study summed up the patient's gender, age, medical history, NIHSS and routine blood test results. Univariate logistic regression was used to analyze all the above variables. Then variables with statistically significant were put into multivariate logistic regression analysis and NAAP was developed. Decision curve analysis and ROC analysis confirmed the clinical usefulness of NAAP. Our results suggested that using NAAP to predict unfavorable outcome of ischemic stroke after three months might be better than using the original NIHSS.

NAAP which was developed in the Chinese population was similar to many western prognostic models. Not only NIHSS was included in many models, but also age, as a common and important predictor, was included in the models [7]. Studies suggested that age was an independent risk factor for poor outcome in patients with ischemic stroke. Besides, age combined with NIHSS could be used to assess the risk of bleeding after thrombolysis treatment for ischemic stroke [18-21]. In our study, patients with favorable outcome were younger than those with unfavorable outcome (66.9±13.0 vs75.6±11.3 years old, $p<0.001$). By logistic regression and ROC analysis, age showed a good predictive performance for prognosis of unfavorable outcome in patients with ischemic stroke (OR 1.07, 95%CI: 1.030-1.103; AUC 0.705, optimal cut-off >79 years old). The medical history of ischemic stroke patients was also good predictors, such as diabetes, coronary heart disease, atrial fibrillation and other diseases [22-24]. Therefore, in our study, medical history of ischemic stroke patients was also included in the regression analysis. Patients in favorable outcome group were less likely to have atrial fibrillation (4.8% vs. 22.2%, $P<0.001$). Our result suggested AF was also a good predictor in the new model (OR 4.21, 95%CI: 1.331-13.315; AUC 0.587). Atrial fibrillation is one of the common causes of ischemic

stroke. Early detection and treatment of atrial fibrillation is an important measure to prevent ischemic stroke [25-28]. Many studies showed that atrial fibrillation was associated with severe cerebral infarction. No matter thrombolytic therapy was administered for ischemic stroke or not, patients with atrial fibrillation were more likely to have poor outcome than those without atrial fibrillation [29-32].

Many biomarkers have been shown to be associated with the prognosis of cerebral infarction, such as hemoglobin, albumin, total bilirubin, fasting blood glucose, creatinine, uric acid, prealbumin etc. [12, 13, 33-38]. These biomarkers were analyzed comprehensively by logistic regression in our study. Serum prealbumin was found to be one of the good predictors in the multivariate regression model. Concentration of serum prealbumin of favorable outcome group was higher than that of unfavorable outcome group (218.8±57.6 vs. 186.0±55.6, $P < 0.001$). Prealbumin was found to be a good predictor in the new model (OR: 0.992, 95%CI: 0.985-1.000; AUC: 0.661, optimal cut-off ≤180 mg/L). There might be two reasons to explain this. First, prealbumin was a kind of homotetrameric protein which carries thyroid hormone and retinol, which was one of the best indicators of patients' nutritional status[39]. Low concentrations of serum prealbumin suggested malnutrition which was an independent risk factor for poor outcome in acute stroke [40, 41]. Second, low concentration of serum prealbumin was found to be related to stroke-associated infections [12]. Stroke-associated infection was an independent risk factor for poor outcome of acute cerebral infarction [42].

Strength of this study was that the four predictors included in NAAP, NIHSS, age, AF and PA, could be obtained more easily than other predictors in acute ischemic stroke, which was beneficial to the early determination of prognosis of cerebral infarction. For example, some studies included MRI findings as predictors. Prognosis

of ischemic stroke was determined by assessing the volume of cerebral infarction [7]. However, patients often failed to perform MRI in early stage of ischemic stroke in emergency room. In addition, a new blood biomarker, serum prealbumin was the first time to be included in NAAP, which could improve predictive effectiveness of predicting prognosis of ischemic stroke.

Limitations

First, our study was a single-center study among Chinese population in Guangzhou. The results might not be able to represent the population in China. Second, this study was only a development phase. Prospective multi-center studies are required to validate the prognostic performance of the modified prognostic model.

Conclusion

The modified prognostic model, NAAP may be a better prognostic tool for predicting short-term unfavorable outcome for ischemic stroke than NIHSS alone.

List of abbreviations

ALB	Albumin
AF	Atrial Fibrillation
APOA1	Apolipoprotein A1
APOB	Apolipoprotein B
AUC	Area under the ROC curve
CHOL	Cholesterol
CT	Computed Tomography
CREA	Creatinine
DCA	Decision Curve Analysis
DWI	Diffusion Weighted Imaging
FBG	Fasting Blood Glucose detection
GCS	Glasgow Coma Scale
HGB	Hemoglobin
LYM	Lymphocyte
MON	Monocytes
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NEU	Neutrophil
NIHSS	National Institute of Health stroke scale
OR	Odds Ratio
PA	Prealbumin
PLT	Platelet
ROC	Receiver operating characteristic
TBIL	Total Bilirubin
TG	Triglyceride
UA	Uric Acid
WBC	White Blood Cell Count

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

HM and QW designed the study and undertook the statistical analysis. HM, QW and JM were involved in collecting data. PL, SL, THR and HJ contributed to manuscript revision. The corresponding author XC supervised the whole study. All authors have read and approved the final manuscript.

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