Cardiogenic Parameters Effectively Predict Hemorrhagic Transformation in Patients with Non-Large Artery Atherosclerosis Infarction

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Abstract

**Background:** Non-large artery atherosclerosis (LAA) infarcts are relatively rare compared to LAA type infarcts. Hemorrhagic transformation (HT) is one of the complications of acute ischemic stroke (AIS), and we aim to investigate the risk factors for the development of HT in patients with non-LAA type AIS.

**Patients and methods:** From January 2015 to January 2020, we included a total of 52 patients with non-LAA type AIS who met the criteria for the occurrence of HT, for which 136 patients without HT were matched. Patients were followed up every 3 months by phone or in the clinic, with a minimum of 1 year of follow-up per patient. The risk factors associated with prognosis were derived after univariate analysis and multifactorial logistic regression analysis, and a nomogram model was developed based on these risk factors. The accuracy of the model was evaluated by creating a calibration plot and the receiver operating characteristic curve (ROC).

**Results:** Through univariate analysis and logistics regression analysis, we found that the patient's creatine kinase-MB (CK-MB), ejection fraction (EF) and platelets (PLT) were independently related to the HT in patients with non-LAA type AIS. We accordingly developed smoothing curves to predict the probability of HT and found that the HT rate increased with increasing CK-MB and decreased with increasing EF and PLT. The nomogram based on these three factors had an area under curve (AUC) of 0.875 for the development group and 0.889 for the external validation group. The calibration plot showed a good prediction accuracy.

**Conclusions:** Patients with non-LAA type AIS are relatively uncommon and presenting with HT is even rarer. Our nomogram built on cardiogenic parameters and PLT can accurately predict the occurrence of HT in these non-LAA type AIS patients, which has good clinical significance.

Introduction

With the progress of aging, the incidence of cerebrovascular disease has been continuously increasing, and it has become one of the main causes of death and disability, seriously threatening the life and health of the elderly(1). The current problem of stroke is a huge challenge we face and is causing great concern. Among acute ischemic stroke (AIS), the large artery atherosclerosis (LAA) is the most common, with more than half of the AIS in the deng's (2) study being LAA, the rest including cardioembolism, small-artery occlusion, and other causes(3, 4). The classification of approximately 35% of patients is still unclear. Therefore, we should still pay attention to non-LAA AIS patients.

Among the many factors influencing stroke, the cerebrocardiac axis has a long history of research and has been a popular topic among scholars. In the late 1940s, Byer et al.(5) reported for the first time that central nervous system diseases can cause abnormal T waves in the ECG. Clinically, the secondary changes in electrical activity of the heart caused by various brain diseases (acute cerebrovascular disease, acute craniocerebral injury, intracranial inflammation) are called cerebrocardical syndrome. Previous studies had shown that N-terminal pro-brain natriuretic peptide (NT-proBNP) and creatine kinase-
MB (CK-MB are closely associated with elevated troponin(6). Elevated myocardial enzyme profiles secondary to AIS are common clinically, and most of them are dominated by CK and CK-MB, especially elevated CK-MB, further indicating the presence of myocardial lesions(7). We had explored this in depth in our previous studies. In LAA patients, we found that the patient’s neutrophil-to-lymphocyte ratio was an important risk factor for the development of HT(8); In non-LAA patients, we found cardiogenic parameters to be a factor in the occurrence of poor prognosis in these patients(9). These prediction models established by us above can predict patient’s outcome well. The purpose of this study is to gain more insight into the risk factors for the development of HT in patients with AIS who are non-LAA.

**Materials And Methods**

This study was approved by the Ethics Committee of the Weifang Medical University and conformed to the Helsinki Declaration. From January 2015 to January 2020, a total of 52 patients with non-LAA HT were included, along with 136 patients with non-LAA who did not undergo HT. We used a total of 107 patients hospitalized between January 2015 and January 2018 as the development group, while 81 patients from January 2018 to January 2020 were used as external validation group.

Exclusion criteria

Exclusion criteria: 1, excluding other vascular infarction, cerebral venous thrombosis; 2, patients with transient ischemic attack, cerebral hemorrhage or subarachnoid hemorrhage; 3, late hospitalization (> 24 hours after stroke onset); 4, a definitive diagnosis of LAA type AIS; 5, lost to follow-up or lack of outcome variables.

**Clinical And Laboratory Assessments**

Cerebrovascular events were classified according to the the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) criteria(10). All blood indicators were tested on an empty stomach in the early morning of the second day after admission. The demographics, chronic diseases, hematology parameters, and imaging results of all patients were collected using standardized data records. Cardiogenic parameters include left ventricular diastolic diameter (LVDD), left ventricular systolic diameter (LVSD), left atrium diameter (LAD), left ventricular septal thickness (LVST), ventricular posterior wall thickness (LVWT), CK, CK-MB, and EF. All echocardiography was performed on the second day of admission by echocardiologists specializing in cardiogenic imaging. Troponin and myoglobin were not included in this study due to excessive missing data.

**Follow-up**
Each patient was followed up for a minimum of 1 year, and we assessed the prognosis of the patients by telephone, questionnaires, and outpatient review. Two independent investigators evaluated all clinical data blind; any disagreement was resolved by a third researcher.

**Statistical analysis**

Categorical variables were compared with the chi-square test, and continuous variable were compared with the Kruskal Wallis rank sum test or t-test. Logistics regression analysis was used for multivariate analyses. The nomogram was constructed via such analyses performed with rms 26 in R version. After logistic regression analysis and calculation of factors(P < 0.05), we ranked nomogram variables using their P values and assessed the performance of the nomogram by calculating the area under curve (AUC). The smoothing curves of the prediction probabilities were built by the survival package and the rms package, and the receiver operating characteristic curve (ROC) is built in the pROC package. All calculations were based on R version 3.6.1.

**Results**

**Patient characteristics**

Table 1 shows the baseline data of the patients. A total of 188 patients with non-LAA AIS were included in this study, and 107 patients hospitalized between January 2015 and January 2018 were selected as the development group, while 81 patients from January 2018 to January 2020 were used as external validation group. Of these 188 patients, 60 were women and 128 were men, with a mean age of 70.20 years. The mean age of the patients who experienced HT was 70.81 years, while the mean age of the patients who did not experience HT was 69.96 years. The mean EF was 56.0 in the HT group compared with 64.11 in the non-HT group; the mean CK-MB was 15.90 in the HT group compared with 13.18 in the non-HT group; and the mean platelets (PLT) was 192.06 in the HT group compared with 239.57 in the non-HT group. All three of these were statistically different.
|                  | Non-HT group | HT group | P value |
|------------------|--------------|----------|---------|
| Age              | 69.96 ± 13.12| 70.81 ± 11.05 | 0.995 |
| SBP              | 146.18 ± 23.59 | 149.04 ± 22.55 | 0.469 |
| DBP              | 81.54 ± 13.98 | 84.77 ± 16.05 | 0.224 |
| WBC              | 7.44 ± 2.61 | 10.28 ± 3.48 | < 0.001 |
| Neutrophil       | 5.19 ± 2.46 | 8.38 ± 4.27 | < 0.001 |
| Lymphocyte       | 1.52 ± 0.71 | 1.22 ± 0.52 | 0.006 |
| RBC              | 4.37 ± 0.67 | 4.54 ± 0.59 | 0.068 |
| HB               | 132.29 ± 21.60 | 137.25 ± 17.90 | 0.152 |
| PLT              | 239.57 ± 74.46 | 192.06 ± 54.75 | < 0.001 |
| Albumin          | 36.45 ± 3.75 | 35.84 ± 6.48 | 0.676 |
| ALT              | 27.24 ± 46.44 | 31.29 ± 32.13 | 0.224 |
| AST              | 32.88 ± 37.94 | 37.69 ± 24.42 | 0.018 |
| LVDD             | 49.26 ± 5.62 | 49.65 ± 4.43 | 0.533 |
| LVSD             | 33.31 ± 6.15 | 32.85 ± 5.00 | 0.817 |
| LAD              | 45.47 ± 7.46 | 46.38 ± 5.89 | 0.154 |
| LVST             | 10.93 ± 2.14 | 10.59 ± 1.48 | 0.492 |
| LVWT             | 10.47 ± 1.40 | 10.40 ± 1.37 | 0.946 |
| EF               | 64.11 ± 5.70 | 56.00 ± 6.14 | < 0.001 |
| TB               | 14.42 ± 8.44 | 16.33 ± 8.50 | 0.045 |
| BUN              | 6.40 ± 3.68 | 7.30 ± 3.42 | 0.038 |
| Cr               | 84.51 ± 52.58 | 108.02 ± 96.54 | 0.661 |
| TC               | 4.30 ± 1.10 | 3.78 ± 1.37 | 0.052 |

SBP systolic blood pressure, DBP Diastolic blood pressure, WBC white blood cell, RBC red blood cell, HB hemoglobin, PLT platelet, ALT alanine aminotransferase, AST aspartate aminotransferase, LVDD left ventricular diastolic diameter, LVSD left ventricular systolic diameter, LAD left atrial diameter, LVST left ventricular septal thickness, EF ejection fraction, TB total bilirubin, BUN Blood urea nitrogen, Cr creatinine, TC total cholesterol, TG triglyceride, HDL high density lipoprotein, LDL low density lipoprotein, CK creatine kinase, CK-MB creatine kinase-MB, DM diabetes mellitus, AF Atrial brillation, NIHSS National Institutes of Health Stroke Scale on admission
|                  | Non-HT group       | HT group          | P value |
|------------------|--------------------|-------------------|---------|
| TG               | 1.42 ± 0.79        | 1.37 ± 0.90       | 0.323   |
| HDL              | 1.24 ± 0.48        | 1.30 ± 0.52       | 0.477   |
| LDL              | 2.28 ± 0.74        | 2.20 ± 0.83       | 0.932   |
| CK               | 136.42 ± 158.50    | 154.96 ± 106.79   | 0.003   |
| CK-MB            | 13.18 ± 4.36       | 15.90 ± 5.68      | 0.002   |
| Na               | 140.04 ± 3.39      | 136.12 ± 13.08    | 0.163   |
| K                | 3.89 ± 0.39        | 4.08 ± 0.61       | 0.081   |
| Ca               | 2.17 ± 0.15        | 2.01 ± 0.40       | 0.072   |
| Hb1c             | 6.08 ± 0.93        | 6.03 ± 1.54       | 0.795   |
| Sex              | 30.90%             | 34.60%            | 0.623   |
| Hypertension     | 22.80%             | 23.10%            | 0.967   |
| DM               | 72.80%             | 73.10%            | 0.969   |
| AF               | 39.00%             | 17.30%            | 0.005   |
| Hyperlipidemia   | 55.90%             | 40.40%            | 0.057   |
| Smoke            | 60.30%             | 67.30%            | 0.375   |
| Drink            | 65.40%             | 75.00%            | 0.209   |
| NIHSS            | 5.85 ± 5.21        | 9.00 ± 5.49       | <0.001  |

SBP systolic blood pressure, DBP Diastolic blood pressure, WBC white blood cell, RBC red blood cell, HB hemoglobin, PLT platelet, ALT alanine aminotransferase, AST aspartate aminotransferase, LVDD left ventricular diastolic diameter, LVSD left ventricular systolic diameter, LAD left atrial diameter, LVST left ventricular septal thickness, LVWT left ventricular septal thickness, EF ejection fraction, TB total bilirubin, BUN Blood urea nitrogen, Cr creatinine, TC total cholesterol, TG triglyceride, HDL high density lipoprotein, LDL low density lipoprotein, CK creatine kinase, CK-MB creatine kinase-MB, DM diabetes mellitus, AF Atrial brillation, NIHSS National Institutes of Health Stroke Scale on admission.

From the univariate analysis, patients were found to have statistically significant differences in white blood cell, neutrophils, lymphocytes, PLT, aspartate transaminase, EF, blood urea nitrogen, CK, CK-MB, atrial fibrillation, and admission NIHSS score. After multifactorial logistics regression correction, we found that patients’ EF (OR:0.836, 95% CI:0.765–0.914, P < 0.001), CK-MB (OR:0.235, 95% CI:1.087–1.402, P = 0.001) and PLT (OR:0.984, 95% CI:0.976–0.993, P = 0.001), a total of 3 variables had an independent effect on the prognosis of patients (Table 2). Figure 1 demonstrates the association between EF, CK-MB and PLT and the probability of HT in patients. As shown in the figure, the probability of HT in
non-LAA patients gradually increased with the increase of CK-MB; conversely, as EF and PLT increased, their probability of HT decreased. Gray shading demonstrates the distribution density of patients.

| Table 2
Multivariate logistic to the functional outcomes according to the functional outcomes |
|---------|---------|---------|
| OR      | 95% CI  | P       |
| NIHSS   | 0.958   | 0.864–1.061 | 0.407 |
| EF      | 0.836   | 0.765–0.914 | <0.001 |
| WBC     | 1.286   | 0.723–2.286 | 0.392 |
| Neutrophil | 1.03   | 0.587–1.809 | 0.918 |
| Lymphocyte | 0.776  | 0.295–2.039 | 0.606 |
| PLT     | 0.984   | 0.976–0.993 | 0.001 |
| TB      | 0.99    | 0.928–1.057 | 0.773 |
| BUN     | 0.992   | 0.857–1.148 | 0.913 |
| AST     | 1.002   | 0.990–1.013 | 0.796 |
| AF      | 1.636   | 0.533–5.021 | 0.39 |
| CK      | 0.997   | 0.993–1.001 | 0.124 |
| CK-MB   | 1.235   | 1.087–1.402 | 0.001 |

WBC white blood cell, PLT platelet, AST aspartate aminotransferase, EF ejection fraction, TB total bilirubin, BUN Blood urea nitrogen, CK-MB creatine kinase-MB, AF Atrial fibrillation, NIHSS National Institutes of Health Stroke Scale on admission

So on this basis, we built the nomogram (Fig. 2). The established model has good predictive power with AUC = 0.875 in the development group and AUC = 0.889 in the validation group (Fig. 3). Meanwhile, the calibration plots for the development and validation groups, again, show that the model has good predictive power (Fig. 4). Decision curve analysis (DCA) in both groups revealed a good net benefit (Fig. 5).

**Discussion**

Using a development cohort derived from the prospective continuous hospital stroke registry of the Weifang Medical University, we found that cardiogenic parameters were good predictors of HT in non-LAA patients. The external validation was then a cohort of patients from the same center at different time periods. In our previous study, neutrophil-to-lymphocyte ratio was found to be one of the risk factors for HT in patients with LAA, and the model developed accordingly had an AUC of 0.832, which also predicted the outcome well for both PH and HI(8). In another study of ours, it was found that cardiogenic
parameters were risk factors for worse prognosis of patients with non-LAA AIS, the nomogram based on cardiogenic parameters and NIHSS scores established was a good predictor of the prognosis of patients with non-LAA, and its AUC reached 0.954\(^{(9)}\). Therefore, we raised the question: whether cardiogenic parameters have a significant impact on the occurrence of HT in patients with non-LAA AIS. Hence, we explored this. In the present study, we found that cardiogenic parameters (EF and CK-MB) and PLT in non-LAA patients were risk factors for the development of HT. The model built on this basis had an AUC of 0.875, and external validation showed excellent verifiability of the model with an AUC of 0.889.

LAA is a key subtype of the TOAST classification system\(^{(10)}\). Unfortunately, approximately 35% of ischemic events remain cryptogenic, mainly because no underlying etiologic mechanism is identified, even after performing all available diagnostic tests\(^{(11)}\). Thus, despite the predominance of LAA types, non-LAA still plays an important role in AIS, and we should still pay attention to non-LAA patients.

HT is not uncommon in stroke patients, but is far from being taken seriously by clinicians. HT may be caused by AIS or secondary brain edema, injury after ischemia reperfusion or adverse reactions such as recombinant tissue plasminogen activator (rt-PA) or urokinase thrombolysis\(^{(12)}\). With the increasing use of thrombolytic stroke therapy, this phenomenon may become more common\(^{(13)}\). Current treatment guidelines recommend anticoagulants, thrombolysis and endovascular manipulation for eligible patients with cardiogenic stroke\(^{(14)}\) \(^{(15)}\). Despite these recommendations, these treatments are underutilized due to concerns about the risk of HT\(^{(16)}\). Therefore, how to reduce the probability of HT is a consideration for clinicians.

Cerebrocardiogenic syndrome is a dysfunction of the autonomic nervous system that leads to cardiovascular dysfunction after acute encephalopathy, especially after stroke or traumatic brain injury, usually accompanied by electrocardiographic and myocardial enzyme changes. It has been reported in the literature that the mechanism of cardiogenic alterations secondary to acute cerebrovascular disease may be: (1) The regulation of cardiogenic autonomic nerve is unbalanced. Hypothalamus, brainstem and limbic system are the regulatory centers of cardiogenic autonomic nerve, regulating the activities of sympathetic and parasympathetic nerves. These parts of the injury will cause abnormal release of renin-angiotensin, resulting in abnormal activity of the high-level autonomic nerve and uncontrolled balance regulation of sympathetic and parasympathetic nerves. The predominance of the sympathetic nervous system causes disturbances in the regulation of the cardiovascular nerve center, resulting in abnormal changes in the patient's heart rhythm, leading to arrhythmias\(^{(17)}\). (2) Various craniocerebral diseases cause nerve center damage, leading to neurological and humoral regulation disorders, and a large amount of catecholamine (CA) and other transmitters are released into the blood. It has been found that the degree of brain damage is directly proportional to the release of CA, and the more severe the nerve center damage, the higher the concentration of CA in the peripheral blood. High concentrations of CA in the blood cause PLT to aggregate and form thrombi, blocking small blood vessels in the heart and causing localized myocardial ischemia\(^{(18)}\). The significant increase in CA may be directly related to changes in myocardial enzymes. At the same time, arginine-vasopressin (AVP), angiotensin\(^{\text{I}}\) (Ang\(^{\text{I}}\)) and nitrous oxide (NO) are also significantly increased, which can cause coronary artery spasm, and even
necrosis of the myocardium, resulting in increased myocardial enzyme spectrum, abnormal ST-T, various arrhythmia, QT interval prolongation, and U wave abnormality on ECG(19, 20). This means that the sicker the patient is, the more likely the ECG and cardiogenic enzymes will be abnormal.

The occurrence of HT is widely related to the destruction of the blood brain barrier (BBB), and autonomic dysfunction promotes the destruction of BBB. The BBB consists of endothelial cells of the microvasculature and basement membrane that protect the brain from harmful chemicals, changes in blood composition and concentration gradients(21). After ischemic injury, the permeability of the BBB increases significantly, leading to the spillage of plasma components and the formation of edema(22, 23). Stroke-induced chronic cardiogenic dysfunction has been reported to be associated with slow sympathetic nerve activity(24). Multiple mechanisms may contribute to elevated serum CK-MB concentrations in the early stages of stroke, such as central activation of the sympathoadrenal system. Apparently serum CK-MB levels showed dynamic perturbations with hematoma volume, suggesting that myocardial degeneration and necrosis were involved in the induction and progression of cerebral hemorrhage. In addition, disruption of the BBB is associated with increased diffusion of noradrenaline into the circulation. Potentially important roles of the immune system and neurovascular units in BBB maintenance, whose dysregulation may lead to autonomic dysfunction. Autonomic dysfunction is widely associated with the action of the renin-angiotensin system in the periphery and brain. Infusion of angiotensin II (Ang II), a potent vasoactive peptide, elevates blood pressure and increases sympathetic output. The central effects of Ang II on autonomic function and its downstream effects, including oxidative stress, neuroinflammation and BBB disruption, have been recognized(25). The study provides further evidence that the BBB is a critical interface and that disruption of the BBB may lead to altered brain function, autonomic dysregulation, and disease progression or progression.

Changes in cardiogenic function are related to cerebral microbleeds (CMB). Tomohiko Watanabe et al. (26) found an increased incidence of CMB in patients with hyposystolic left ventricular function. Their study showed that CMB is frequently observed in patients with cardiovascular disease and is associated with age and left ventricular systolic dysfunction. Study shows CMB is associated with cerebral hypoperfusion(27, 28). Patients with heart failure and reduced EF have a consequent change in cardiogenic output and blood pressure and therefore lower cerebral blood flow. In other words, reduced cardiogenic function reduces systemic blood flow, including cerebral blood flow, and leads to chronic underperfusion and consequent cerebrovascular damage(29–32). Studies have demonstrated that experimental stroke in rats without primary heart disease or underlying vascular lesions induces cardiogenic abnormalities, including functional changes, such as reduced cardiogenic EF, and morphological changes, such as cardiomyocyte hypertrophy and interstitial fibrosis. Therefore, low EF may be related to the increased incidence of HT in patients

Conclusion

Cardiogenic parameters play a key role in the development of non-LAA HT, and autonomic dysfunction may be one of the mechanisms of its development. In clinical work, the finding may lead to a different
way of thinking for clinicians when treating patients with non-LAA AIS.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Weifang Medical University and conformed to the Helsinki Declaration.

Consent for publication

Not applicable

Availability of data and materials

The datasets during the current study available from the corresponding author on reasonable request.

Conflict of interest

The authors declare no financial or other conflicts of interest.

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Author contributions

Conceive and design experiments: Wen-Bo Zhang and Meiyan Sun; Data collection and follow-up: Zhengang Wang, Yingui Sun, Keliang Lu, Wenbo Liu, Kaifang Wang; Article writing and modification: Xiaoyong Zhao, Junqiao Zhang, Xiaoyun Teng, Wenbo Zhang.

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