

Predictive Value of NT-proBNP for Functional Outcome of Ischemic Stroke Without Cardiac Disease: A Prospective, Observational Study

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Purpose: Our study aimed to evaluate the prognostic value of NT-proBNP in predicting adverse outcomes among patients with anterior circulation infarction (ACI) and posterior circulation infarction (PCI), specifically in those without pre-existing cardiac comorbidities.

Patients and Methods: This single-center, prospective observational study enrolled patients with acute ischemic stroke (AIS) within 7 days of symptom onset. We aimed to elucidate predictive role of NT-proBNP levels in determining adverse outcomes in AIS patients. Additionally, the study sought to explore the relationship between NT-proBNP levels and the risk of poor functional outcomes in both ACI and PCI patients without underlying cardiac comorbidities.

Results: A total of 821 patients were included in our study. Both univariate and multivariate logistic analyses indicated that higher NT-proBNP was an independent risk factor for adverse outcomes of ischemic stroke patients at 90 days. In noncardiogenic patients, the risks of adverse outcomes during follow-up were significantly elevated in the medium and high NT-proBNP groups (medium group: OR 1.75, 95% CI 1.03–2.98, $P=0.039$; high group: OR 2.46, 95% CI 1.30–4.67, $P=0.006$), with a dose-dependent trend. The association was similarly observed in patients with isolated ACI (medium group: OR 2.02, 95% CI 1.06–3.83, $P=0.031$; high group: OR 2.70, 95% CI 1.25–5.79, $P=0.011$). High NT-proBNP levels were independently associated with END in patients without underlying cardiac comorbidities (high group: OR 2.14, 95% CI 1.06–4.31, $P=0.033$) and this association was also observed in ACI patients (high group: OR 5.39, 95% CI 1.70–17.04, $P=0.004$). Moreover, when incorporated into the clinical prediction model, NT-proBNP exhibited excellent sensitivity and specificity for predicting stroke-related functional outcomes.

Conclusion: NT-proBNP demonstrates potential as a valuable biomarker in the clinical predictive model for functional outcomes specifically in ACI patients suggesting that elevated NT-proBNP levels in these patients should prompt closer monitoring and more comprehensive patient management.

Trial Registration: <https://www.chictr.org.cn/>, ChiCTR2300067696.

Keywords: NT-proBNP, anterior circulation infarction, posterior circulation infarction, functional outcomes

Introduction

Early prediction of functional outcomes in ischemic stroke patients is a crucial aspect of cerebrovascular disease management. Accurate early prediction has the potential to influence stroke management decisions and ultimately impact stroke outcomes. Cardiac injury is extremely common in patients with cerebrovascular disease.^{1,2} As early as 1947, Byer et al³ first reported that cerebrovascular disease can lead to myocardial injury and arrhythmia, providing an important reference for understanding the relationship between stroke and cardiac complications. Cardiac factors are among the key determinants of poor outcomes in ischemic stroke, with sympathetic system activation potentially triggering a cascade of cardiac dysfunctions in stroke patients.^{4,5} These dysfunctions can subsequently worsen stroke outcomes. Elevated plasma

catecholamine levels and cardiac injury markers in stroke patients are linked to an increased risk of sudden death.^{6,7} Currently, reliable biological markers for accurately predicting stroke functional outcomes remain insufficient.

N-terminal pro-brain natriuretic peptide (NT-proBNP), a neurohormone released by ventricular myocardial cells, reflects ventricular pressure and volume overload.⁸ Prior studies have demonstrated that elevated BNP levels occur in non-cardiac conditions, including ischemic stroke. NT-proBNP levels correlate with ischemic stroke complications, mortality risk, and adverse outcomes, though findings vary across different studies.^{9–11} We hypothesize that NT-proBNP's predictive role in ischemic stroke may vary depending on lesion location. Our study aims to investigate NT-proBNP's predictive value for adverse outcomes in anterior circulation infarction (ACI) and posterior circulation infarction (PCI) through a prospective observational study, seeking to establish its potential as a clinically viable biomarker for predicting stroke functional outcomes.

Materials and Methods

Participants

The data were derived from the SPARK (effect of Cardiac Function on Short-term Functional Prognosis in Patients with Acute Ischemic Stroke) study, a prospective, observational, single-center investigation conducted at Tianjin Huanhu Hospital from January 19 to March 20, 2023. The study was registered on the Chinese Clinical Trial Registry (<https://www.chictr.org.cn/>); registration number: ChiCTR2300067696) with the primary objective of determining whether cardiac function influences the functional prognosis of acute ischemic stroke (AIS) patients. The inclusion criteria were as follows: (1) age >18 years old; (2) admission within 7 days of symptom onset, confirmed as AIS by magnetic resonance imaging (MRI) (including diffusion-weighted images (DWI)); (3) standardized neurology treatment upon admission, with NT-proBNP testing completed within 24 hours of admission; (4) complete medical records and laboratory data. Patients with transient ischemic attack were not included in the study. Patients were excluded from the study if they met any of the following criteria: death during hospitalization, loss to follow-up, or having incomplete NT-proBNP data.

Data Collection and Definitions

Demographic data, medical history, treatment details, and laboratory indices were systematically collected from the medical records of screened patients. NT-proBNP levels were stratified into low, medium, and high groups using tertile distribution, a method that divides the data into three equal parts. The stroke subtype criteria followed the established Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification.¹² All patients underwent comprehensive cardiac evaluations and cerebrovascular assessments following admission.

All patients in this study underwent comprehensive MRI, encompassing T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC), and fluid-attenuated inversion recovery (FLAIR) sequences. The anterior circulation, supplied by the intracranial carotid artery system, encompasses the frontal, temporal, parietal lobes, and basal ganglia, representing the anterior three-fifths of the cerebral hemispheres. Conversely, the posterior circulation, supplied by the vertebrobasilar artery system, includes the brainstem, cerebellum, occipital lobes, and parts of the thalamus, comprising the posterior two-fifths of the cerebral hemispheres.¹³

Early neurological deterioration (END) was defined as an increase in National Institutes of Health Stroke Scale (NIHSS) score of ≥ 2 points within 24 hours of admission.¹⁴ Symptomatic hemorrhagic transformation (sHT) was defined as an increase of ≥ 4 points or a 1-point decrease in consciousness level in NIHSS score from baseline, along with evidence of intracranial hemorrhage on CT/MRI and clinical judgment confirming a relationship between deteriorating symptoms and intracranial bleeding.¹⁵

Follow-up assessments were conducted by neurology specialists via telephone to evaluate mortality and functional outcomes at 90 days using mRS score. A favorable outcome was defined as an mRS score of 0–2, while poor outcome as an mRS score of 3–6.

Statistical Analysis

SPSS 26.0 software was employed for statistical analysis, with statistical significance defined as two-sided $P < 0.05$. Categorical variables were analyzed using χ^2 or Fisher's exact tests, while continuous variables were assessed with the Mann–Whitney U -test. Univariate analysis factors with $P < 0.05$ were incorporated into logistic regression to determine odds ratios (OR) and 95% confidence intervals (CI). Binary logistic regression was utilized to examine the impact of three NT-proBNP groups on the prognosis of stroke patients. The analysis comprised three progressively adjusted models: an unadjusted baseline model (Model 1), a model adjusted for age, gender, and NIHSS score (Model 2), and a comprehensive model additionally controlling for multiple clinical variables including age, gender, systolic blood pressure, NIHSS score, hypertension, diabetes, coronary heart disease, atrial fibrillation, heart failure, pre-stroke mRS score, smoking, drinking, intravenous thrombolysis, endovascular treatment, anticoagulation treatment, and TOAST (Model 3). The predictive performance of NT-proBNP for adverse outcomes was evaluated through receiver operating characteristic (ROC) curves and area under the curve (AUC) analysis, with statistically significant factors from the Model 3 integrated into the clinical prediction model.

Results

Characteristics of Patients

A total of 1357 patients were initially screened for the study. Of these, 100 patients were excluded due to 10 in-hospital deaths and 90 lost to follow-up. An additional 436 patients with incomplete NT-proBNP data after admission were also eliminated from the analysis. Consequently, a total of 821 patients were included in the final analysis. The patient selection process was illustrated in Figure 1. Within this cohort, 487 patients (59.3%) achieved favorable prognosis, while 334 patients (40.7%) experienced poor outcomes. During hospitalization, 79 patients developed END, and 64 patients experienced SHT.

Risk Factors of Poor Outcomes

Univariate analysis demonstrated that patients with poor outcomes, compared to those with favorable outcomes, were more likely to be female, older, and had a higher prevalence of cardiovascular and cerebrovascular comorbidities, including hypertension, diabetes, coronary artery disease, atrial fibrillation, and prior stroke. Patients with poor outcomes also exhibited higher NIHSS scores at admission, elevated pre-stroke mRS scores, increased systolic blood pressure and blood glucose levels on admission, and significantly higher NT-proBNP levels. Specifically, NT-proBNP levels were

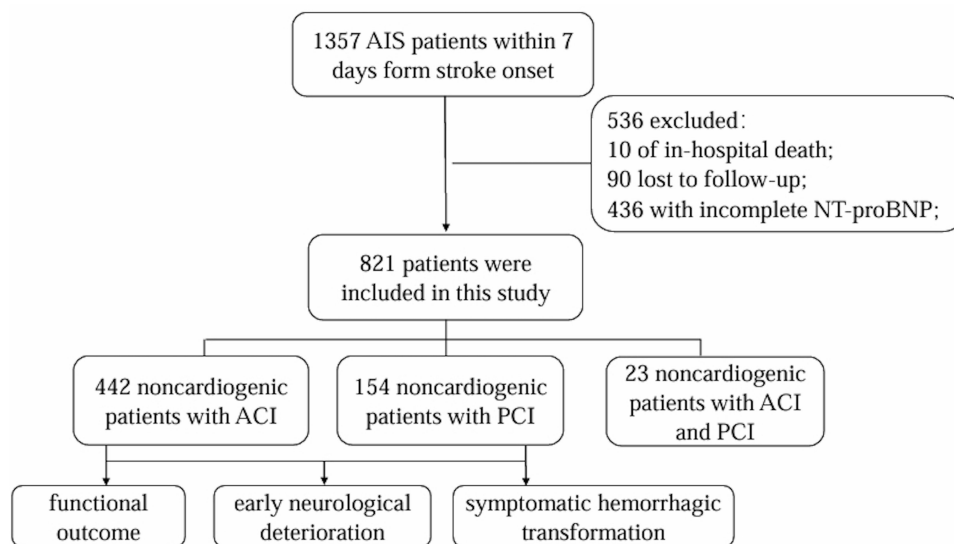


Figure 1 Flowchart of patient inclusion.

103.7 (± 194.64) pg/mL in the favorable outcome group, compared to 270.35 (± 818.88) pg/mL in the poor outcome group (Table 1). Multivariable logistic regression analysis identified advanced age, higher NIHSS scores at admission, elevated pre-stroke mRS scores, increased systolic blood pressure, higher NT-proBNP levels, and stroke subtype according to TOAST classification as independent risk factors for poor outcomes in AIS patients (Table 2).

Correlation Between NT-proBNP and Patients Without Cardiac Disease

Among the enrolled patients, 164 cases had concurrent cardiac diseases, while 619 cases (75.4%) were free of cardiac comorbidities. NT-proBNP levels were stratified into three groups: low group (≤ 82.94 pg/mL), medium group (82.95–280.10 pg/mL), and high group (≥ 280.11 pg/mL). After adjusting for multiple confounding factors, NT-proBNP levels were significantly associated with poor outcomes in patients with cardiac comorbidities (high group: OR 11.90, 95% CI 2.00–70.89, $P=0.007$) (Figure 2).

Among patients without cardiac comorbidities, the correlations between NT-proBNP levels and adverse outcomes were comprehensively illustrated in Figure 3. In Model 1, compared to the low NT-proBNP group, both medium and high groups demonstrated progressively increased risks of poor outcomes (medium group: OR 2.46, 95% CI 1.69–3.58, $P=0.000$; high group: OR 5.56, 95% CI 3.81–8.12, $P=0.000$). In Model 2 and Model 3, the elevated risks of poor

Table 1 Characteristics and Univariate Analysis of Included Patients

Variables	Total	Favorable Outcomes	Poor Outcomes	P-value
Age, years	821	487	334	
Gender, n (%)	66 (± 15)**	63 (± 14)**	70 (± 13)**	0.000
Male, n (%)	605 (73.7)	373 (76.6)	232 (69.5)	0.024
Female, n (%)	216 (26.3)	114 (23.4)	102 (30.5)	
Hypertension, n (%)	635 (77.3)	363 (74.5)	272 (81.4)	0.022
Diabetes, n (%)	302 (36.8)	158 (32.4)	144 (43.1)	0.002
Cardiac Diseases, n (%)				
Coronary Heart Disease	163 (19.9)	68 (14.0)	95 (28.4)	0.000
Myocardial Infarction	31 (3.8)	13 (2.7)	18 (5.4)	0.061
Atrial Fibrillation,	69 (8.4)	28 (5.7)	41 (12.3)	0.001
Heart Failure	19 (2.3)	10 (2.1)	9 (2.7)	0.638
Congenital Heart Disease	5 (0.6)	1 (0.2)	4 (1.2)	0.165
Valve Disorder	12 (1.5)	5 (1.0)	7 (2.1)	0.244
Prior Stroke (%)	283	123 (25.3)	160 (47.9)	0.000
Smoking, n (%)	428 (52.1)	264 (54.2)	164 (49.1)	0.156
Drinking, n (%)	254 (30.9)	162 (33.3)	92 (27.5)	0.091
NIHSS score	6 (± 7)**	4 (± 4)**	10 (± 8)**	0.000
Pre-stroke mRS score	0 (± 0)**	0 (± 0)**	0 (± 2)**	0.000
SBP, mmHg	150 (± 34)**	145 (± 32)**	158.07 (± 24.24)*	0.000
DBP, mmHg	86 (± 19)**	86 (± 18)**	87 (± 21)**	0.536
Serum Glucose, mmol/L	5.75 (± 2.76)**	5.46 (± 2.51)**	6.27 (± 3.39)**	0.000
LDL-C mmol/L	2.72 (± 1.06)**	2.71 (± 1.00)**	2.76 (± 1.17)**	0.356
NT-proBNP pg/mL	153.8 (± 363.05)**	103.7 (± 194.64)**	270.35 (± 818.88)**	0.000
Stroke Subtype by TOAST				0.000
Large-artery atherosclerosis	438 (53.3)	227 (46.6)	211 (66.2)	
Cardioembolism	75 (9.1)	34 (7.0)	41 (12.3)	
Small-artery occlusion	149 (18.1)	112 (23.0)	37 (11.1)	
Other etiology	16 (1.9)	12 (2.5)	4 (1.2)	
Undetermined	143 (17.4)	102 (20.9)	41 (12.2)	

Notes: Italics indicate $P < 0.05$. *Normally distributed continuous variables expressed as $\bar{x} \pm s$. **Other non-normally distributed continuous variables expressed as $M \pm IQR$.

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; LDL-C, Low Density Lipoprotein Cholesterol.

Table 2 Results of Multivariate Analysis

Variables	B	S.E.	OR	95% CI	P-value
Age	0.045	0.010	1.046	0.025–0.067	0.000
Gender	0.282	0.247	1.326	0.817–2.153	0.253
Hypertension	−0.144	0.260	0.866	0.521–1.441	0.866
Diabetes	0.035	0.252	1.036	0.632–1.696	0.890
Coronary Heart Disease	0.269	0.272	1.309	0.768–2.230	0.323
Atrial Fibrillation	−0.144	0.536	0.866	0.303–2.474	0.788
Prior Stroke	0.175	0.240	1.191	0.744–1.906	0.466
Drink	−0.265	0.240	0.768	0.480–1.228	0.270
NIHSS score	0.324	0.029	1.383	1.306–1.465	0.000
Pre-stroke mRS score	0.737	0.143	2.089	1.578–2.767	0.000
SBP	0.012	0.005	1.012	1.003–1.021	0.010
Serum Glucose	0.047	0.041	1.048	0.967–1.136	0.252
NT-proBNP	0.000	0.000	1.000	1.000–1.001	0.002
Stroke Subtype by TOAST	0.618	0.289	1.854	1.053–3.266	0.032

Note: Italics indicate $P < 0.05$.

outcomes persisted across medium and high NT-proBNP groups (Model 2: medium group: OR 1.93, 95% CI 1.16–3.19, $P = 0.011$; high group: OR 2.92, 95% CI 1.63–5.26, $P = 0.000$; Model 3: medium group: OR 1.75, 95% CI 1.03–2.98, $P = 0.039$; high group: OR 2.46, 95% CI 1.30–4.67, $P = 0.006$), with consistently associations. Statistically significant indicators associated with adverse outcomes in Model 3 included gender, age, NIHSS score at admission, NT-proBNP levels, pre-admission mRS score, and systolic blood pressure at admission.

Correlation Between NT-proBNP and ACI and PCI

In AIS patients without cardiac comorbidities, the stroke subtypes were distributed as follows: 442 patients (71.4%) with ACI, 154 patients (24.9%) with PCI, and 23 cases (3.7%) involving both ACI and PCI. Among patients with isolated ACI, the risk of poor prognosis during follow-up progressively increased in the medium and high NT-proBNP groups compared to the low group across all three statistical models, demonstrating a clear dose-response relationship (Figure 4). In Model 3, compared with the low NT-proBNP group, patients in the medium and high groups exhibited significantly increased risks of poor outcomes, with 2.02-fold and 2.70-fold higher risks, respectively (medium group: OR 2.02, 95%

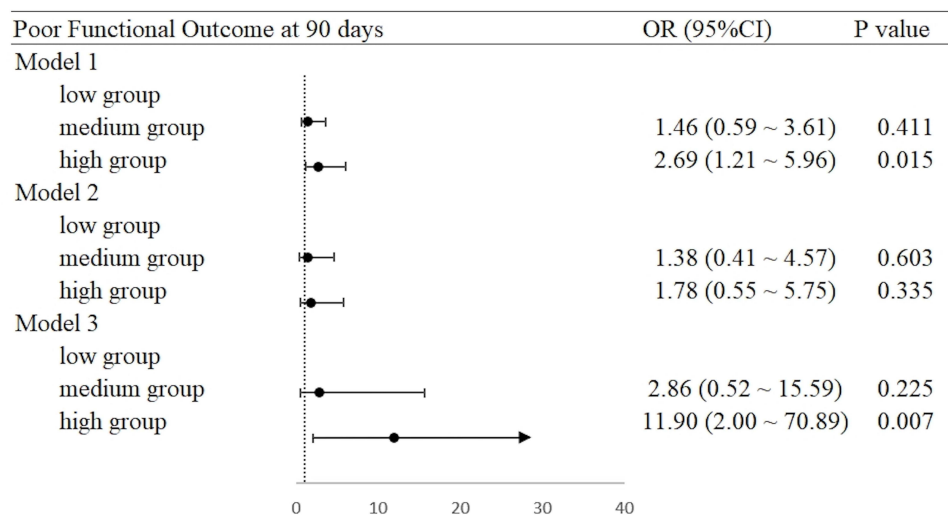


Figure 2 Association between NT-proBNP and poor outcomes in cardiogenic patients.

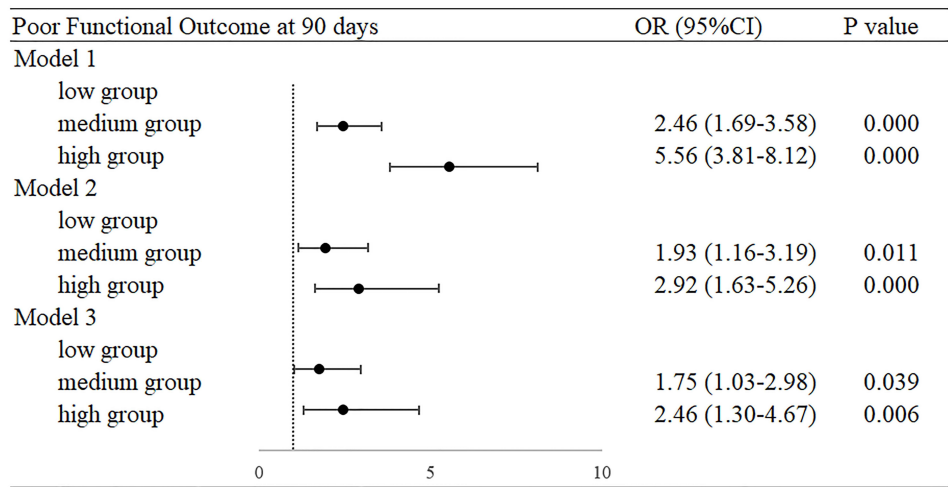


Figure 3 Association between NT-proBNP and poor outcomes in noncardiogenic patients.

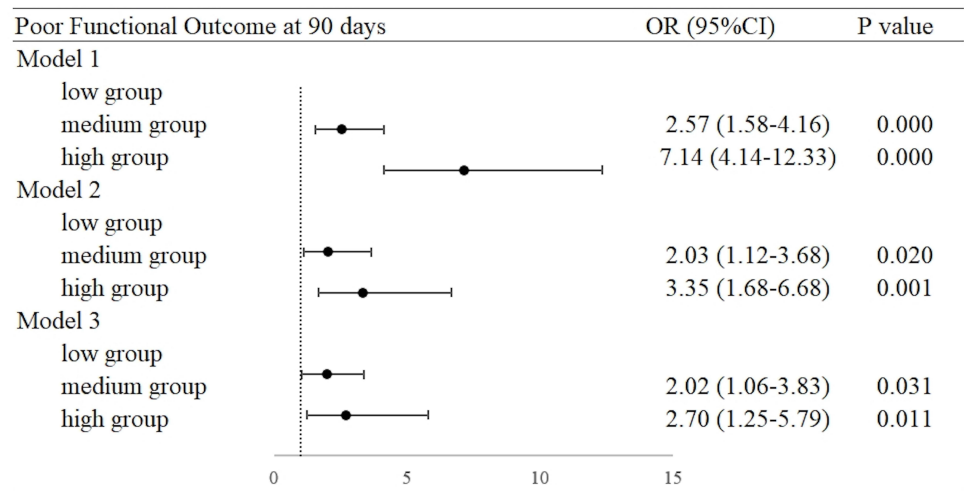


Figure 4 Association between NT-proBNP and poor outcomes in noncardiogenic patients with ACI.

CI 1.06–3.83, $P=0.031$; high group: OR 2.70, 95% CI 1.25–5.79, $P=0.011$). The indicators related to poor prognosis in ACI were the same as those in AIS patients without cardiac diseases.

In patients with pure PCI, the unadjusted model revealed a gradual increase in the risk of poor outcomes at 90 days for medium and high NT-proBNP groups compared to the low group (medium group: OR 2.77, 95% CI 1.13–6.81, $P=0.027$; high group: OR 3.27, 95% CI 1.21–8.86, $P=0.020$). However, after adjusting for potential confounding factors, the predictive significance of elevated NT-proBNP levels on poor prognosis was attenuated and no longer statistically significant (Figure 5).

The correlations between NT-proBNP levels and END and sHT in ACI and PCI patients without cardiac comorbidities were presented in Table 3. Using the low group as the reference, it was found that in all patients, high NT-proBNP levels were associated with END (high group: OR 2.14, 95% CI 1.06–4.31, $P=0.033$), which was also observed in patients with ACI (high group: OR 5.39, 95% CI 1.70–17.04, $P=0.004$). Logistic regression analysis could not be completed considering no cases with END in the low group of PCI. Relationship between NT-proBNP levels and sHT was only observed in all stroke patients without cardiac diseases (high group: OR 4.22, 95% CI 1.76–10.09, $P=0.001$), with no significant correlation in ACI and PCI.

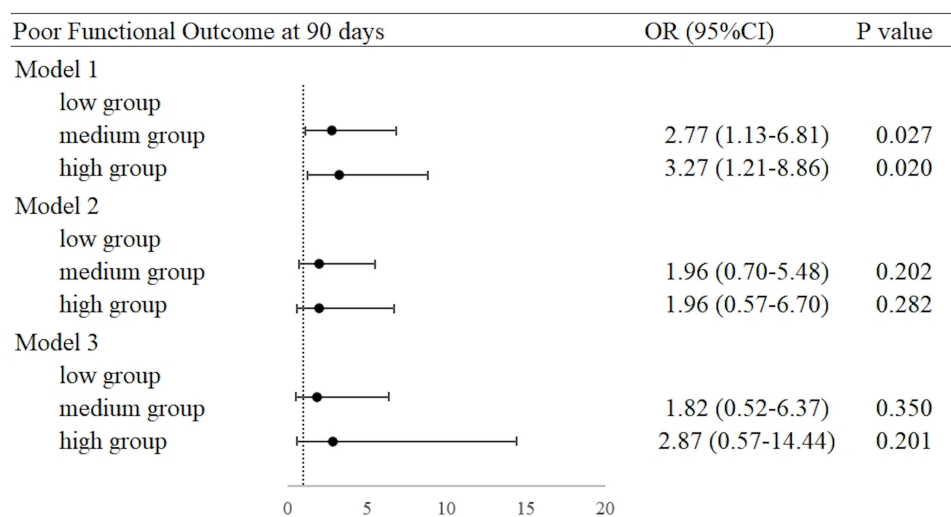


Figure 5 Association between NT-proBNP and poor outcomes in noncardiogenic patients with PCI.

Predictive Value of NT-proBNP for Poor Outcomes

The predictive value of NT-proBNP for adverse outcomes in stroke patients without cardiac diseases was assessed using ROC curve analysis (Figure 6). The area under the curve (AUC) with NT-proBNP as the sole predictor was 0.692, demonstrating a sensitivity of 0.752 and specificity of 0.424. The optimal cutoff value for NT-proBNP was determined to be 107.3 pg/mL. Integration of the clinical prediction model into the ROC curve significantly enhanced the predictive performance, elevating the AUC to 0.874 with improved sensitivity (0.812) and specificity (0.777). In ACI patients, the AUC using NT-proBNP as the only predictor was 0.707, with a sensitivity of 0.769 and specificity of 0.579. The optimal cutoff value for NT-proBNP was 101.35 pg/mL. After incorporating the clinical prediction model into the ROC curve, the AUC increased to 0.857, with sensitivity and specificity of 0.757 and 0.828, respectively.

Discussion

This study aimed to elucidate the relationship between NT-proBNP and functional outcomes in ischemic stroke patients. In this investigation, NT-proBNP was identified as an independent risk factor for adverse outcomes in AIS. Numerous prior studies have illuminated the potential utility of serum NT-proBNP as a biomarker for predicting adverse outcomes in ischemic stroke. A comprehensive meta-analysis of 11 clinical studies demonstrated that elevated NT-proBNP levels were significantly associated with poor functional outcomes in ischemic stroke patients (OR 1.68, 95% CI 1.13–2.50).⁹

Table 3 Association Between NT-proBNP and END and sHT in Subtypes of Stroke

Subtypes of Stroke	NT-proBNP	END			sHT		
		n	OR (95% CI)	P-value	n	OR (95% CI)	P-value
All Stroke	Low group	16	1 (Reference)		2	1 (Reference)	
	Medium group	27	1.83(0.96–3.50)	0.066	4	0.51(0.09–2.82)	0.440
	High group	19	2.14(1.06–4.31)	0.033	12	5.39(1.70–17.04)	0.004
ACI	Low group	8	1 (Reference)		1	1 (Reference)	
	Medium group	9	1.17(0.44–3.10)	0.755	1	0.25(0.03–2.29)	0.221
	High group	18	4.22(1.76–10.09)	0.001	4	0.40(0.04–3.64)	0.417
PCI	Low group	0	NA	NA	1	1 (Reference)	
	Medium group	2	NA	NA	1	0.36(0.04–3.54)	0.379
	High group	3	NA	NA	3	0.61(0.06–6.06)	0.670

Note: Italics indicate $P < 0.05$.

Abbreviations: ACI, anterior circulation infarction; PCI, posterior circulation infarction.

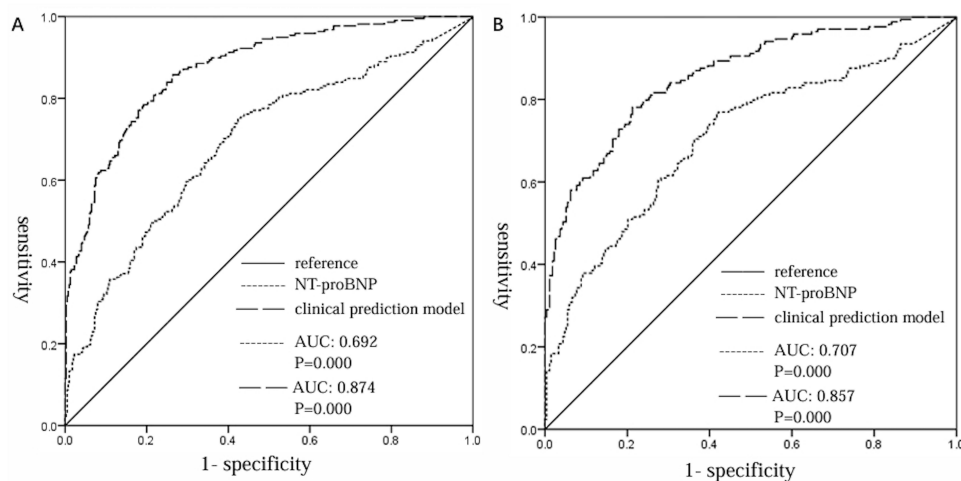


Figure 6 ROC curves. **(A)** Noncardiogenic patients; **(B)** Noncardiogenic patients with ACI.

Yang et al¹⁶ demonstrated that elevated NT-proBNP levels increase the risk of mortality, vascular events, and adverse functional outcomes within one year of ischemic stroke, suggesting NT-proBNP as a potential prognostic factor for those patients. These findings were supported by Chaudhuri et al's prospective study, which revealed that plasma N-BNP elevation was associated with adverse outcomes at 90-day follow-up and correlated with poor prognosis in cardioembolic stroke.¹⁷ In this study, we also found that high NT-proBNP levels were associated with poor functional outcomes in AIS patients with cardiac diseases. Currently, it was widely acknowledged that NT-proBNP levels had particularly good predictive value for prognosis in cardioembolic stroke and atrial fibrillation patients.^{18,19} A meta-analysis demonstrated NT-proBNP's excellent diagnostic efficacy in differentiating cardioembolic from non-cardioembolic strokes.²⁰ Furthermore, NT-proBNP can predict stroke risk in heart failure patients with preserved ejection fraction.²¹

Interestingly, we also found that NT-proBNP levels were associated with adverse outcomes in ischemic stroke patients without cardiac diseases. This finding differed from the research of AA et al.²² Their study suggested that in patients with MRI-confirmed ischemic stroke and no apparent myocardial injury, blood biomarkers such as cardiac troponin T (cTnT) and NT-proBNP showed no significant correlation with clinical outcomes. We hypothesize that the association between NT-proBNP and poor prognosis in stroke patients without cardiac diseases may be attributed to myocardial injury induced by the stroke itself. Approximately 30% of patients exhibit early electrocardiographic abnormalities in the initial stages of AIS, even after excluding cardioembolic stroke cases.⁵ A comprehensive retrospective study with a 5-year follow-up demonstrated that new cardiac complications emerging within 4 weeks after AIS were prevalent. These complications, encompassing acute coronary syndrome, arrhythmias, and heart failure, were significantly associated with all-cause mortality risk during the subsequent 5-year period.²³ Iltumur et al²⁴ confirmed that elevated BNP levels and decreased left ventricular ejection fraction (LVEF) early in the course of AIS indicated early onset of left ventricular dysfunction and myocardial injury. Chen et al²⁵ observed that LVEF <60% was significantly associated with poor functional outcomes specifically in stroke patients without pre-existing cardiac diseases, whereas this association was not evident in cardioembolic stroke patients. The notable correlation between NT-proBNP levels and adverse outcomes in stroke patients without cardiac diseases suggested that the stroke pathophysiological process may independently induce cardiac complications, potentially influencing overall stroke prognosis. NT-proBNP maybe emerged as a potential indirect biomarker reflecting the complex neurogenic cardiac injury mechanism.

The mechanism between stroke prognosis and NT-proBNP remains incompletely understood. On one hand, NT-proBNP can be released in response to ventricular muscle stimulation and demonstrates an increasing trend among stroke patients.²⁴ Stroke can trigger activation of the hypothalamic-pituitary-adrenal (HPA) axis, subsequently stimulating the sympathetic nervous system and promoting catecholamine release. The excessive β -receptor activation by catecholamines may induce calcium overload and oxidative stress, ultimately resulting in myocardial cell dysfunction and elevated

NT-proBNP levels.⁷ Otaki et al²⁶ conducted a comparative analysis of multiple cardiac biomarkers and demonstrated that BNP and NT-proBNP emerged as robust predictive markers for cardio-cerebrovascular events following stroke. On the other hand, ventricular dysfunction and autonomic nervous system impairment or sympathetic nervous system hyperactivation may occur following acute neuronal stress or injury, wherein NT-proBNP responds to the stroke event. Furthermore, NT-proBNP potentially reflects the extent of post-stroke brain damage, thereby providing insights into adverse stroke prognosis. Notably, NT-proBNP could be secreted within the brain, with significant increases observed in cerebrospinal fluid following brain injury.²⁷ The potential mechanism of brain-secreted NT-proBNP penetrating the compromised blood-brain barrier and subsequently increasing plasma levels as a reflection of stroke-induced brain damage remains unresolved and requires further investigative research.

This study revealed that NT-proBNP demonstrates significant predictive potential for adverse outcomes in ACI, while exhibiting no comparable association in PCI. Researchers hypothesized that ACI patients are more susceptible to myocardial damage during disease progression. Notably, infarct location emerges as a critical predictive factor for post-stroke cardiac complications. A comprehensive registry study encompassing 46,603 patients demonstrated that approximately 1% of Transient Ischemic Attack (TIA)/stroke patients experienced acute myocardial infarction during the acute phase, with a notably higher incidence observed in ACI patients.²⁸ This potential association may be related to the crucial role of the insular cortex in regulating the circulatory system. Previous studies have demonstrated that patients with right insular damage are more prone to experiencing prolonged QTc interval, tachyarrhythmias, and left bundle branch block.²⁹ Specifically, the right insular cortex serves as a key center for autonomic nervous system modulation, and its damage may disrupt cardiac electrophysiological balance by affecting the coordination between sympathetic and parasympathetic nervous systems. Stress-induced cardiomyopathy demonstrated a significant association with ACI, with a particularly notable correlation involving the insular and peri-insular brain areas.³⁰ Bleilevens et al³¹ further confirmed in mouse model that the changes in hemodynamics and the incidence of myocardial infarction after stroke were related to the infarct volume of the insular cortex. Consequently, some studies combine insular infarction, arrhythmias, and cardiac autonomic dysfunction as predictive markers of early mortality risk in stroke patients.^{7,32,33} However, in anterior circulation, insular lesions were not the sole determinants of cardiac complications. A comprehensive epidemiological investigation encompassing multiple ethnic populations demonstrated that parietal infarction could precipitate myocardial infarction and subsequent long-term cardiogenic mortality, emerging as a significant prognostic indicator for fatal cardiovascular events.³⁴ Although we observed a correlation between the functional prognosis of ACI and NT-proBNP levels, further validation was essential to definitively establish the association between infarct location and NT-proBNP biomarkers.

Elevated NT-proBNP levels demonstrated a significant association with END in stroke patients devoid of cardiac comorbidities, with concordant observations in ACI. Notably, no statistically significant correlation was identified between sHT and NT-proBNP levels across both ACI and PCI cohorts. Several studies have confirmed that elevated NT-proBNP levels were intricately associated with cerebral hemorrhage, with progressively higher levels potentially indicating extensive hematoma volumes and correspondingly more severe neurological prognoses.^{35,36} We did not observe significant correlations between NT-proBNP levels and sHT in ACI and PCI cohorts. We hypothesize that this finding may be attributable to the exclusion of cardioembolic stroke in our research design. Patients with cardioembolic stroke or those associated with atrial fibrillation exhibited a substantially elevated risk of hemorrhagic transformation compared to non-cardioembolic stroke patients. Meanwhile, the relatively limited number of sHT cases among stroke patients without cardiac comorbidities in our study potentially elucidated the observed negative results. Notably, high NT-proBNP levels demonstrated a significantly association with END risk in ACI compared to PCI, suggesting that clinicians should exercise heightened vigilance and prioritize NT-proBNP level monitoring in ACI patients.

Concurrently, we discovered that NT-proBNP, when integrated with other clinical indicators, could serve as a valuable clinical predictor for assessing stroke prognosis, particularly in ACI patients. Numerous studies have indeed explored predictive models incorporating NT-proBNP as a key biomarker. The rapid detectability of NT-proBNP during the early stage of stroke offers a significant advantage in early identification of patients with potentially adverse prognoses, potentially expediting critical clinical decision-making. This is especially pertinent for cryptogenic stroke patients, where the underlying pathogenesis may be transient, such as paroxysmal atrial fibrillation, which might escape initial diagnostic

detection. Abnormal NT-proBNP levels could provide crucial insights into such cases, suggesting the necessity of extended cardiac monitoring to enhance arrhythmia detection rates and mitigate the incidence of stroke with undetermined origins.

Limitations

There are several limitations in this study. First, potential selection bias may significantly influence the primary results, attributable to the exclusion of approximately 30% of patients due to incomplete NT-proBNP data. Secondly, the relatively limited sample of patients experiencing END and sHT during AIS progression, particularly in PCI patients, may substantially compromise the statistical robustness of correlational analyses between NT-proBNP and these clinical parameters. Thirdly, while our investigation revealed a predictive potential for NT-proBNP in ACI, the biomarker's individual prognostic value demonstrated modest performance in ROC curve analysis. Notably, the predictive accuracy was significantly enhanced when NT-proBNP was integrated with additional clinical indicators. We believe that NT-proBNP could be used as cardiac indicator to predict the prognosis of stroke, but it still needs to be combined with other clinical indicators for accurate prediction.

Conclusion

This study further substantiated the correlation between NT-proBNP and functional outcomes in AIS patients. Among patients with cardiac diseases, high NT-proBNP levels were associated with poor outcomes. Notably, even in patients without concomitant heart diseases, NT-proBNP demonstrated significant predictive value for adverse functional outcomes and END, particularly in ACI patients. We propose that NT-proBNP can serve as a valuable biomarker in clinical prediction models for functional outcomes in AIS patients, with particular emphasis on ACI populations. Elevated NT-proBNP levels warrant greater attention in clinical practice among patients with ACI.

Data Sharing Statement

The data is available upon a reasonable request from the corresponding author.

Ethics Approval

The study was conducted in accordance to the Declaration of Helsinki, and has obtained approval from the Ethics Committee of Tianjin Huanhu Hospital. The number of the approval was 2022-158. All the patients have been informed and signed informed consent before the experiment.

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Disclosure

The authors report no conflicts of interest in this work.

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