

Prediction Value of High Serum Pentraxin-3 for Short-Term Recurrence of Cerebral Infarction in Patients Accompanied with Intracranial Atherosclerotic Stenosis Within One Year

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Objective: Elevated serum pentraxin-3 levels are generally considered a risk factor for atherosclerosis. However, there is limited data on the relationship between pentraxin-3 and cerebral infarction (CI) accompanied by intracranial atherosclerotic stenosis (ICAS). This study aims to investigate the association between pentraxin-3 (PTX-3) and short-term recurrence in cerebral infarction caused by ICAS patients within one year.

Methods: A prospective observational study was conducted. Cerebral infarction accompanied by intracranial atherosclerotic stenosis (CI-ICAS) patients were selected from January 2020 to December 2023. Recurrent ischemic stroke (RIS) is defined as a new neurological deficit that appears after a period of clinical stabilization, lasting more than 24 hours, with an attributable new ischemic lesion that can be confirmed by CT or MRI. Serum pentraxin-3 levels were determined on admission. Multivariate logistic regression analysis was used to investigate the relationship between serum pentraxin-3 and RIS.

Results: Among 398 patients enrolled, 112 cases (28.1%) had recurrence within one year. The elevation of serum PTX-3 level in patients accompanied with ICAS was independently correlated with recurrent stroke. Therefore, it is worth considering the possibility of intervening in higher PTX-3 levels. Serum pentraxin-3 was significantly higher in patients with RIS (15.16 vs 10.21 $\mu\text{mol/L}$, $P < 0.001$). Correlation analysis showed that PTX-3 was correlated with age, LDL, Hs-CRP, Baseline NIHSS score, and Hcy ($P < 0.001$). Univariate logistic regression analysis showed that pentraxin-3 remained an independent predictor of recurrent ischemic stroke after adjusting for major confounding factors (OR = 1.21, 95% CI: 1.06–1.39, $P = 0.007$).

Conclusion: The elevation of serum pentraxin-3 level in patients with ischemic stroke was independently correlated with the recurrence of stroke within one year. Therefore, intervention in serum pentraxin-3 levels may be worth considering.

Keywords: recurrent ischemic stroke, cerebral infarction, pentraxin-3

Introduction

Ischemic stroke, which accounts for about 80% of strokes, can lead to severe disability and death.¹ Recurrent ischemic stroke (RIS) is defined as a new neurological deficit that appears after a period of clinical stabilization, lasting more than 24 hours, with an attributable new ischemic lesion that can be confirmed by CT or MRI.^{2–5} The recurrence rate of cerebral infarction in patients accompanied by intracranial atherosclerotic stenosis within one year is 28%.^{6–9} There has been enough evidence from basic and clinical studies to show that recurrent ischemic stroke is closely related to inflammatory response.^{10,11} Inflammation may increase the vulnerability of atherosclerotic plaque,^{12,13} which promotes

plaque to rupture more easily, leading to the formation of in situ thrombosis or artery-to-artery embolization events.¹⁴ On the basis of the original neurological deficit, RIS further increases the degree of neurological deficit, resulting in more serious disability.¹⁵ Therefore, it is very important to find biological indicators that can predict recurrent stroke.

PTX-3 is an acute inflammatory protein that is widely distributed in vivo.^{16,17} It exists in endothelial cells, macrophages, monocytes, and fibroblasts,¹⁸ and is closely related to atherosclerosis-related diseases such as cerebral infarction and coronary heart disease.^{19–22} The increase of PTX-3 indicates a poor prognosis of ischemic stroke,^{23–25} and the increase of PTX-3 means an increase in the incidence of branch atheromatous disease (BAD).^{26–28}

There is a high recurrence rate in CI patients accompanied by ICAS. We found that the instability of atherosclerotic plaque and inflammatory response may be important factors in its occurrence. However, it is unclear about the relationship between PTX-3, as an inflammatory protein, and recurrent ischemic stroke. This study aims to further clarify that their relationship in ischemic stroke with ICAS has a high short-term stroke recurrence rate.

Materials and Methods

Study Population

Patients with cerebral infarction and intracranial atherosclerotic stenosis in the Second Affiliated Hospital of Nantong University from January 2020 to December 2023 were prospectively included. Patients were included if they: (1) were acute cerebral infarction patients with intracranial atherosclerotic stenosis proved by CTA or MRA; (2) aged ≥ 18 years old; (3) had NIHSS ≤ 21 points. The patients were excluded if they: (1) had intracranial arterial occlusion; (2) had stroke mimics; (3) were inability to complete intracranial vascular assessment; (4) had intracranial hemorrhage transformation; (5) had severe heart, kidney, and liver diseases; (6) had infectious and inflammatory diseases. This study was conducted in acceptance with the Declaration of Helsinki and approved by the Ethics Committee of the Second Affiliated Hospital of Nantong University (2022KT268). All participants signed an informed consent form.

Clinical Data

Demographic characteristics, medical history, and clinical variables were all collected from medical records. Stroke severity was assessed using the NIHSS score. Fasting blood samples were collected the next morning to detect PTX-3 and other routine blood test indexes. Serum PTX-3 levels were detected by enzyme-linked immunosorbent assay (Jianglai Bio). Recurrent stroke is defined as a sudden new focal neurological deficit with a duration greater than 24 hours, or an acute cerebral infarction with a focal neurological deficit of less than 24 hours but confirmed by imaging.³

Statistical Analysis

Continuous variables were presented as mean $\pm$ SD or median (interquartile range). Independent *t* test, Mann–Whitney *U*-test, one-way ANOVA, or Kruskal–Wallis *H*-test as appropriate were employed for continuous variables. Chi-square test or Fisher's exact test was used for categorical data. Spearman correlation coefficients of serum PTX-3 with other factors among CI-ICAS patients. Multivariate logistic regression analysis was used to explore the relationship between categorical serum PTX-3 levels and RIS. Results were considered as statistically significant if two-sided $P < 0.05$. The statistical analysis software GraphPad prism 8.0 and SPSS 23.0 (IBM, New York, USA) was adopted for statistical analysis.

Results

In this study, a total of 512 patients diagnosed with cerebral infarction and intracranial atherosclerotic stenosis were enrolled, all of whom had been admitted to the Department of Neurology in the Second Affiliated Hospital of Nantong University between January 2020 and December 2023. Among them, 109 were excluded according to the exclusion criteria: stroke mimic disease ($n = 12$), combined with hemorrhagic transformation ($n = 14$), intracranial arterial occlusion ($n = 17$), failure in one-year follow-up ($n = 14$), failure in skull magnetic resonance examination ($n = 28$), or complicated with severe heart, kidney, and liver diseases ($n = 24$). Finally, 398 patients were included in the analysis, 63.4% of whom were male patients. The average age of the included patients was 63.58 ± 10.38 years. Recurrent stroke occurred in 112 patients (28.1%) within one year.

Table 1 compares patients with or without recurrent stroke in demographic characteristics, clinical, and laboratory data. Patients with recurrent stroke have higher ages ($P<0.001$), higher smoking rates ($P = 0.027$), higher diabetes rates ($P<0.001$), higher baseline NIHSS scores ($P<0.001$), higher baseline SBP ($P = 0.008$), higher levels of hypersensitive C-reactive protein ($P = 0.032$), higher levels of homocysteine ($P = 0.002$), higher levels of low-density lipoprotein cholesterol and PTX3 ($P<0.001$), compared with those without recurrent stroke.

Table 2 shows that the serum PTX-3 is associated with advanced age ($P<0.001$), higher baseline NIHSS score ($P<0.001$), high levels of homocysteine ($P<0.001$), high levels of hypersensitive C-reactive protein ($P<0.001$), and high levels of low-density lipoprotein cholesterol ($P<0.001$).

Table 3 shows the results of the binary logistic regression of recurrent stroke. In the unadjusted model, patients with higher levels of PTX-3 are more likely to have recurrent stroke. The association remains significant after adjusting for the potential confounding factors.

To further assess the clinical significance of PTX-3 in recurrent stroke, we performed a ROC curve analysis as depicted in **Figure 1**. We observed that the area under curve (AUC) of PTX-3 was 0.778 (95% CI, 0.718–0.838) with the ability to discriminate recurrent stroke. The optimal cutoff value for PTX-3 as to be 12.11 in the ROC curve analysis, yielding the largest Youden's index value (a sensitivity of 69.6% and a specificity of 80.4%).

Table 1 Baseline Characteristics of Participants with or without Recurrence

Variables	Total (n=398)	With Recurrence (n=112)	Without Recurrence (n=286)	p-value
Age years ($\bar{x} \pm s$)	63.58 $\pm$ 10.38	69.50 $\pm$ 10.78	62.00 $\pm$ 9.98	0.000
Gender, Male, n (%)	118 (29.65)	32 (28.57)	86 (21.61)	0.753
Demographic characteristics				
Smoking, n (%)	60 (15.08)	24 (21.43)	36 (12.58)	0.027
Drinking, n (%)	103 (25.88)	32 (28.57)	71 (33.02)	0.443
Hypertension, n (%)	96 (24.12)	33 (29.46)	63 (22.03)	0.119
Diabetes, n (%)	70 (17.59)	32 (28.57)	38 (13.29)	<0.001
Coronary heart disease, n (%)	16 (0.04)	3 (0.027)	13 (11.61)	0.394
Hyperlipidemia, n (%)	51 (12.81)	13 (11.61)	38 (13.29)	0.652
Prior stroke, n (%)	33 (8.29)	10 (0.089)	23 (0.080)	0.773
Transient ischemic attack, n (%)	17 (4.3)	5 (0.045)	12 (0.042)	0.905
Clinical characteristics				
Baseline SBP, mmHg	143.27 $\pm$ 18.16	138 $\pm$ 16.11	145 $\pm$ 18.72	0.008
Baseline DBP, mmHg	83.16 $\pm$ 11.31	81.50 $\pm$ 9.34	82.00 $\pm$ 11.99	0.348
Baseline NIHSS score, median (IQR)	4.00 (3.00, 5.00)	5.50 (4.00, 8.00)	3.00 (2.00, 4.00)	0.000
Laboratory data				
FBG, mmol/L, median (IQR)	5.53 (4.95, 6.47)	5.64 (4.98, 6.51)	5.52 (4.94, 6.46)	0.434
TG, mmol/L, Median(IQR)	1.77 (1.17, 2.39)	1.58 (1.01, 2.40)	1.82 (1.23, 2.38)	0.177
CH, mmol/L, Median(IQR)	4.01 (3.32, 4.780)	4.02 (3.26, 4.81)	4.01 (3.33, 4.77)	0.983
HDL-C, mmol/L, Median(IQR)	1.08 (0.95, 1.27)	1.10 (0.96, 1.38)	1.06 (0.94, 1.25)	0.101
LDL-C, mmol/L, Median(IQR)	2.11 (1.56, 2.37)	2.19 (1.95, 2.77)	1.99 (1.46, 2.21)	0.000
UA, μ mol/L, Median(IQR)	336.20 (286.00, 399.23)	335.50 (289.25, 382.50)	336.40 (285.00, 402.50)	0.447
Hcy, μ mol/L, Median(IQR)	10.60 (9.90, 12.60)	14.20 (11.55, 15.90)	10.20 (9.70, 11.20)	0.002
Hs-CRP, mg/L, Median(IQR)	0.87 (0.14, 1.47)	1.16 (0.24, 1.65)	0.78 (0.12, 1.39)	0.032
PTX3, μ g/mL, Median(IQR)	10.37 (9.22, 14.62)	15.76 (10.48, 19.14)	10.21 (9.12, 11.66)	0.000

Table 2 Spearman Correlation Coefficients of Serum PTX3 with Other Factors Among CI-ICAS Patients

Variables	r	p
Age	0.296	<0.001
Baseline SBP	−0.054	0.285
Baseline DBP	−0.062	0.218
FBG	−0.030	0.551
UA	0.024	0.635
CH	−0.052	0.303
LDL	0.183	<0.001
TG	0.025	0.619
HDL	−0.044	0.381
Hs-CRP	0.252	<0.001
Baseline NIHSS score	0.291	<0.001
Hcy	0.398	<0.001

Table 3 Multivariate Analysis of Correlation Factors Associated with Recurrence

	Unadjusted		Multivariable-Adjusted	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age	1.05 (1.03–1.08)	0.012	1.01 (0.97–1.05)	0.739
Smoking	0.53 (0.30–0.93)	0.028	1.53 (0.47–4.93)	0.480
Coronary heart disease	0.58 (0.16–2.06)	0.399	0.61 (0.09–4.44)	0.623
Diabetes	2.61 (1.53–4.45)	0.000	2.98 (1.20–7.43)	0.019
Hyperlipidemia	0.86 (0.44–1.68)	0.652	1.34 (0.50–3.59)	0.567
LDL, mmol /L	2.96 (2.00–4.37)	0.000	2.78 (1.48–5.20)	0.001
Hcy, umol /L	1.93 (1.68–2.22)	0.000	1.67 (1.40–1.98)	0.000
TG, mmol/L	1.58 (1.13–2.21)	0.007	0.89 (0.66–1.20)	0.444
Hs-CRP, mg/L	1.32 (1.04–1.67)	0.022	0.64 (0.38–1.07)	0.090
UA, μmol/L	1.00 (1.00–1.00)	0.220	1.00 (0.99–1.00)	0.257
FBG, μmol/L	1.05 (0.93–1.18)	0.457	1.10 (0.91–1.33)	0.337
PTX3, ug/mL	1.43 (1.32–1.55)	0.000	1.21 (1.06–1.39)	0.007
NIHSS score	2.10 (1.78–2.51)	0.000	1.93 (1.53–2.44)	0.000

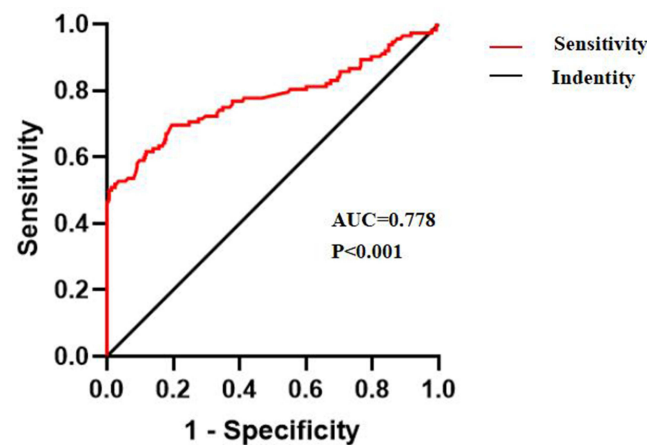


Figure 1 ROC curve for evaluating the predictive value of PTX-3 for RIS in patients with ICAS within one year.
Abbreviations: PTX-3, pentraxin-3; RIS, recurrent ischemic stroke; ICAS, intracranial atherosclerotic stenosis.

Discussion

This study reveals a significantly increased risk of RIS among patients with intracranial atherosclerotic stenosis and cerebral infarction, who have higher serum PTX-3 levels, after adjusting for a series of potential confounding factors. To the best of our knowledge, this is the first study to investigate the association between PTX-3 and recurrent stroke in patients accompanied with intracranial atherosclerotic stenosis.

Previous studies on the risk factors of recurrent stroke include various biological indicators and individual factors, but the differences in studies are mainly related to the definition of recurrent stroke, and also the differences of the study population.^{29–31} Consistent with previous studies, in our study, we also found that higher NIHSS scores, higher levels of CRP, homocysteine, and LDL were risk factors for recurrent stroke.^{32–35} Recurrent stroke has been clearly defined as a sudden new focal neurological deficit with a duration of greater than 24 hours, or an acute cerebral infarction with a focal neurological deficit of less than 24 hours but confirmed by imaging.³ In previous studies, the incidence of recurrent stroke within one year was higher.⁶ Therefore, it is of great significance to study the occurrence of recurrent stroke in the short term.

Although the specific mechanism of recurrent stroke and PTX-3 remains unclear, it may be discussed in the following. Previous inflammatory biological markers in the blood showed that they could predict that cerebral infarction with intracranial atherosclerotic stenosis caused recurrent stroke, which reflected the important role of inflammatory response in recurrent stroke.¹¹ Serum PTX-3 is an important inflammatory mediator.¹⁶ It coexists in multiple cells including endothelial cells with CRP neutrophils and interleukins,¹⁷ etc. It plays a role in the formation of atherosclerosis, and also plays a role in coronary heart disease and cerebral infarction.²⁰ Secondly, PTX-3 has dual effects. On the one hand, it has a protective effect in the early stage of blood–brain barrier damage; while, on the other hand, it will participate in further damage in case of sharp deterioration of damage.^{36,37} Therefore, it plays a dual role of protection and injury in the vascular endothelium of intracranial atherosclerosis. In some cases with vulnerable plaques, however, it can further increase the damage degree of plaque, leading to plaque destruction and hemorrhage, and subsequently the occurrence of cerebral infarction.³⁸ Finally, PTX-3 has the ability to lead to the accumulation of platelets through an inflammatory response, leading to the occurrence of local in situ thrombosis, and then leading to a series of stroke events.³⁹ All of the above can show that PTX-3 plays an important role in recurrent stroke, and also indicate their correlation.

Some limitations should be noted in this study. First, this is a single-center study with a relatively small sample size, thereby limiting the ability to extend the findings. Secondly, the PTX-3 level is detected only once on admission, but not dynamically monitored during the study. The pattern of dynamic change of PTX-3 may provide better predictive information. Thirdly, different degrees of intracranial atherosclerotic stenosis and different plaque load may play an important role in recurrent stroke, but they are not included in this study. Finally, we have not included factors such as population income differences and diet that may affect atherosclerosis and PTX-3.

Conclusions

In conclusion, an elevated serum PTX-3 level is independently associated with recurrent stroke in patients with intracranial atherosclerotic stenosis. Therefore, how to reduce the level of PTX-3 in patients with cerebral infarction is worth thinking about.

Data Sharing Statement

We declare that all the data in this article are authentic, valid, and available from Zhiyong Cao for reasonable request.

Ethics Approval and Consent to Participate

This study was conducted in acceptance with the Declaration of Helsinki and approved by the Ethics Committee of the Second Affiliated Hospital of Nantong University (2022KT268). All participants signed an informed consent form.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare that there are no conflicts of interest.

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