

Prognostic value of serum pentraxin 3 for intracerebral hemorrhage mortality

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Pentraxin 3 is considered an important inflammatory marker is known to increase in patients with ischemic stroke, but the relationship between pentraxin 3 and intracerebral hemorrhage mortality is unclear. The purpose of this study is to investigate the level of pentraxin 3 in serum and its impact on prognosis in 307 patients with intracerebral hemorrhage. During the 5-year follow-up, the mortality rate of patients with intracerebral hemorrhage was 22.5%. The serum pentraxin 3 level of the brain-dead patients was higher than that of the control group ($P < 0.05$). Logistic regression analysis indicated a high correlation between the pentraxin 3 level and the mortality rate 95% (hazard ratio: 3.671; confidence interval: 1.558-4.297). The receiver operating characteristic curve showed that pentraxin 3 (Area Under Curve = 0.801) had a higher diagnostic value than C-reactive protein (Area Under Curve = 0.701). The pentraxin 3 level increased significantly after intracerebral hemorrhage and has an important predictive value for a prognosis for intracerebral hemorrhage mortality.

Keywords

Intracerebral hemorrhage; Serum pentraxin 3; Neuroinflammation; Mortality

1. Introduction

Spontaneous intracerebral hemorrhage (ICH) refers to primary intraparenchymal bleeding, accounting for 10%-15% of all stroke, and the mortality rate in the acute phase is as high as 30%-40% [1]. After ICH, the hematoma compresses the surrounding brain tissue mechanically, which causes primary injury. Meanwhile, the hematoma components such as red blood cells and their degradation products can stimulate cytotoxicity, excitotoxicity, oxidative stress response and inflammatory response, leading to secondary injury [2], brain edema, destruction of the blood-brain barrier (BBB), neuronal apoptosis. Inflammatory reaction runs through all stages of ICH injury and plays a vital role in it. As part of the inflammatory response, inflammatory cytokines and immune cells play variable roles in ICH's progress [3].

After ICH, inflammatory mechanisms involve activation of microglia, infiltration of inflammatory cells and release of cytokines and inflammatory chemokines, leading to cell death

and aggravating brain injury [2]. This higher frequency of pro-inflammatory genes in ischemic stroke could explain the immunoinflammatory activation of the acute phase of stroke [4]. One study [5] indicated that the level of serum inflammatory factors in patients with ICH is significantly increased, and they participate in the pathological process of brain injury. However, the dynamic changes in inflammatory response factors after ICH are not clear. A series of cells participate in the production of pentraxin 3 (PTX3), including myeloid dendritic cells, monocytes, macrophages, vascular endothelial cells, smooth muscle cells, renal epithelial cells, fibroblasts, adipocytes, glia, cumulus cells, mesenchymal cells and synovial cells [6]. PTX3 commonly would not be expressed in brain tissue but can be increased significantly after exposure to pro-inflammatory factors [7].

PTX3 is a member of the pentraxin superfamily, was first recognized as a cytokine-inducing gene in endothelial cells and fibroblasts in the early 1990s. Pentraxin family proteins can be classified into two groups according to the primary structure subunits: short-chain pentraxin and long-chain pentraxin. The former includes C-reactive protein (CRP) and serum amyloid P (SAP), while PTX3 belongs to the latter. PTX3 is a product of the acute-phase reaction of injured tissues, mainly from the heart and blood vessels. Compared with CRP from the liver, PTX3 is likely to be a more sensitive and specific biological predictor of tissue injury. Many kinds of cells *in vivo* can secrete PTX3, reflecting the inflammation in vascular endothelial cells. Pentraxins are a multifunctional protein superfamily playing an important role in an inflammatory response.

PTX3 is a multifunctional protein superfamily member, which plays a vital role in the inflammatory reaction [8]. According to the previous study [9], PTX3 increases in sepsis and various infectious diseases, and its increase is related to the severity of these diseases. Also, plasma PTX3 levels were detected to increase in various disease states, such as ischemic heart disease, vasculitis and pulmonary contusion, in which inflammation plays an important role and is associated with

Table 1. Demographics and serum Pentraxin 3 levels in controls and patients.

	Controls (n = 132)	All (n = 307)	P	All (n = 307)		P
				Alive (n = 238)	Deceased (n = 69)	
Gender (M/F)	76/56	181/126	0.788	139/99	42/27	0.714
Age (years, mean \pm SD)	66.91 \pm 22.07	67.22 \pm 19.97	0.693	61.47 \pm 12.84	72.88 \pm 19.21	< 0.001
Hypertension (n%)	-	254 (82.7)	-	195 (81.9)	59 (85.5)	0.833
Diabetes (n%)	-	75 (24.4)	-	54 (22.7)	21 (30.4)	0.312
Previous stroke (n%)	-	33 (10.7)	-	12 (5.0)	11 (15.9)	0.006
Hypercholesterolemia (n%)	-	88 (28.7)	-	65 (27.3)	23 (33.3)	0.474
Current smoking (n%)	-	181 (58.9)	-	132 (55.5)	49 (71.0)	0.252
Atrial fibrillation (n%)	-	65 (21.2)	-	49 (20.6)	16 (23.2)	0.709
Admission GCS	-	9.37 \pm 2.78	-	12.66 \pm 4.32	5.78 \pm 1.96	< 0.001
Admission NIHSS	-	8.99 \pm 2.36	-	6.23 \pm 1.89	15.37 \pm 4.95	< 0.001
Hematoma Evacuation (n%)	-	236 (76.8)	-	187 (78.6)	49 (56.5)	0.631
Initial systolic blood pressure (mmHg)	-	163.58 \pm 18.94	-	159.32 \pm 23.61	171.29 \pm 32.16	0.006
WBC ($\times 10^9$)	8.96 \pm 2.33	9.26 \pm 2.34	0.431	8.66 \pm 1.98	12.34 \pm 3.71	0.079
Glucose (mmol/L)	7.31 \pm 1.29	7.46 \pm 1.21	0.556	6.70 \pm 1.92	8.65 \pm 1.78	0.092
Total cholesterol (mmol/L)	4.26 \pm 0.97	4.76 \pm 0.28	0.852	4.69 \pm 0.61	4.81 \pm 1.03	0.278
C-reactive protein (mg/L)	2.0 (0.11-12.1)	3.2 (0.43-21.2)	0.076	2.1 (0.43-6.85)	8.66 (2.09-21.2)	< 0.001
Pentraxin 3 (ng/mL)	3.19 (0.03-8.97)	8.99 (0.11-30.97)	< 0.001	5.29 (0.11-12.32)	19.34 (2.95-30.97)	< 0.001

Data are presented as the mean (standard deviation), median, range or percentage.

SD: Standard Deviation; GCS: Glasgow coma scale; NIHSS: National Institute of Health Stroke Scale.

disease activity [10, 11]. PTX3 is produced by inflammatory cytokines such as Toll-like receptor agonists, interleukin-1 β (IL-1) and Tumor necrosis factor- α (TNF- α).

PTX3 is proven to increase in many inflammatory diseases, and the serum PTX3 level is associated with sepsis development. After 6 hours of chest pain in patients with acute myocardial infarction (AMI), PTX3 level in plasma approaches peak level earlier than CRP. Therefore, PTX3 is seen as a better indicator than CRP, creatine kinase (CK), Troponin T (TnT), N terminal pro B-type natriuretic peptide (NT-proBNP) [12, 13]. It is also known that the PTX3 level is correlated with the severity and mortality of patients with systemic inflammatory response syndrome [14].

There are few studies on the relationship between PTX3 and brain injury. Several recent studies have suggested that PTX3 is closely related to ischemic stroke [15]. PTX3 levels in patients with acute ischemic stroke increased obviously and positively correlated with stroke severity [16]. A study [16] has shown that high levels of PTX3 imply poor long-term outcomes in patients with acute ischemic stroke and are more sensitive than CRP. However, some other studies have shown that plasma PTX3 levels were not associated with ischemic stroke [17, 18]. After ICH, the expression levels of TNF- α and IL-1 increased significantly, while both could regulate the expression of PTX3. Some experimental results have shown that serum PTX3 level is independently correlated with high mortality after severe traumatic brain injury, indicating that the PTX3 may be a useful brain injury marker and prognostic evaluation factor [19]. However, its relationship with ICH changes and its relationship with prognosis are unclear, which is the purpose of this work.

2. Methods

2.1 Study population

From January 2014 to December 2016, a total of 307 patients with ICH were prospectively recruited into this study at the Department of Neurosurgery of the First Affiliated Hospital of Xi'an Medical University. Their symptom occurred within 12 hours before admission. Inclusion criteria: All ICH patients included in the study met the diagnostic criteria formulated by the 4th National Academic Conference on Cerebrovascular Diseases and were confirmed by a CT scan of the brain. Exclusion criteria: (i) traumatic intracranial hemorrhage or hemorrhage caused by infarction, tumors and cerebrovascular malformations; (ii) patients with evident damaged liver or kidney functions or malignant tumors; (iii) patients with chronic inflammatory diseases (rheumatological diseases, IBD), taking immunosuppressive agents, hormones or inflammatory inhibitors for within a month; (iv) patients with atrial fibrillation; (v) patients with coagulation dysfunction and menstrual women. Another 132 volunteers were selected as the control group in the physical examination center. All subjects in this study signed informed consent after understanding the purpose and risk of this study. The ethics committee has approved this study of the First Affiliated Hospital of Xi'an Medical University.

2.2 Data collection

We collected the clinical data of patients at admission, including gender, age, laboratory data, Glasgow coma scale (GCS), National Institute of Health Stroke Scale (NIHSS), Hematoma evacuation and initial systolic blood pressure. Venous blood samples were drawn within 24 h of symptoms and were examined for WBC, glucose, total cholesterol, and

CRP levels. The risk factor information was also collected, such as hypertension, diabetes, previous stroke, hypercholesterolemia, smoking history, and heart diseases.

2.3 Detection of serum PTX3 level

Blood samples were centrifuged in sterile test tubes for 10 minutes (4 °C, 3000 R/min), then serum was collected and placed at -80 °C for examination. The serum PTX3 level of ICH patients was detected by enzyme-linked immunosorbent assay (ELISA) method, using the ELISA purchased from R&D Systems, McKinley Place NE, Minneapolis, MN, USA.

2.4 Follow-up

The patients discharged from the hospital were followed up by outpatient service or telephone, and the survival status of 1, 3 and 5 years was recorded.

2.5 Statistical analysis

Statistical analysis was performed by SPSS software version 16.0 (SPSS Inc., Chicago, IL). Data were expressed in the format of mean \pm SD or median (range). Continuous and categorical variables were compared between groups using the Mann-Whitney U-test or Kruskal-Wallis rank-sum test. Multivariate analysis using logistic regression was performed for factors discriminating phases or clinical diseases. The receiver operating characteristic (ROC) curves were constructed, and the area under the curve (AUC) was computed to evaluate the performance of PTX3 for discriminating survived and deceased ICH patients. The following covariates were also taken into consideration during the analysis: age (per year), gender, hypertension, diabetes, hypercholesterolemia, smoking, heart disease, NIHSS scores at the time of admission, log-transformed CRP (per 1 log unit), and serum glucose (per 1 mmol/L). Univariate and multivariate analysis was performed on factors associated with the overall survival of deceased ICH patients. Kaplan-Meier curves of overall survival in patients with deceased ICH patients were plotted according to the serum PTX3 levels. P -value < 0.05 was considered statistically significant.

3. Results

3.1 Demographic and clinical characteristics of the study subjects and PTX3 levels

The 307 patients with ICH included 181 males and 126 females aged 67.22 ± 19.97 years, among which the 238 survivors included 139 males and 99 females aged 61.47 ± 12.84 years, and the 69 deceased patients included 42 males and 27 females aged 72.88 ± 19.21 years, and the 132 controls included 76 males and 56 females aged 66.91 ± 22.07 years. There was no significant gender ratio nor age difference between the patients and controls (Table 1).

The serum PTX3 levels in patients with ICH [8.99 (0.11-30.97) ng/mL] were significantly higher than those in control group [3.19 (0.03-8.97) ng/mL, $P < 0.001$, Table 1]. The PTX3 levels between survived and deceased ICH patients had significant differences. The serum PTX3 in deceased patients [19.34 (2.95-30.97) ng/mL] were significantly higher than

those in survived [5.29 (0.11-12.32) ng/mL, Table 1]. The baseline characteristics of the study population according to mortality status are summarized in Table 1. Deceased patients were likely to be older, have a history of stroke. Also, white blood cell count, CRP levels, and serum glucose levels were higher in deceased patients.

CRP and other biomarkers are commonly used markers of inflammation but suffer from its lack of specificity for infections. PTX3 tends to increase from the onset of the event. Compared with other inflammatory indexes, it has higher specificity [22]. It is an independent predictor of severe sepsis and mortality after adjusting for potential confounders [20]. Higher PTX3 levels were found in non-survivors than survivors and are associated with a two-fold increase in mortality.

3.2 PTX3 levels according to ICH prognosis

Considering the above-observed result that the deceased patients had significantly higher PTX3 levels than survivors, the ROC curves were plotted to evaluate the performance of serum PTX3 in predicting alive and deceased patients. The AUC value of PTX3 levels was 0.801 for survived versus deceased ($P < 0.001$, Fig. 1), with a cut-off value of 9.997 ng/mL in PTX3 for survived and deceased ICH patients. The sensitivity and specificity were 0.927 and 0.932, respectively.

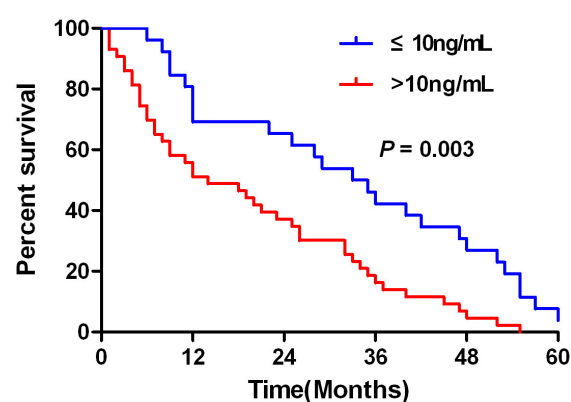


Fig. 1. Survival curves of Pentraxin 3 tertiles. The percent survival was different according to the PTX3 tertiles ($P < 0.001$). PTX3 levels were significantly associated with higher mortality.

3.3 Univariate and multivariable analysis of variables for long-term mortality

The Cox proportional hazard regression test's univariate analysis showed that PTX3 levels were significantly associated with higher mortality. The hazard ratio (HR) was 3.684 (95% confidence interval (CI): 1.276-5.966) (Table 2). The multivariable analysis also revealed a high association between PTX3 levels and mortality (Fig. 2).

Table 2. Univariate and multivariable analysis of variables for long-term mortality.

Predictors	Univariate analysis			Multivariable analysis		
	Crude HR	95% CI	P	Adjusted HR	95% CI	P
Age (per 1-year)	4.651	2.881-7.632	< 0.001	3.671	1.558-4.297	0.002
Previous stroke	1.963	1.129-3.556	0.001	1.231	1.007-1.964	0.033
GCS (increase per unit)	3.116	1.007-4.358	< 0.001	1.524	1.006-2.334	0.003
NIHSS (increase per unit)	2.158	1.071-4.307	< 0.001	1.456	1.015-2.489	0.006
Glucose (per 1 mmol/L)	1.029	0.961-1.789	0.097	-	-	-
Total cholesterol (mmol/L)	0.563	0.325-1.074	0.051	-	-	-
WBC (per 1000/mm ³)	1.121	1.007-2.366	0.002	1.055	0.921-1.378	0.097
CRP (per 1 log unit)	1.346	1.009-3.214	< 0.001	1.091	1.004-1.978	0.029
PTX3 (increase per log unit)	3.684	1.276-5.966	< 0.001	2.776	1.198-3.651	< 0.001

GCS: Glasgow coma scale; NIHSS: National Institute of Health Stroke Scale; CRP: C-reactive protein; PTX: Pentraxin.

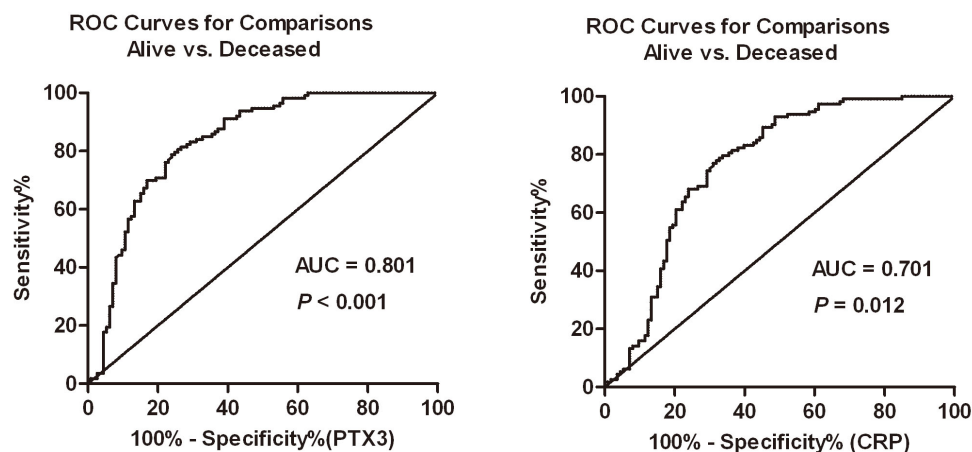


Fig. 2. Receiver operating characteristic curves of PTX3 and CRP. Receiver operating characteristic curves for comparison alive and deceased. *P* for difference < 0.001. PTX3 had a more excellent prognostic value than CRP. PTX3: Pentraxin 3, CRP: C-reactive protein.

3.4 Association of PTX3 levels with overall survival of ICH deceased

Univariate and multivariate analysis showed that PTX3 level is a significant independent factor associated with the overall survival of ICH deceased, besides age, admission GCS and admission NIHSS [HR (95% CI) = 6.551 (1.782-8.965), *P* = 0.001, Table 3]. The Kaplan-Meier curves showed that patients' overall survival with ICH decreased with PTX3 levels > 10 ng/mL was significantly lower than those with PTX3 levels ≤ 10 ng/mL (*P* = 0.003, Fig. 1).

4. Conclusions

We took a single venous blood sample for each patient at the arrival to detect the PTX3 levels and chose a straightforward prognosis data model consisting of survival and death to derive a clear conclusion. We found that plasma levels of PTX3 increased in patients with ICH, especially in the deceased patients. Usually, the basic levels of PTX3 in serum is low, but it may increase 3-5 times the baseline level within 6 or 8 hours under inflammatory conditions [6, 22]. The levels of PTX3 in the healthy control group were 3.19 (0.03-8.97) ng/mL, while in the ICH group was 8.99 (0.11-30.97) ng/mL in the brain-dead group was the highest at 19.34 (2.95-30.97).

We also found leukocytosis in peripheral blood. The number of neutrophils in peripheral blood within 72 hours after ICH was associated with poor prognosis [23]. However, it had no association with long-term prognosis.

In conclusion, inflammation played an important role in secondary brain injury after ICH. Inflammatory signals trigger the infiltration of peripheral inflammatory cells and release inflammatory mediators, leading to cell death and brain damage. We demonstrated the correlation between the expression levels of PTX3, CRP and prognosis after ICH. Compared with CRP, PTX3 is a robust and independent predictor of long-term mortality in ICH patients. Higher levels of PTX3 were independently associated with increased mortality after ICH.

Author contributions

All authors had full access to all the data and took responsibility for the data integrity and data analysis accuracy. All authors contributed to the conception and design during the acquisition, analysis and interpretation of the results, including drafting and critical review of the manuscript to improve the content and the final approval of the published version.

Table 3. Univariate and multivariate analysis of the overall survival of intracerebral hemorrhagic.

	NO. of patients	Overall Survival (%)			Univariate analysis	Multivariate analysis	
		1 year	3 year	5 year	P	HR (95%CI)	P
Gender					0.871	1.099 (0.271-2.336)	0.147
Male	42	61.9	35.7	14.3			
Female	27	66.6	33.3	14.8			
Age (year)					0.032	2.557 (1.098-4.681)	0.019
≤ 65	29	79.3	41.4	20.7			
> 65	40	52.5	22.5	10.0			
Admission GCS					0.002	0.567 (0.013-0.953)	0.007
≤ 8	39	38.4	15.3	7.6			
> 8	30	63.3	33.3	16.7			
Admission NIHSS					0.006	1.965 (1.027-3.589)	0.010
≤ 15	41	41.5	17.1	7.3			
> 15	28	64.3	32.1	14.3			
Previous stroke					0.027	1.457 (0.473-2.226)	0.095
Yes	11	45.5	18.2	9.1			
No	58	67.2	41.3	13.7			
CRP (mg/L)					0.018	1.187 (0.971-2.457)	0.123
≤ 5	32	75.0	59.3	18.7			
> 5	37	40.5	16.2	8.1			
PTX3 (ng/mL)					0.003	6.551 (1.783-8.965)	0.001
≤ 10	26	70.4	38.5	15.4			
> 10	43	51.2	16.3	6.9			

GCS: Glasgow coma scale; NIHSS: National Institute of Health Stroke Scale; CRP: C-reactive protein; PTX: Pentraxin.

Ethics approval and consent to participate

All subjects in this study signed informed consent after understanding the purpose and risk of this study. The ethics committee has approved this study of the First Affiliated Hospital of Xi'an Medical University.

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Conflict of interest

None of the authors report any conflicts of interest.

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