

RESEARCH ARTICLE

Increased concentration of serum periostin is associated with poor outcome of patients with aneurysmal subarachnoid hemorrhage

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Objective: To explore the role of serum periostin in patients with aneurysmal subarachnoid hemorrhage (aSAH).

Method: We conducted a retrospective study and 124 aSAH patients treated in Shenzhen People's hospital during March 1st 2015 to December 30th 2016 were included. Baseline information, neurological status and clinical outcome were recorded. Blood samples on admission were collected and enzyme linked immunosorbent assay (ELISA) kits were used to detect the serum level of periostin. Spearman's Correlation Analysis was used to analyze the correlation between periostin and clinical severity. Receiver operating characteristic (ROC) curve was performed to investigate variables' prognostic value in patients with aSAH.

Results: The average age of patients included was 57.23 years old. Preliminary analysis revealed that serum periostin was significantly correlated with clinical severity. Patients with poor outcome at 12 months had higher level of periostin than patients with good outcome. Multivariate logistic regression analysis showed elevated level of periostin was significantly associated with poor outcome and the AUC was 0.85 for periostin in predicting poor outcome of patient with aSAH.

Conclusion: Elevated serum periostin concentrations are significantly associated with clinical severity and poor outcome of aSAH patients, which indicate serum periostin can be used as a prognostic biomarker in patients with aSAH.

KEYWORDS

biomarkers, DCI, outcome, periostin, subarachnoid hemorrhage

1 | INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) is a fateful neurological disorder which affects millions of people and aSAH always results in high mortality and disability, as well as high medical expenses.¹ It was estimated that the annual incidence of aSAH worldwide was about 9/100 000 person/year² and as many as 29% of aSAH patients died in the first 3 month.³ What's more, more than 1/3 of aSAH patients suffered cognitive impairment and experienced a decline of quality of life.⁴ Cerebral vasospasm (CVS) and early brain injury (EBI) are regarded as the main causes of poor outcome of patients with aSAH.⁵

Accumulated evidences have showed that inflammatory response, oxidative stress and peripheral immune response are significantly associated with CVS⁶ and EBI.⁷ Recently, Biochemical markers involving in the pathologic process after SAH have been proven to be early diagnostic indexes for predicting clinical outcome of patients with aSAH.^{4,8}

Periostin is a 90 KD secreted protein that is broadly expressed in the body, including stomach, breast, uterus and thyroid tissue.⁹ Previous studies have identified periostin as a biomarker of inflammation^{10,11} and oxidative stress¹² and evidences also showed that periostin played a key role in promoting tumor progression under hypoxia.^{13,14} What's more, Matsunaga E reported that periostin was

TABLE 1 Baseline information of patients included

Variables	N (%)
Female (%)	78 (62.90)
Age (y)	57.23 ± 8.77
Accompanied diseases	
Hypertension	41 (33.06)
Diabetes	16 (12.90)
Smoking	21 (16.94)
GCS	11.84 ± 3.29
Hunt-hess	
I-II	77 (62.09)
III-IV	47 (37.91)
Fisher	
I-II	56 (45.16)
III-IV	68 (54.84)
Acute hydrocephalus	13 (10.48)
Intraventricular hemorrhage	32 (25.81)
Admission time (h)	12.78
Aneurysm locations	
Anterior circulation artery	94 (75.81)
Posterior circulation artery	29 (24.19)
Surgical approaches	
Clipping	86 (69.35)
Coiling	38 (30.65)

expressed at higher level in primate cerebral cortex than mouse cerebral cortex and what's more, periostin exhibited neurite outgrowth activity.¹⁵ Periostin was observed in neurons and increased in astrocytes at 24 hours after transient middle cerebral artery occlusion (tMCAo), which indicated that periostin might play an important role in the pathologic process after stroke.¹⁶ Recently, study showed that serum periostin concentrations in patients with traumatic brain injury (TBI) was significantly higher than healthy individuals and level of periostin was significantly associated with clinical severity.¹⁷ While in SAH mouse model, periostin neutralization could alleviate EBI. 1 µg r-periostin could significantly aggravated brain edema after SAH,¹⁸ which indicated that periostin may play a important role in pathologic process after SAH. While no study has revealed the role of serum periostin in patients with aSAH till now. So we performed this study to explore the role of periostin in patients with aSAH.

2 | METHOD

2.1 | Study population

This was retrospective study and all included patients were treated in the department of neurosurgery of Shenzhen People's hospital during March 1st 2015 to December 30th 2016. Patients were diagnosed as aneurysmal subarachnoid hemorrhage by head computed tomography (CT) and further confirmed by subsequent head CT angiography

(CTA) or digital subtraction angiography (DSA). We excluded patients whose blood sample collection was more than 72 hours from symptom onset. Patients who were accompanied with infectious diseases, autoimmune disease or serve organ dysfunction 2 weeks before hospitalization and those who had history of neurological diseases were also excluded. All included patients received standard treatments which included hemostasis, reduce cerebral edema, prophylactic anti-seizure and anti-vasospasm before surgery. All participants or their relatives were informed and an consent was written for each patients. Our study was approved by the ethical committee at Shenzhen People's hospital.

2.2 | Clinical assessment

Baseline information (sex, gender, comorbidities, etc.) of patients included were collected. Neurological assessment was conducted by using Glasgow Coma scale (GCS) and hunt-hess grade. Fisher grade was accessed for each patients based on the presentation of head CT on admission. Head CT was routinely performed for all patients on the first day and at any time during hospital stay if patients suffered clinical deterioration. Delayed cerebral ischemia (DCI) was defined as previous described.¹⁹ All 12-month follow-up was performed by using telephone interviews and poor outcome was defined as Glasgow outcome scale (GOS) score 1-3 and good outcome was defined as GOS score 4-5.

2.3 | Blood samples measurements

Two milliliters of blood samples were collected in early morning and immediately centrifuged at 2000 g for 15 minutes at -4°C. The serum was collected and stored at -80°C. Human Periostin ELISA Kit (RAB1075, SIGMA) was used to detect serum level of periostin according to the manufacture's instruction.

2.4 | Statistical analysis

The descriptive analysis (mean, standard deviation, median) was used for continuous variables and percentage for categorical variables. t test or One-Way ANOVA analysis was used for the comparisons between groups for continuous variables. Box-plot was used to present levels of periostin between different groups. In order to assess the risk factors of poor outcome, variables were first analyzed by performing univariate logistic regression analysis and then multivariate logistic regression analysis would be used to analyzed the factors with $P < .1$. Receiver operating characteristic (ROC) curves were used to accessed the variables' prediction ability. Statistical analyses were conducted by using SPSS 21.

3 | RESULTS

3.1 | Baseline information

Finally, there were 124 patients with aSAH included in this study. There were 78 females and 46 males with an overall average age of

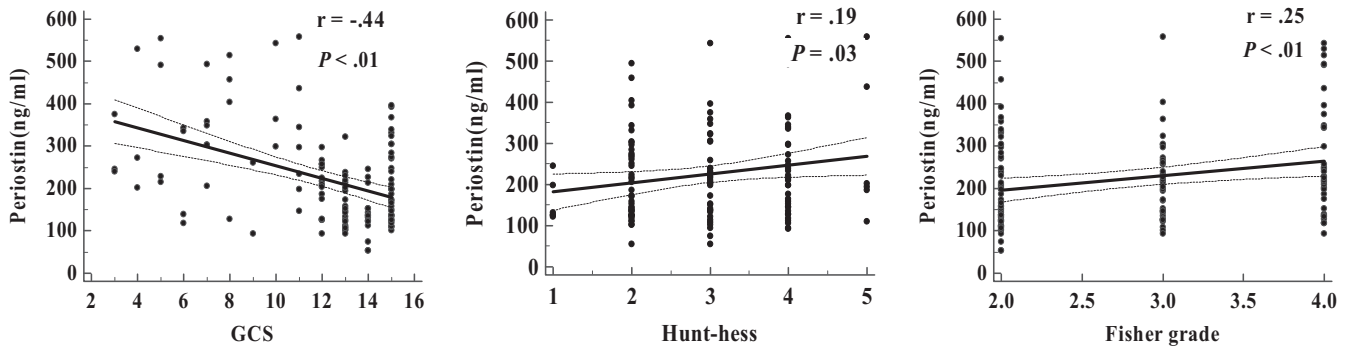


FIGURE 1 Correlation between periostin and clinical severity

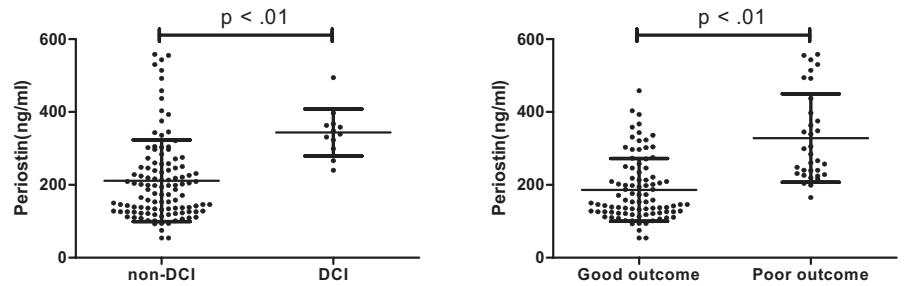


FIGURE 2 Level of serum periostin concentrations in aSAH patients

TABLE 2 Univariate and Multivariate logistic regression analysis of risk factors associated with poor outcome

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.03 (0.99-1.08)	.18	-	-
Female	0.44 (0.20-0.99)	.05	0.94 (0.24-3.67)	.93
Hypertension	0.99 (0.41-2.33)	.96	-	-
Diabetes	0.91 (0.23-3.59)	.89	-	-
Current smoking	5.21 (1.94-13.99)	<.01	6.04 (1.22-12.85)	.03
Intraventricular hemorrhage	1.96 (0.69-3.91)	.51	-	-
GCS	0.85 (0.76-0.95)	<.01	1.18 (0.95-1.46)	.13
Hunt-hess grade III-IV	5.58 (2.14-8.32)	<.01	3.02 (0.73-12.41)	.13
Fisher grade III-IV	2.56 (1.52-4.29)	<.01	2.72 (1.13-6.55)	.03
acA	1.48 (0.67-2.98)	.71	-	-
Clipping	1.32 (0.53-3.29)	.55	-	-
DCI	19.35 (3.96-44.49)	<.01	9.10 (2.12-17.99)	.04
Periostin (ng/mL)	1.01 (1.00-1.02)	<.01	1.02 (1.01-1.03)	<.01

57.23 years old. There were 41 patients with Hypertension, 16 patients with Diabetes and 24 current smokers. Among these included patients, there were 47 patients with Hunt-hess grade III-IV and 77 patients with Hunt-hess grade I-II on admission. The average GCS score was 11.84 (range from 3 to 15). There were 133 intracranial aneurysms with 94 located in anterior circulation artery and 39 in posterior circulation artery. Details of demographic information were showed in Table 1.

3.2 | Level of periostin correlated with clinical severity

Correlation analysis revealed that periostin was significantly correlated with clinical severity. Correlation coefficient was -0.44 between serum periostin level and GCS score on admission. Besides, periostin was positively correlated with Fisher grade and Hunt-hess grade ($r = 0.25$, 95% CI [0.07-0.41], $P < .01$), ($r = -.19$, 95% CI [0.01-0.35], $P = 0.19$, respectively). Details were presented in Figure 1.

Variables	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P value	OR (95%CI)	P value
Age	1.12 (1.04-1.20)	<.01	1.09 (1.00-1.17)	.04
Female	0.56 (0.17-1.84)	.34	-	-
Hypertension	1.15 (0.32-4.07)	.83	-	-
Diabetes	5.72 (1.44-12.75)	.01	4.70 (1.10-20.69)	.04
Current smoking	0.42 (0.05-3.43)	.42	-	-
Intraventricular hemorrhage	1.04 (0.99-1.09)	.13	-	-
GCS	0.93 (0.79-1.09)	.36	-	-
Hunt-hess grade III-IV	3.08 (0.91-10.38)	.07	0.50 (0.10-2.90)	.44
Fisher grade III-IV	2.26 (1.06-4.48)	.04	1.67 (0.70-3.97)	.25
Clipping	1.45 (0.84-3.48)	.91	-	-
Periostin (ng/mL)	1.01 (1.00-1.02)	<.01	1.01 (1.01-1.01)	.03

TABLE 3 Univariate and Multivariate logistic regression analysis of risk factors associated with DCI

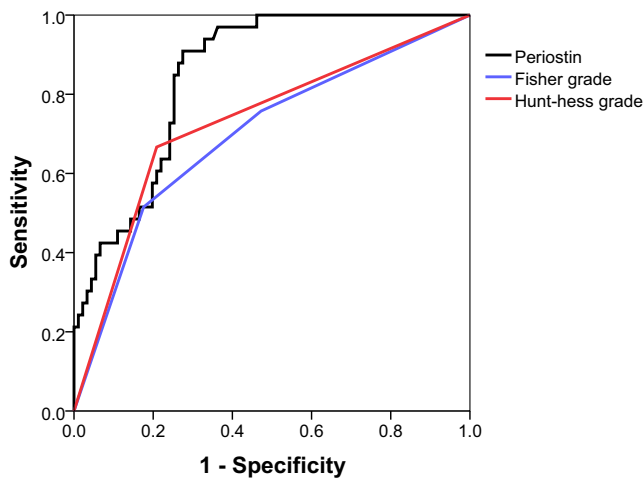


FIGURE 3 Values of periostin, Fisher grade and Hunt-hess in predicting poor outcome in patients with aSAH

3.3 | Serum periostin concentrations in aSAH patients

There were 12 patients suffered with DCI during hospital stay and patients with DCI had higher level of serum periostin than those with non-DCI (343.75 ± 64.65 vs 211.32 ± 112.04 , $P < .01$). Figure 2.

TABLE 4 Diagnostic value of variables for poor outcome of aSAH patients

Variables	Sensitivity (%)	Specificity (%)	AUC (95%CI)
Periostin	90.91	72.53	0.85 (0.78-0.91)
Fisher grade	51.52	82.42	0.70 (0.61-0.78)
Hunt-hess grade	66.67	79.12	0.73 (0.64-0.81)

Besides, level of periostin was elevated in patients with poor outcome at 12 month than patients with good outcome (328.48 ± 121.40 vs 186.30 ± 85.69 , $P < .01$).

3.4 | Prognostic effect of periostin on poor outcome

Multivariate regression analysis were used to analyze risk factors associated with poor outcome of patients with aSAH after using univariate analysis. The results showed that current smoking, DCI, high grade Fisher grade (III-IV) and elevated level of periostin were significantly associated with poor outcome. Results of the multivariate analyses are shown in Table 2. Besides, we also performed multivariate logistic regression analysis of occurrence of DCI and the results showed high serum concentration of periostin was an independent risk factor of DCI. Results were presented in Table 3. ROC was used to accessed the value of periostin in predicting poor outcome. The AUC of periostin, Hunt-hess grade and Fisher grade in predicting poor outcome was 0.85, 0.73, 0.70, respectively, which indicated that periostin was an good diagnostic role in predicting poor outcome of aSAH patients (Figure 3 and Table 4).

4 | DISCUSSION

Periostin is a extracellular matrix protein which haven't been investigated in aSAH. In this retrospective study, we found that patients with poor outcome had higher level of periostin than patients with good outcome at 12 months. Level of periostin was negatively correlated with GCS on admission and positively correlated with hunt-hess grade and fisher grade. Further analysis revealed that serum level of periostin was an independently associated with poor outcome and DCI. Additional analysis revealed that the AUC of periostin, Hunt-hess grade and Fisher grade in predicting poor outcome was 0.85, 0.73, 0.70, respectively. Consequently, serum periostin could be used as an biomarker in patients with aSAH.

Previous studies have identified periostin was involved in process of inflammation, oxidative stress and it played a key role in promoting tumor progression under hypoxia. Periostin have been investigated as a biomarker in various diseases. Periostin was found to plays an important role in repairing the biological matrix of the lung and serum periostin can predict clinical progression both in asthma and idiopathic pulmonary fibrosis.²⁰ Besides, periostin was found to involve in the progression of cancer and metastatic processes, as well as acting an regulator of epithelial mesenchymal transition (EMT).²¹ Serum periostin was elevated in patient with advanced non-small cell lung cancer and could be used as an reliable marker to predict patients' chemotherapy response and survival.²² Few studies have explored the role of periostin in neurological diseases till now. Matsunaga et al reported that periostin was expressed at higher level in primate cerebral cortex than mouse cerebral cortex and periostin exhibited neurite outgrowth activity in brain tissues.¹⁵ Recent studies have revealed that periostin was overexpressed in neural stem cell (NSCs) following hypoxia ischemia and hypoxia could increased periostin expression.^{13,23} Hypoxia, oxidative stress and inflammatory reaction could be involved in the pathological processes of traumatic brain injury (TBI)²⁴ and stroke,²⁵ so periostin was supposed to elevated in these neurological diseases. Periostin1 and periostin2 (its splicing variant) were both investigated in transient middle cerebral artery occlusion (tMCAo) model. The results showed that periostin 2, not periostin 1 was overexpressed at 24 hours after tMCAo. Exogenously injection of periostin 2 could reduce infarct volume, which indicated that periostin 2 exhibit anti-hypoxia property and an protective effect.¹⁶ While on the contrary, previous study found that periostin was higher expressed in heart failure and inhibited expression of periostin could increase survival rate, which indicated that inhibition of periostin might be a potential therapy for heart failure.²⁶ Another study conducted by Xiao-Qiao Dong et al revealed its role in traumatic brain injury. Serum periostin in patients with TBI was higher than patients in control group and level of periostin was significantly correlated with GCS. Our study showed similar results to this report. Patients who had DCI during hospital stay had higher level of periostin and periostin concentration was negatively correlated with GCS. While AUC of periostin in predicting 30-day mortality of patients with TBI was 0.815. Periostin might play different role in pathological procession of TBI and SAH. Previous study demonstrated that anti-periostin antibody could prevented post-SAH neuro-behavioral impariments and EBI. Recombinant-periostin significantly aggravated EBI.¹⁸ However, serum periostin in patients with SAH hadn't been investigated yet and it was still unknown if periostin could be used as a prognostic biomarker in SAH. This was the first study to explored the role of periostin in patients with SAH. We found periostin was highly expressed in patients with poor outcome. Besides. AUC of periostin was 0.850 in predicting poor outcome at 12 months. Our study proved that periostin could be used as a prognostic biomarker in patient with SAH.

There were some limitations in this retrospective study. Patients included in this study was relatively small and patients received both clipping and coiling were enrolled, which may caused extra biases because of different brain trauma caused by clipping and coiling. Besides, blood

samples were routinely collected in the first morning and patients might treated with certain amount of liquid, which might have some effect on the level of serum periostin. Finally, in this study, we only explored preoperative level of periostin in patients with SAH and dynamic change of serum of periostin haven't been investigated till now.

In conclusion, aSAH patients with poor outcome had higher level of periostin than patients with good outcome at 12 months. Serum periostin was significantly correlated with GCS, Hunt-hess grade and Fisher grade. AUC was 0.850 of periostin in predicting poor outcome at 12 months which indicated that periostin could be used as a prognostic biomarker in patients with aSAH.

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