Research Square

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Serum Periostin and Cognitive Impairment in Ischemic Stroke Patients: a Prospective Cohort Study

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Abstract

Background. Recent evidence suggest elevated periostin is associated with cardiovascular diseases. The aim of this study was to investigate the relationship between serum periostin and post-stroke cognitive impairment (PSCI) at 3 months.

Methods. In this prospective cohort study, we enrolled patients with ischemic stroke and hospitalized within 7 days of symptoms onset from January 2019 to January 2020. Serum periostin levels were measured using enzyme-linked immunosorbent assay after admission. Cognitive function assessment was performed at 3-month follow-up visit using the Montreal Cognitive Assessment (MoCA). We defined the PSCI as total MoCA score < 25.

Results. A total of 315 ischemic stroke patients were enrolled for the study. PSCI was observed in 173 patients, which accounted for 54.9% (95% confidence interval [CI] 52.1%–57.7%) of the cohort. Serum periostin levels were higher in patients with PSCI than in those without PSCI (median 19.6 vs 14.8 ng/mL; $P = 0.001$). In logistic regression analysis, the highest quartile of periostin levels were significantly correlated to PSCI (odds ratio [OR], 9.69; 95% CI, 5.06–25.61; $P = 0.001$), as compared with the lowest quartile. This association remained significant after adjustment for age, gender, educational years, stroke severity, and vascular risk factors. Subgroup analyses further confirmed these results. Furthermore, restricted cubic spline regression demonstrated a linear association between periostin levels and PSCI ($P = 0.001$ for linearity).

Conclusions. This study found that higher serum periostin levels are associated with an increased risk of PSCI at 3 months after ischemic stroke onset.

Introduction

Post-stroke cognitive impairment (PSCI) is regarded as the most prevalent syndrome after stroke [1]. Reported frequency of PSCI ranges widely from 10–82% [2, 3]. PSCI is associated with impairment of activities of daily living, functional disability, and increased risk of mortality [4, 5]. It may also cause ischemic stroke recurrence [6]. However, the pathogenesis of PSCI remains unclear. In addition, precise biomarkers that could improve the prediction of cognitive impairment after ischemic stroke are still lacking.

Periostin is a 90 KD multifunctional matricellular protein belonging to the member of fascilin family, which actively contributes to tissue injury, fibrosis, atherosclerosis, and inflammatory reaction [7–9]. Previous studies reported that the alternation and overexpression of periostin was found in a variety of diseases including ischemic stroke and other cerebrovascular diseases [10–12]. Recently, a cohort study of 162 large artery atherosclerotic stroke patients showed that serum periostin levels were positively correlated to the national institutes of health stroke scale (NIHSS) score and stroke volume [10]. Also, a growing body of evidences indicated that periostin is involved in the neuropathological processes, such as inflammation, disruption of blood-brain barrier, and neuronal cell death [13, 14], which may lead to

cognitive impairment. To date, the relationship between cognitive function status and periostin levels has not been clarified yet.

Therefore, we conducted this prospectively study to investigate whether the serum perostin levels at admission are associated with PSCI at 3 months.

Methods

Study design and patients

This observational prospective cohort study screened consecutive acute ischemic stroke patients hospitalized in The Sixth People's Hospital of Chengdu, between January 2019 and January 2020. Patients were recruited in this study if they: (1) aged 18 years or old; (2) hospitalized within 7 days of symptoms onset; (3) had severe motor and language disabilities that precluding the cognitive evaluation. Exclusion criteria for this study were a history of traumatic brain injury, drug and alcohol dependence, Parkinson disease, Alzheimer's disease, psychiatric disorders known to influence cognitive function, and lost to follow up. This study was approved by the ethics committee at The Sixth People's Hospital of Chengdu, and all participating patients had provided informed consent before entering the study. The study was carried out according to the tenets of the Declaration of Helsinki.

Data collection

Demographic data, educational status, and vascular risk factors (including hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, previous stroke, and current smoking and drinking) were recorded at admission. We also collected body mass index, blood pressure, stroke severity and stroke etiology [15]. Baseline stroke severity was assessed by certified neurologist using NIHSS score [16]. Stroke subtype was classified using Trial of Org 10172 in Acute Stroke Treatment criteria [17].

Laboratory testing

Blood samples were obtained from each subject within 24 h after admission. The specimens were centrifuged at 1500 g for 15 min and the isolated serum frozen at − 80°C for further analysis. Serum periostin levels were measured using a commercially available ELISA kit (BioVendor, RAG019R). Intra-assay and inter-assay coefficients of variation were < 10.0% and < 12.0%, respectively. All procedures were performed in strict accordance to manufacturers' instructions by laboratory technicians blinded to the clinical characteristics and outcomes. The other laboratory data including fasting blood glucose, low-density lipoprotein and Hyper-sensitive C-reactive protein (Hs-CRP) were also recorded.

Cognitive evaluation

Cognitive function assessment was performed at 3 months after stroke by the trained psychologist who was blinded to the clinical data, using the Montreal Cognitive Assessment (MoCA) [18]. Patients with education < 12 years tended to have worse performance on the MoCA. To correct for education effects, 1 point was added for participants with education < 12 years on their total MoCA score [19]. According to

previous studies [18, 20, 21], a total MoCA score < 25 was diagnosed as PSCI. Also, the degree of cognitive impairment was categorized as follows: severe cognitive impairment (MoCA score, 0–19), mild cognitive impairment (MoCA score, 20–24), and no cognitive impairment (MoCA score, 25–30) [20].

Statistical Analysis

All statistical analysis was done with the SPSS software, version 24.0 (IBM, New York, NY) and R statistical software version 3.6.2. Categorical variables were expressed as percentages and analyzed with the chi-square test or Fisher's exact test. Continuous variables were summarized as mean (standard deviations) or medians (interquartile ranges) and compared by Student's t test, Mann-Whitney U test, analysis of variance or Kruskal-Wallis test [18]. We conducted 2 multiple adjusted logistic regression models to estimate the association of periostin levels with PSCI. Model 1 adjusted for age, and sex. Model 2 included age, sex and covariates with a *P* value < 0.1 in the univariate analysis (including educational years, hypertension, diabetes mellitus, and NIHSS score). Restricted cubic spline regression was used to detect the shape of association between periostin and PSCI, fitting a restricted cubic spline function with four knots (at the 5th, 35th, 65th, and 95th percentiles) [18]. We further performed subgroup analyses and investigated the potential modified effect of 6 interesting factors on the association between serum periostin and PSCI. Interactions between periostin and subgroup variables on the PSCI were tested by the likelihood ratio test with adjustment for the aforementioned covariates unless the variable was used as a subgroup variable. In all analyses, a *P* value < 0.05 was considered statistically significant.

Results

In our study cohort, a total of 315 consecutively admitted patients (mean age, 66.8 ± 8.9 years; 53.3% male) with acute ischemic stroke met the entry criteria. The median periostin levels were 17.6 ng/mL (interquartile range 14.2–20.7 ng/mL). Baseline epidemiological and clinical characteristics of the study population stratified by the quartile of serum periostin concentrations were demonstrated in Table 1. Subjects with elevated serum periostin levels were more likely to have a higher Hs-CRP levels (*P* = 0.038) and NIHSS score (*P* = 0.021).

Table 1
Baseline characteristics of the study population according to the periostin quartile.

Variable	All patients, n = 315	Periostin quartile				*P* value
		1st, n = 78	2nd, n = 78	3rd, n = 81	4th, n = 78	
Demographic characteristics						
Age, year	66.8 ± 8.9	65.4 ± 9.1	67.2 ± 9.1	66.6 ± 9.0	68.1 ± 8.7	0.290
Male sex, n (%)	168 (53.3)	40 (51.3)	38 (48.7)	42 (51.9)	48 (61.5)	0.395
Education years < 12, n (%)	201 (63.8)	49 (62.8)	49 (62.8)	52 (64.2)	51 (65.4)	0.984
Body mass index, kg/m^2	24.9 ± 2.9	24.7 ± 2.6	25.5 ± 3.3	25.0 ± 2.6	24.4 ± 3.2	0.116
Vascular risk factors, n (%)						
Hypertension	183 (58.1)	41 (52.6)	48 (61.5)	49 (60.5)	45 (57.7)	0.669
Diabetes mellitus	84 (26.7)	22 (28.2)	14 (17.9)	25 (30.9)	23 (29.5)	0.243
Hyperlipidemia	46 (14.6)	14 (17.9)	10 (12.8)	13 (16.0)	9 (11.5)	0.654
Coronary heart disease	37 (11.7)	9 (11.5)	5 (6.4)	9 (11.1)	14 (17.9)	0.167
Previous stroke	45 (14.3)	11 (14.1)	11 (14.1)	8 (9.9)	15 (19.2)	0.418
Current cigarette smoking	122 (38.7)	30 (38.5)	26 (33.3)	33 (40.7)	33 (42.3)	0.678
Current alcohol drinking	84 (26.7)	20 (25.6)	20 (25.6)	22 (27.2)	22 (28.2)	0.979
Clinical data						
NIHSS, score	8.0 (5.0, 11.0)	8.0 (5.0, 9.0)	7.0 (5.0, 11.0)	8.0 (5.0, 11.0)	9.0 (6.0, 12.0)	0.021
Systolic blood pressure, mmHg	137.7 ± 16.5	135.6 ± 18.1	139.4 ± 15.1	137.8 ± 15.4	137.8 ± 17.7	0.570

Abbreviations: Hs-CRP, Hyper-sensitive C-reactive protein; NIHSS, National Institutes of Health Stroke Scale.

Variable	All patients, n = 315	Periostin quartile				*P* value
		1st, n = 78	2nd, n = 78	3rd, n = 81	4th, n = 78	
Diastolic blood pressure, mmHg	80.6 ± 10.0	80.3 ± 10.6	81.4 ± 8.7	79.8 ± 9.5	80.9 ± 11.1	0.784
Prior intravenous thrombolysis, n (%)	41 (13.0)	10 (12.8)	7 (9.0)	12 (14.8)	12 (15.4)	0.627
Stroke subtypes, n (%)						0.819
Large artery atherosclerosis	128 (40.6)	31 (42.3)	34 (43.6)	31 (38.3)	30 (38.5)	
Cardioembolism	58 (18.4)	10 (12.8)	15 (19.2)	17 (21.0)	16 (20.5)	
Small artery occlusion	104 (33.0)	27 (34.6)	26 (33.3)	27 (33.3)	24 (30.8)	
Others	25 (7.9)	8 (10.3)	3 (3.8)	6 (7.4)	8 (10.3)	
Laboratory data						
Low-density lipoprotein, mmol/L	2.4 (2.0, 3.0)	2.4 (2.0, 3.1)	2.4 (1.9, 3.0)	2.4 (2.0, 2.9)	2.3 (1.9, 2.8)	0.565
Hs-CRP, mg/L	6.5 (2.8, 10.2)	5.2 (2.5, 8.4)	5.8 (2.7, 9.6)	7.1 (3.3, 10.4)	8.7 (3.3, 12.4)	0.038
Fasting blood glucose, mmol/L	5.9 ± 2.5	5.7 ± 1.9	5.9 ± 2.9	6.2 ± 2.9	5.7 ± 2.0	0.638

Abbreviations: Hs-CRP, Hyper-sensitive C-reactive protein; NIHSS, National Institutes of Health Stroke Scale.

During the 3-month follow-up, 76 participants (24.1%) had mild PSCI and 97 (30.8%) had severe PSCI. Serum periostin levels were significantly higher in patients with severe PSCI than in those without PSCI (*P* for trend = 0.001) (Fig. 1). Patients in the PSCI group had less education (69.4% versus 57.0%; *P* = 0.024), a higher NIHSS score (median 9.0 versus 7.0; *P* = 0.001), and higher prevalence of hypertension (65.9% versus 48.6%; *P* = 0.002) as well as diabetes mellitus (31.8% versus 20.4%; *P* = 0.023) (Table 2).

Table 2
Comparison of baseline data stratified by the cognitive functional status.

Variables	With PSCI, n = 173	Without PSCI, n = 142	*P* value
Demographic characteristics			
Age, year	68.6 ± 8.3	64.7 ± 9.4	0.001
Male sex, n (%)	91 (52.6)	77 (54.2)	0.774
Education years < 12, n (%)	120 (69.4)	81 (57.0)	0.024
Body mass index, kg/m^2	24.8 ± 3.0	25.0 ± 2.8	0.423
Vascular risk factors, n (%)			
Hypertension	114 (65.9)	69 (48.6)	0.002
Diabetes mellitus	55 (31.8)	29 (20.4)	0.023
Hyperlipidemia	24 (13.9)	22 (15.5)	0.685
Coronary heart disease	20 (11.6)	17 (12.0)	0.910
Previous stroke	25 (14.5)	20 (14.1)	0.926
Current cigarette smoking	72 (41.6)	50 (35.2)	0.245
Current alcohol drinking	53 (30.6)	21 (21.8)	0.109
Clinical data			
NIHSS, score	9.0 (6.0, 11.5)	7.0 (5.0, 9.0)	0.001
Systolic blood pressure, mmHg	136.4 ± 15.5	139.2 ± 17.7	0.132
Diastolic blood pressure, mmHg	80.1 ± 9.1	81.6 ± 10.9	0.138
Prior intravenous thrombolysis, n (%)	21 (12.1)	20 (14.1)	0.619
Stroke subtypes, n (%)			0.180
Large artery atherosclerosis	64 (37.0)	64 (45.1)	
Cardioembolism	37 (21.4)	21 (14.8)	
Small artery occlusion	61 (35.3)	43 (30.3)	
Others	11 (6.4)	14 (9.9)	
Laboratory data			
Low-density lipoprotein, mmol/L	2.4 (2.0, 2.9)	2.3 (2.0, 3.1)	0.506

Abbreviations: Hs-CRP, Hyper-sensitive C-reactive protein; NIHSS, National Institutes of Health Stroke Scale; PSCI, post-stroke cognitive impairment.

Variables	With PSCI, n = 173	Without PSCI, n = 142	*P* value
Hs-CRP, mg/L	7.2 (3.3, 10.5)	5.6 (3.5, 9.8)	0.096
Fasting blood glucose, mmol/L	6.0 ± 2.5	5.7 ± 2.0	0.301
Periostin level, (ng/mL)	19.6 (16.1, 21.9)	14.8 (12.6, 17.7)	0.001
Periostin quartile, n (%)			0.001
1st	22 (12.7)	56 (39.4)	
2nd	32 (18.5)	46 (32.4)	
3rd	56 (32.4)	25 (17.6)	
4th	63 (36.4)	15 (10.6)	

Abbreviations: Hs-CRP, Hyper-sensitive C-reactive protein; NIHSS, National Institutes of Health Stroke Scale; PSCI, post-stroke cognitive impairment.

The results of univariate and multivariate logistic regression analyses of perostin level predicting PSCI at 3 months were summarized in Table 3. In univariate logistic regression analysis, the highest quartile of periostin (odds ratio [OR], 9.69; 95% confidence interval [CI] 5.06–25.61; $P = 0.001$) was confirmed to be associated with PSCI. This association remained significant after covariate adjustment for age, sex, educational status, hypertension, diabetes mellitus, and NIHSS score. Similar significant findings were observed when the serum periostin was added as a continuous variable. Restricted cubic spline regression model further confirmed the dose-response relationships between periostin levels and PSCI at 3 months ($P < 0.001$ for linearity; Fig. 2).

Table 3
Multivariate regression analysis for the associations between serum periostin and PSCI.

Variables	Crude model		Model 1		Model 2	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Periostin levels (per 1.0 ng/mL increase)	1.26 (1.18–1.35)	0.001	1.27 (1.19–1.36)	0.001	1.24 (1.18–1.39)	0.001
Periostin quartile						
1st	Reference		Reference		Reference	
2nd	1.77 (0.91–3.46)	0.104	1.64 (0.82–3.25)	0.162	1.70 (0.83–3.49)	0.148
3rd	4.71 (2.88–11.28)	0.003	5.94 (2.94–11.90)	0.001	5.93 (2.83–12.38)	0.001
4th	9.69 (5.06–25.61)	0.001	10.80 (5.01–23.28)	0.001	11.26 (4.94–25.63)	0.001
Abbreviations: CI, confidence interval; OR, odds ratios; PSCI, post-stroke cognitive impairment.						
Model 1 adjusted for age and gender.						
Model 2 adjusted for age, gender, educational years, hypertension, diabetes mellitus, and NIHSS score.						

In subgroup analyses stratified by age, gender, hypertension, diabetes mellitus, educational status, and stroke severity, the positive relationships between serum periostin concentrations and the risk of 3-month PSCI were found in all subgroups and reached statistically significance. Furthermore, no significant interaction between periostin levels and these interesting factors on the PSCI was observed (all *P* for interaction > 0.05; Fig. 3).

Discussion

Our prospective study recruited a group of acute ischemic patients and investigated relationship between serum periostin concentrations and cognitive function status. We found that higher serum periostin levels were associated with an increased risk of PSCI at 3 months. Furthermore, this association was independent for demographic characteristics, vascular risk factors and stroke severity. Hence, periostin in serum might represent a novel prognostic biomarker of PSCI.

Reported frequency of PSCI is ranges widely from 10–82% [2, 3]. The discrepancy of PSCI incidence may be mainly attributed to differences in race, age, educational status, diagnostic criteria, and study methods. Most studies have assessed cognitive function at 3 months after a stroke using cross-sectional

design [21–25], whereas some studies have adopted longitudinal designs [3, 26]. Several diagnostic tools have been applied to investigate the presence of PSCI, such as National Institute of Neurological Disorders and Stroke and Canadian Stroke Network (NINDS-CSN), Mini-Mental State Examination (MMSE), and MoCA. In studies performed among populations of white dominance, the prevalence of 3-month cognitive impairment after ischemic stroke ranges from 24–39% according to the MMSE, while the prevalence in the same population is up to 96% using a battery of neuropsychological tests [24, 26]. However, in studies using a total MoCA score < 26 as the definition of PSCI, the prevalence of PSCI approximates to 50% [22, 23]. In the present study, we adopted a total MoCA score < 25 as the definition of PSCI because this cutoff had a good sensitivity (77%) and specificity (83%) for mild cognitive impairment [19]. We observed that PSCI occurred in 54.9% of patients, which is similar to the findings of other observational studies that have used the same diagnostic criteria [20, 24].

Periostin is a secreted extracellular matrix protein that plays an important role in tissue repair, oncology, cardiovascular and central nervous systems, and in various inflammatory settings and diseases [7]. Previous studies found that increased periostin levels were associated with clinical severity and poor prognosis in patients with ischemic stroke [10], intracerebral hemorrhage [11], and aneurysmal subarachnoid hemorrhage [12]. Our study extended the current knowledge about the role of periostin in cerebrovascular diseases as it confirmed a positive relationship between circulating periostin concentrations and cognitive impairment after stroke. Both of clinical studies showed that periostin may play a crucial role in pathologic process after brain tissue injury.

According to the results from animal experiment, periostin 2 (splicing variant of periostin) was overexpressed at 24 hours after transient middle cerebral artery occlusion model. Exogenously injection of periostin 2 could reduce infarct volume [13]. Periostin has also been reported to promote neural stem cell proliferation and differentiation after hypoxic-ischemic injury. Intracerebroventricular administration of periostin was shown to significantly improve spatial learning and memory, indicating that periostin may alleviate cognitive deficits [27]. Periostin continued to be expressed up to 4 weeks after cerebral ischemia in various cells, such as astrocytes, microglia, and neuronal progenitor cells [14]. Therefore, the increase in circulating periostin levels might occur to repair the brain tissue and improve cognitive function after ischemic stroke. On the contrary, other studies demonstrated a detrimental effect of periostin [28, 29]. Anti-periostin antibody improved post-subarachnoid hemorrhage neurobehavior, brain edema, and blood-brain barrier disruption. Recombinant-periostin significantly aggravated early brain injury [28]. Furthermore, the inhibition of periostin expression may improve cardiac systolic ejection function and animal survival rate [29]. Thus, researchers have not reached a consensus on the net effect of periostin. However, this mechanism warrants to be verified in future studies. Further studies are needed to detect the precise mechanisms underlying the association between elevated circulating periostin concentrations and cognitive impairment after ischemic stroke.

There were several limitations that should be addressed in this study. First, all 315 ischemic stroke patients in our study were prospective recruited from a tertiary referral hospital, so it is difficult to generalize from the results of this study. Second, patients with a history of cognitive impairment or a

severe condition after stroke, whowere unable to complete psychological assessment, were excluded from the study. This selection bias would probably reduce the power of study. Third, serum periostin levels were only measured at one time point after admission, which may lead to some misclassification of exposure. Furthermore, multiple factors may influence the accuracy of a single neuropsychological test in the diagnosis of PSCI, including educational status, physiological condition, and sensitivity or specificity of the test itself. The combined application of other evaluation tests in addition to MoCA, such as NINDS-CSN and MMSE, could improve the accuracy of the diagnosis. Therefore, the interpretation of our results should be cautious, and further multi-center studies with larger sample sizes are needed to validate our findings.

In summary, our study provided preliminary data showing that increased serum perostin concentrations at baseline were independently associated with increased risk of PSCI among ischemic stroke patients. Further preclinical studies are warranted to investigate the underlying pathogenesis as well as targeted interventions in PSCI prevention and treatment.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee at The Sixth People's Hospital of Chengdu, and all participating patients had provided informed consent before entering the study. The study was carried out according to the tenets of the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author.

Competing interests

All the authors declare that there is no conflict of interest.

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None.

Authors' contributions

GZL, ML conceived and coordinated the study, designed, performed and analyzed the experiments, wrote the paper. JL, CZ, JY, BW, XJL carried out the data collection, data analysis, and revised the paper. ML

designed the study, carried out the data analysis, and revised the paper. All authors reviewed the results and approved the final version of the manuscript.

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Figures

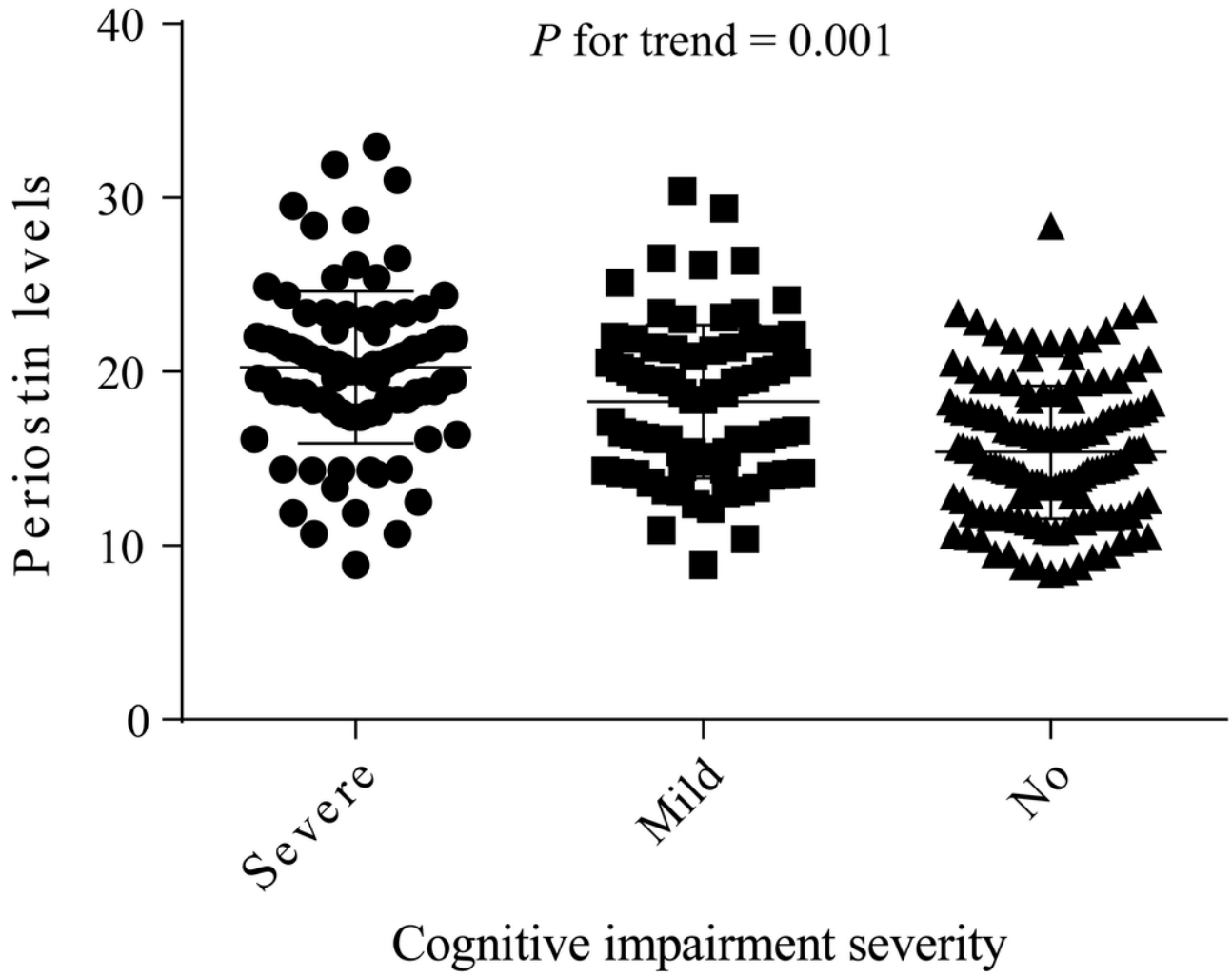

Figure 1

Comparison of serum periostin levels and cognitive impairment severity at 3 months.

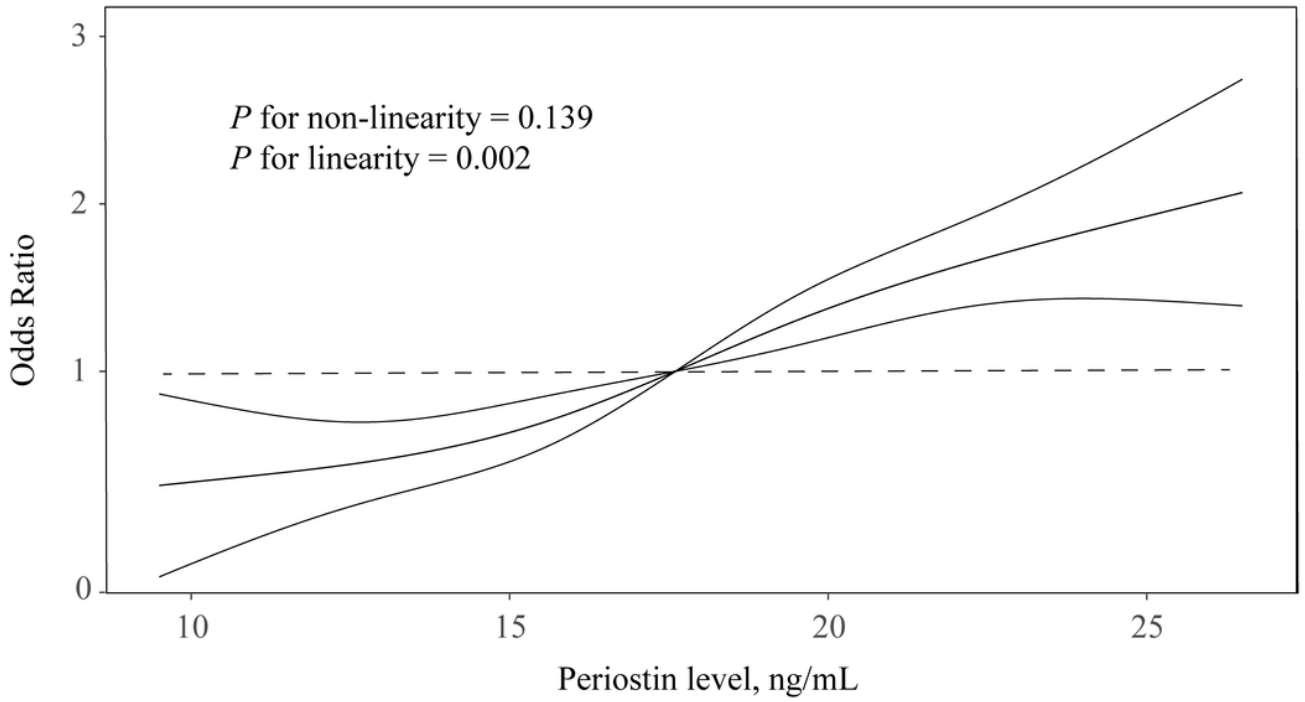

Figure 2

Restricted cubic spline regression assessed the association between serum periostin and risk of post-stroke cognitive impairment. Odds ratios and 95% confidence intervals derived from restricted cubic spline regression, with knots placed at the 5th, 35th, 65th, and 95th percentiles of the periostin levels. The reference point for serum periostin is the midpoint (17.6 ng/mL) of the reference group from categorical analysis. Odds ratios were adjusted for the same variables as model 2 in Table 3.

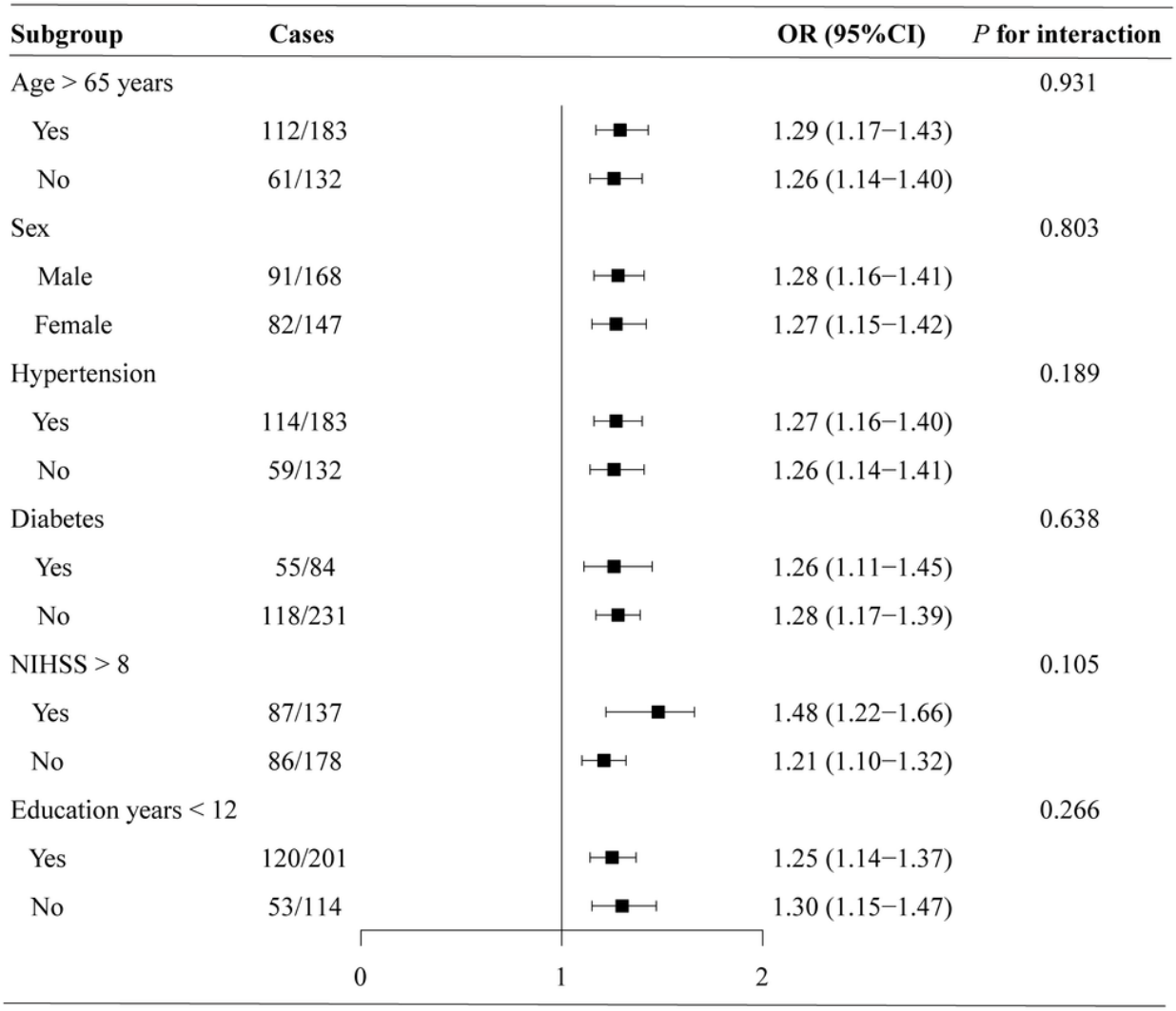

Figure 3

Subgroup analyses of the association between serum periostin and post-stroke cognitive impairment. OR was calculated for per 1.0 ng/mL increase in serum periostin after adjustment for the same variables as model 2 in Table 3, except for the stratified variable. CI indicates confidence interval, NIHSS, National Institutes of Health Stroke Scale, and OR, odds ratios.