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BRIEF COMMUNICATION

Serum Growth Differentiation Factor 15 Levels Are Associated With Depression After Ischemic Stroke

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BACKGROUND: The effect of serum growth differentiation factor 15 (GDF-15) on poststroke depression (PSD) remains unknown. This study aimed to investigate the association between serum GDF-15 and PSD among patients with ischemic stroke.

METHODS AND RESULTS: This study was based on a random sample from CATIS (China Antihypertensive Trial in Acute Ischemic Stroke). A total of 572 patients from 7 participating hospitals with GDF-15 levels were included in this analysis. The study outcome was depression (Hamilton Depression Rating Scale score ≥8) at 3 months after ischemic stroke. A total of 231 (40.4%) patients with stroke experienced PSD within 3 months. The multivariate-adjusted odds ratio of PSD associated with the highest tertile of serum GDF-15 was 2.92 (95% CI, 1.36–6.27) compared with the lowest tertile. Each SD increase in log-transformed GDF-15 was associated with a 42% (95% CI, 2%–97%) increased risk of PSD, and a linear association between serum GDF-15 and the risk of PSD was observed (*P* for linearity=0.006).

CONCLUSIONS: Elevated serum GDF-15 levels in the acute phase of ischemic stroke were independently associated with PSD, suggesting that GDF-15 may be a valuable prognostic biomarker for PSD.

Key Words: acute ischemic stroke ■ growth differentiation factor 15 ■ Hamilton rating scale for depression ■ poststroke depression

Stroke is the main cause of mortality and long-term disability and has become an important public health concern worldwide. Among all complications of stroke survivors, poststroke depression (PSD) is the most frequent psychiatric problem. In 2005, a systematic review conducted by Hackett et al[1] estimated that the incidence rate of PSD was up to 33% (95% CI, 29%–36%). The consequences of PSD can extend beyond just mental health; it can also adversely affect rehabilitation and quality of life and increase the risk of death after stroke. The predictive capacities of the traditional risk factors for PSD have been well established, but these established risk factors could not fully explain the development of PSD. Therefore, the identification of novel risk factors to predict PSD early is urgently required to provide clinical evidence for better prevention and intervention of PSD and thus contribute to better stroke outcomes.

Growth differentiation factor 15 (GDF-15), also known as macrophage inhibitory cytokine-1, is a distant member of the transforming growth factor β cytokine superfamily.[2] The expression levels of GDF-15 could significantly increase in response to inflammation and oxidative stress. GDF-15 is independently associated with coronary atherosclerosis presence, which affects the incidence of ischemic stroke. In patients with

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ischemic stroke, circulating levels of GDF-15 appear to be elevated and closely related to poor prognosis, including neurological outcomes.[3] However, studies on the relationship between GDF-15 levels and depressive symptoms are disputed, and the effect of serum GDF-15 levels on the risk of PSD remains unclear. Herein, we aimed to investigate the association between serum GDF-15 levels and PSD among patients from CATIS (China Antihypertensive Trial in Acute Ischemic Stroke).

METHODS

Requests for data access may be sent to the corresponding author. Detailed methods are described in Data S1.

Study Design, Participants, and Data Collection

This study was conducted among patients with ischemic stroke from CATIS. Details of the trial design, methods, and data collection are presented in Data S1. The present observational study was based on a preplanned ancillary study, which aimed to investigate whether early antihypertensive treatment would reduce poststroke cognitive impairment and PSD in patients with acute ischemic stroke at 3 months after randomization among a random sample of CATIS. In this ancillary study, 660 CATIS participants were systemically selected before randomization from 7 participating hospitals for cognitive function and psychological state evaluation at their 3-month follow-up visit. In the present study, we further excluded 88 participants without GDF-15 data or available follow-up. Finally, 572 participants were included in this analysis (Figure S1).

This study was approved by the ethical committees at Soochow University and the institutional review boards at Tulane University. Written consent was obtained from all study participants or their immediate family members. CATIS is registered at clinicaltrials.gov (identifier: NCT01840072).

Outcome Assessment

The study outcome was depression at 3 months after stroke onset, which was assessed by trained neurologists using the validated version of the Hamilton Rating Scale for Depression (HRSD-24). The HRSD-24 has been translated into Chinese and confirmed as a screening tool for depression in the Chinese population.[4] It is widely accepted that a total HRSD score of 8 is the cutoff point for diagnosing depressive symptoms. In addition, the severity of depression was categorized as follows: a score of ≤7 indicated the absence of depression, a score between 8 and 19 indicated mild depression, and a score of >20 indicated severe depression.

Statistical Analysis

All participants were categorized into 3 groups according to tertiles of serum GDF-15 levels. Baseline characteristics among different tertiles of serum GDF-15 were compared by ANOVA or the Kruskal-Wallis test for continuous variables and χ^2 test for categorical variables. Multivariate logistic regression models were used to assess the association between baseline serum GDF-15 levels and PSD. ORs and 95% CIs for the upper tertiles of GDF-15 compared with the lowest tertile, 1-SD increment of log-transformed, and raw GDF-15 level were calculated. The covariates included in the multivariable model were age, sex, education, time from onset to randomization, clinical center, current smoking, alcohol consumption, systolic blood pressure (BP), blood glucose, galectin-3, body mass index, baseline National Institutes of Health Stroke Scale (NIHSS) scores, medical history (hypertension, hyperlipidemia, and coronary heart disease), family history of stroke, ischemic stroke subtype, and immediate BP reduction. The effect of serum GDF-15 levels on PSD severity was analyzed using an ordinal logistic regression model adjusted for the aforementioned variables. We further conducted subgroup analyses to assess the robustness of the association between serum GDF-15 levels and PSD according to other risk factors (Figure S2). We categorized participants into low and high GDF-15 groups, and the cutoff point (885.68 ng/L) for serum GDF-15 level was obtained from the receiver operating characteristic curve using Youden index.[5] Interactions between serum GDF-15 levels and subgroup variables on PSD were tested in the models with interaction terms by the likelihood ratio test, adjusting for the aforementioned covariates unless the variable was used as a subgroup variable. To test the effect of BP variability on PSD, we conducted sensitivity analyses by further including the ratio of systolic BP at 12 hours, 24 hours, 3 days, 7 days, and 3 months after stroke to baseline systolic BP in multivariable-adjusted models.

Afterward, we evaluated the pattern of the association between serum GDF-15 and PSD using a logistic regression model with restricted cubic splines. The median of the lowest tertile of serum GDF-15 (616.03 ng/L) was used as the reference point and 4 knots were placed at the 5th, 35th, 65th, and 95th percentiles of serum GDF-15.[6] The number of knots used in the cubic spline model was chosen based on maximizing goodness of fit. Furthermore, to assess improvement in the risk prediction of poststroke cognitive impairment, C statistics, net reclassification index (NRI), and integrated discrimination improvement (IDI) were utilized to assess the incremental predictive value of serum GDF-15 levels in the risk of PSD beyond conventional risk factors. We calculated the relative IDI with

reference to Pencina et al.[7] All *P* values were 2-tailed, and a significance level of 0.05 was used. Statistical analysis was conducted using SAS statistical software (version 9.4, SAS Institute Inc).

RESULTS

Baseline Characteristics

Detailed results are described in Data S1. Most baseline characteristics were balanced between the participants who did and did not undergo assay (Table S1). Baseline characteristics of patients according to quartiles of GDF-15 are shown in Table S2.

Association Between Serum GDF-15 and PSD

At the 3-month follow-up, a total of 231 patients (40.4%) had PSD. The serum GDF-15 level in patients with PSD was higher than that in patients without PSD (median [interquartile range], 1035.58 ng/L [753.89–1481.27 ng/L] versus 896.06 ng/L [679.86–1310.61 ng/L]; *P*=0.003). Patients in the third tertile of serum GDF-15 had the highest incidence of PSD (48.2%; *P*=0.002). After adjustment for confounders, the OR of PSD associated with the highest tertile of serum GDF-15 was 2.92 (95% CI, 1.36–6.27; P_{trend}=0.006; Table) compared with the lowest tertile. In continuous analysis, a per-SD increase in raw GDF-15 and log-transformed GDF-15 was associated with 43% (95% CI, 3%–98%) and 42% (95% CI, 2%–97%) increased risk of PSD, respectively. Moreover, multivariate ordinal logistic regression analysis showed a significant association between serum GDF-15 and PSD severity (OR, 2.09; 95% CI, 1.07–4.10 [P_{trend}=0.030]) (Table and Figure 1). In addition, multivariable-adjusted spline regression models showed a linear dose-response association between serum GDF-15 and PSD (*P* for nonlinearity=0.140 and *P* for linearity=0.006, respectively) (Figure 2). In addition, we also found that baseline NIHSS score and clinical center were significantly associated with risk of PSD in the multivariable analysis (Table S3). For more detailed results, please see Data S1 and Table S4.

Subgroup and Sensitivity Analyses

High serum GDF-15 levels were associated with PSD (OR, 1.91; 95% CI, 1.04–3.51 [*P*=0.038]) (Figure S2) after adjustment for potential confounders. In subgroup analyses stratified by age, sex, education, time from onset to hospitalization, systolic BP, history of hypertension, baseline NIHSS score, body mass index, and receiving immediate BP reduction, ORs of PSD were significant in older participants, patients with higher education, baseline NIHSS score, body mass index, history of hypertension, and receiving immediate BP reduction. No significant interaction between serum GDF-15 levels and these interesting factors on PSD was observed (all *P* for interaction >0.05). Sensitivity analyses showed that after considering BP variability at different time points, the significance of the association between GDF-15 and PSD still exists (Table S5).

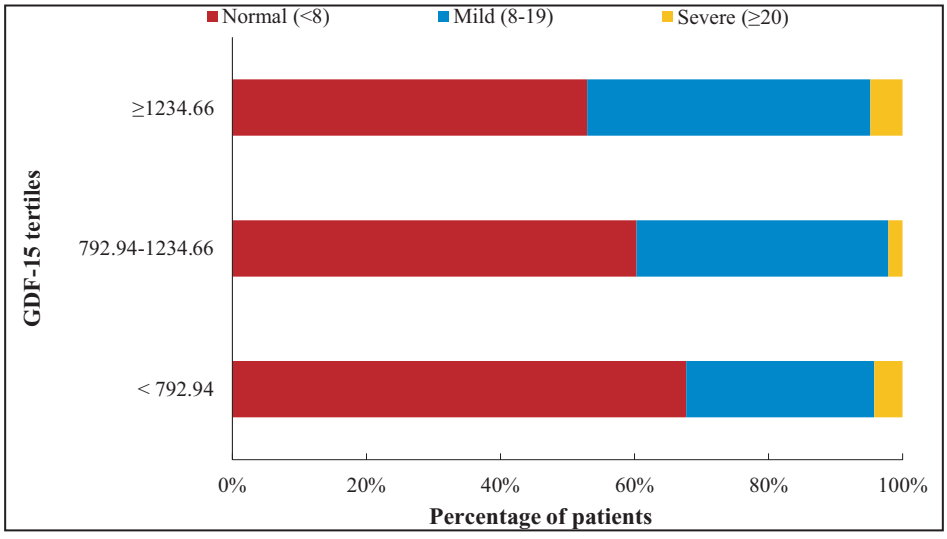

Figure 1. Serum growth differentiation factor 15 (GDF-15) and poststroke depression severity.
Adjusted odds ratio of ordinal logistic regression analysis for highest vs lowest tertile of serum GDF-15: 2.09 (95% CI, 1.07–4.10; *P* value for trend=0.030) for Hamilton Rating Scale for Depression score.

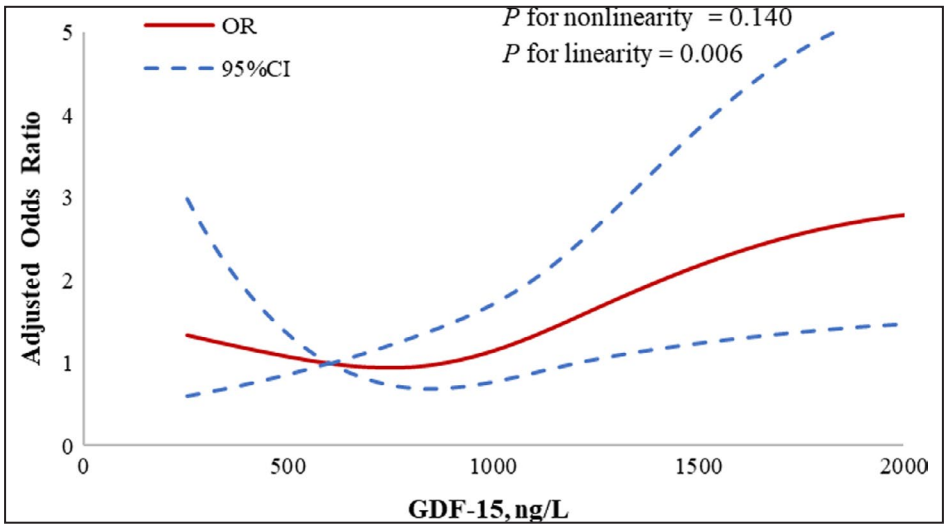

Figure 2. Association of serum growth differentiation factor 15 (GDF-15) with the risk of poststroke depression.
Odds ratios (ORs) and 95% CIs derived from restricted cubic spline regression, with knots placed at the 5th, 35th, 65th, and 95th percentiles of the distribution of serum GDF-15. The reference point for serum GDF-15 is 616.03 ng/L. ORs were adjusted for the same variables as model 2 in Table.

DISCUSSION

To the best of our knowledge, this is the first multicenter study to examine the association between baseline serum GDF-15 concentration and PSD. In this study, we demonstrated a significant association between serum GDF-15 level and increased risk of subsequent depression at 3 months after acute ischemic stroke, even after adjustment for established risk factors. A multiple-adjusted spline regression model suggested a dose-response relationship between serum GDF-15 and PSD, and subgroup analyses and sensitivity analyses further confirmed these associations. Furthermore, adding serum GDF-15 levels to conventional risk factors significantly improved the predictive power for PSD. These findings suggest that serum GDF-15 might be a valuable biomarker in the prediction of PSD, but it still needs to be further replicated by other studies from various populations.

Previous studies have documented that elevated levels of GDF-15 are significantly implicated in cardiovascular dysfunction and diseases, especially ischemic

Table ORs and 95% CIs for the Risk of PSD According to GDF-15 Tertiles

	GDF-15, ng/L			*P* value for trend	Each SD (0.23 ng/L) increase in log-GDF-15	Each SD (792.79 ng/L) increase in GDF-15
	<792.94	792.94–1234.66	≥1234.66			
PSD*						
Events, n (%)	62 (32.6)	77 (40.3)	92 (48.17)			
Unadjusted	1.00	1.39 (0.92–2.12)	1.92 (1.27–2.91)	0.002	1.29 (1.09–1.54)	1.28 (1.06–1.53)
Model 1	1.00	1.35 (0.88–2.07)	1.75 (1.11–2.77)	0.017	1.24 (1.03–1.50)	1.22 (1.01–1.48)
Model 2	1.00	1.63 (0.81–3.28)	2.92 (1.36–6.27)	0.006	1.42 (1.02–1.97)	1.43 (1.03–1.98)
PSD severity†						
Unadjusted	1.00	1.32 (0.87–2.00)	1.82 (1.20–2.75)	0.004	1.29 (1.09–1.54)	1.32 (1.12–1.56)
Model 1	1.00	1.27 (0.83–1.95)	1.68 (1.07–2.66)	0.025	1.25 (1.04–1.51)	1.28 (1.08–1.53)
Model 2	1.00	1.21 (0.65–2.26)	2.09 (1.07–4.10)	0.030	1.26 (1.02–1.55)	1.28 (1.01–1.81)

Odds ratios (ORs) are derived from ordinal regression. GDF-15 indicates growth differentiation factor 15.
Model 1 was adjusted for age, sex, and education level.
Model 2 was adjusted for model 1 and further adjusted for time from onset to randomization, clinical center, current smoking, alcohol consumption, systolic blood pressure (BP), blood glucose, galectin-3, body mass index, baseline National Institutes of Health Stroke Scale scores, medical history (hypertension, hyperlipidemia, and coronary heart disease), family history of stroke, ischemic stroke subtype, and immediate BP reduction.
*Poststroke depression (PSD): Hamilton Rating Scale for Depression (HRSD) score ≥8.
†Severity of depression categorized as normal (HRSD score: 0–7), mild depression (HRSD score: 8–19), and severe depression (HRSD score ≥20).

stroke.[3,8] However, little is known about the relationship between baseline serum GDF-15 levels and PSD. Herein, we conducted this first multicenter study to examine the association between baseline serum GDF-15 levels and 3-month PSD. We found that the highest serum GDF-15 tertile was associated with an ≈2.9-fold increased odds of subsequent PSD, indicating that serum GDF-15 might be a valuable marker in predicting PSD onset. Scuteri et al[9] found that depression was associated with greater BP variability, which can increase the risk of arterial damage and accelerated arterial aging, and was an established risk factor for depression. Of note, in our sensitivity analysis, the association between GDF-15 and PSD was still significant after adjusting for BP variability. Given the high incidence and adverse consequences of PSD, our research has important public health and clinical significance for the early identification and intervention of PSD. According to our results, patients with ischemic stroke who have high serum GDF-15 levels should receive active monitoring and therapeutic intervention to prevent the occurrence of PSD.

The precise mechanisms underlying the observed association between serum GDF-15 and PSD are unclear, but several potential pathophysiological processes may explain the relationship. As a pleiotropic cytokine that affects a variety of immune and inflammatory cells,[2] GDF-15 is overexpressed in macrophages and other cell types under the induction of oxidative stress and inflammation. Elevated levels of inflammatory markers are related to psychological depression.[10] In addition, GDF-15 may also cause endothelial dysfunction by generating oxidative stress in the blood vessel wall.[11] Endothelial dysfunction plays an important role in the pathogenesis of depression, suggesting that GDF-15 may be involved in the pathways affecting PSD.[12] GDF-15 has also been reported to be associated with chronic vascular brain injuries[13] and central systolic BP,[14] both of which are associated with depression.[9] Further functional studies and epidemiology studies are needed to clarify the detailed mechanisms of the association between GDF-15 and PSD. For example, it is of clinical interest to investigate the specific effects of targeting GDF-15 on the risk of PSD.

This study has several important strengths. First, this is the first multicenter study to examine the association between baseline serum GDF-15 concentration and PSD. Second, this study was based on standardized protocols and rigid quality control procedures in data collection and outcome assessment. Third, comprehensive information about relevant covariates was controlled in the multivariable models, so the present study was appropriate and provided a more valid appraisal of the association between serum GDF-15 and PSD. However, some limitations should also be discussed. First, this study is not a specially designed study for the association between GDF-15 and PSD, but an observational study based on CATIS. We included only patients with systolic BP 140 to 220 mm Hg, thus a selection bias might exist. Second, serum GDF-15 concentrations were tested only once at baseline. Therefore, we were unable to explore the association between GDF-15 changes and PSD, although serum GDF-15 levels were reported to remain stable within several days after ischemic stroke onset.[15] Third, hypertension and depression often occurred at the same time in the elderly. Data on prestroke depression were not collected in this study, which may have a potential confounding effect on our findings. However, depression is highly correlated with age, sex, stroke severity, and other baseline characteristics. We adjusted for these covariates in the analysis, therefore the potential bias caused by prestroke depression on the results might be minimal. Finally, the current study did not collect data on the use of antidepressants, and the selection of antidepressants is associated with accelerated arterial aging, which may bias our research results.

CONCLUSIONS

Elevated serum GDF-15 levels in the acute phase of ischemic stroke were associated with an increased risk of 3-month PSD, independent of established conventional risk factors. Further prospective studies conducted among different populations are needed to confirm our findings and clarify the potential biological mechanisms underlying the association between GDF-15 and PSD.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Data S1
Tables S1–S5
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Trial Design and Participants

CATIS was a multicenter, single-blind, blinded end-points randomized clinical trial conducted in 26 hospitals across China. A total of 4071 patients aged over 22 years who had first-ever ischemic stroke confirmed by computed tomography or magnetic resonance imaging within 48 hours of symptom onset and had an elevated systolic blood pressure (BP) between 140 mmHg and 220 mmHg were recruited. Participants with a BP ≥220/120 mm Hg, severe heart failure, acute myocardial infarction or unstable angina, atrial fibrillation, aortic dissection, cerebrovascular stenosis (≥70%), resistant hypertension, deep coma, or treatment with intravenous thrombolytic therapy were excluded. Patients treated with intravenous thrombolytic therapy (ie, intravenous recombinant tissue plasminogen activator [rtPA]) at baseline were excluded because of different requirements for blood pressure reduction.

The present observational study was based on a preplanned ancillary study, which aimed to investigate whether early antihypertensive treatment would reduce poststroke cognitive impairment and PSD in patients with acute ischemic stroke at 3 months after randomization among a random sample of the CATIS. In this ancillary study, 660 CATIS participants were systemically selected before randomization from 7 participating hospitals for cognitive function and psychological state evaluation at their

3-month follow-up visit. Specifically, each of the 7 participating hospitals recruited 80-100 patients consecutively. The exclusion criteria for the ancillary study were visual, hearing, or psychiatric impairment substantial enough to hinder performance on evaluation. The recruitment was completed by November 2012. In the present study, we further excluded 88 participants without GDF-15 data or available follow-up. Finally, 572 participants were included in this analysis (Figure S1).

Data collection

Baseline data on demographic characteristics, lifestyle risk factors, medical history, and clinical features were collected at the time of enrollment. Admission ischemic stroke severity was evaluated with the National Institutes of Health Stroke Scale (NIHSS) by trained neurologists. Ischemic stroke subtype was classified as large artery atherosclerosis (thrombotic), cardiac embolism (embolic), and small artery occlusion lacunae (lacunar) according to patients' clinical symptoms and imaging data. Baseline BP was calculated from three BP measurements conducted at admission by trained nurses when the patients were in the supine position using standard mercury sphygmomanometers according to a common protocol adapted from the procedures recommended by the American Heart Association. Serum galectin-3 concentrations were tested using a commercially available ELISA kit (R&D Systems). Routine laboratory measurements (e.g., blood glucose) were obtained at the participating hospitals at admission.

Serum GDF-15 measurement

Blood samples were collected after at least 8 hours of fasting within 24 hours of hospital admission. All blood samples were separated in the clinical laboratories of participating hospitals and stored at -80 ℃ until laboratory testing. A quantitative sandwich ELISA was performed using the Quantikine Human GDF-15 Immunoassay kit (R&D Systems) to measure serum GDF-15 concentrations at Soochow University. A standard curve was constructed, from which GDF-15 concentrations of unknown samples were determined. The intra- and interassay coefficients of variation were <1.8% and <6.0%, respectively. Laboratory technicians who performed serum GDF-15 measurements were blinded to the baseline characteristics and clinical outcomes of the study participants.

This study was approved by the Ethical Committees at Soochow University and the Institutional Review Boards at Tulane University. Written consent was obtained from all study participants or their immediate family members. The CATIS is registered at clinicaltrials.gov (Identifier: NCT01840072).

Supplemental Results

Baseline characteristics

Most baseline characteristics were well balanced between patients who were assayed for serum GDF-15 and all CATIS patients (**Table S1**), indicating that those assayed basically represent all CATIS participants. The 572 participants in this analysis had a mean age of 60 years, and 399 (69.8%) were men. The median serum GDF-15

concentration was 940.47 ng/L (interquartile range, 702.66-1386.70 ng/L). The participants with higher serum GDF-15 tended to be older; had higher serum galectin-3; and had lower body mass index and prevalence of thrombotic stroke than those with lower serum GDF-15 (**Table S2**).

Association between serum GDF-15 and PSD

At the 3-month follow-up, a total of 231 patients (40.4%) had PSD. The serum GDF-15 level in patients with PSD was higher than that in patients without PSD [1035.58 (753.89-1481.27) vs. 896.06 (679.86-1310.61) ng/L; *P*=0.003]. Patients in the third tertile of serum GDF-15 had the highest incidence of PSD (48.2%; *P*=0.002). After adjustment for confounders, the OR of PSD associated with the highest tertile of serum GDF-15 was 2.92 (95% CI: 1.36-6.27; P_{trend}=0.006; Table 1) compared with the lowest tertile. In continuous analysis, a per-SD increase in raw GDF-15 and log-transformed GDF-15 was associated with 43% (95% CI: 3%-98%) and 42% (95% CI: 2%-97%) increased risk of PSD, respectively. Moreover, multivariate ordinal logistic regression analysis showed a significant association between serum GDF-15 and PSD severity (OR: 2.09; 95% CI 1.07-4.10; P_{trend}=0.030; Table 1; Figure 1). In addition, multivariable-adjusted spline regression models showed a linear dose-response association between serum GDF-15 and PSD (*P* for nonlinearity=0.140; *P* for linearity=0.006; Figure 2). In addition, we also found that baseline NIHSS score and clinical center were significantly associated with the risk of PSD in the multivariable analysis (Table S3).

Subgroup and sensitivity analyses

High serum GDF-15 levels were associated with PSD (OR: 1.91; 95% CI: 1.04-3.51; *P*=0.038; Figure S2) after adjustment for potential confounders. In subgroup analyses stratified by age, sex, education, time from onset to hospitalization, systolic BP, history of hypertension, baseline NIHSS score, body mass index, and receiving immediate blood pressure reduction, ORs of PSD were significant in older participants, those with higher education, baseline NIHSS score, BMI, history of hypertension, and receiving immediate blood pressure reduction. No significant interaction between serum GDF-15 levels and these interesting factors on PSD was observed (all *P* for interaction >0.05). Sensitivity analyses showed that after considering blood pressure variability at different time points, the significance of the association between GDF-15 and PSD still exists (Table S4).

Incremental prognostic value of serum GDF-15 in patients with ischemic stroke

We further examined whether adding serum GDF-15 to conventional risk factors improved the risk prediction of PSD. As shown in Table S5, the likelihood ratio test showed that model fit was significantly improved after adding GDF-15 to the model (*P* <0.001). In addition, NRI was 28.21% (95% CI: 10.35%-46.07%; *P*=0.002), and IDI was 1.86% (95% CI: 0.63%-3.08%; *P*=0.003). The C statistic was 0.740 in the conventional model and 0.754 in the conventional model+GDF-15 (*P*=0.109). Adding GDF-15 to a model containing conventional risk factors did not significantly improve the C statistics but did significantly improve risk reclassification and discriminatory power for 3-month PSD among patients.

Table S1. Baseline characteristics between patients who were enrolled and those were excluded.

Characteristics *	Enrolled	Excluded	*P* value
Number of participant	572	3489	
Demographics			
Age, years	59.98 ± 10.31	62.28 ± 10.94	<0.001
Male	399 (69.8)	2205 (63.0)	0.002
Education, years	6.0 (5.0-9.0)	6.0 (4.0-9.0)	<0.001
Current cigarette smoking	214 (37.4)	1271 (36.3)	0.616
Current alcohol drinking	196 (34.3)	1057 (30.2)	0.057
Clinical features			
Time from onset to randomization, h	11.5 (5.0-24.0)	10.0 (4.5-24.0)	0.607
Systolic BP, mm Hg	167.21 ± 16.60	165.96 ± 16.95	0.102
Diastolic BP, mm Hg	98.11 ± 9.97	96.44 ± 11.26	<0.001
Blood glucose, mmol/L	5.7 (5.0-7.1)	5.8 (5.1-7.3)	0.376
Body mass index, kg/m^2	24.7 (22.9-26.4)	24.8 (22.9-26.8)	0.441
Galectin-3, ng/ml	8.18 (5.81-11.35)	8.76 (6.05-12.19)	0.025
Baseline NIHSS score	4.0 (3.0-7.0)	4.0 (2.0-8.0)	0.260
Medical history			
History of hypertension	438 (76.6)	2771 (79.2)	0.155
History of hyperlipidemia	41 (7.2)	236 (6.7)	0.710
History of diabetes mellitus	95 (16.6)	624 (17.8)	0.476
History of coronary heart disease	61 (10.7)	383 (11.0)	0.841
Family history of stroke	95 (16.6)	658 (18.8)	0.210

Receiving immediate BP reduction	282 (49.3)	1756 (50.2)	0.695

BP, blood pressure; NIHSS, National Institute of Health Stroke Scale.

*Continuous variables are expressed as mean ± standard deviation, or as median (interquartile range). Categorical variables are expressed as frequency (percent).

Table S2. Baseline characteristics of study participants according to serum GDF-15 tertiles.

Characteristics*	Total	GDF-15, ng/L			*P* value for trend
		< 792.94	792.94-1234.66	≥1234.66	
Number of participants	572	190	191	191	
Demographics					
Age, years	59.98 ± 10.31	55.14 ± 9.49	59.24 ± 9.19	65.53 ± 9.52	<0.001
Male	399 (69.8)	129 (67.9)	134 (70.2)	136 (71.2)	0.772
Education, years	6.0 (5.0-9.0)	8.0 (5.0-10.0)	6.0 (5.0-9.0)	6.0 (4.0-9.0)	0.084
Current cigarette smoking	214 (37.4)	76 (40.0)	75 (39.3)	63 (33.0)	0.298
Current alcohol drinking	196 (34.3)	70 (36.8)	73 (38.2)	53 (27.8)	0.064
Clinical features					
Time from onset to randomization, h	11.5 (5.0-24.0)	12.0 (5.0-24.0)	12.0 (6.0-24.0)	10.0 (4.0-24.0)	0.351
Systolic BP, mm Hg	167.21 ± 16.60	167.58 ± 16.96	166.05 ± 15.83	167.99 ± 17.02	0.487
Diastolic BP, mm Hg	98.11 ± 9.97	99.03 ±10.22	98.18 ± 9.30	97.12 ± 10.32	0.175

Blood glucose, mmol/L	5.7 (5.0-7.1)	5.6 (5.1-6.9)	5.7 (5.1-7.2)	5.8 (5.0-7.2)	0.944
Body mass index, kg/m^2	24.7 (22.9-26.4)	25.4 (23.7-27.4)	24.5 (22.9-26.1)	24.2 (22.1-26.0)	<0.001
Galectin-3, ng/ml	8.18 (5.81-11.35)	7.37 (5.29-9.64)	8.63(5.85-11.52)	8.69 (6.50-11.98)	0.001
Baseline NIHSS score	4.0 (3.0-7.0)	4.0 (2.0-7.0)	4.0 (3.0-7.0)	5.0 (3.0-8.0)	0.260
Medical history					
History of hypertension	438 (76.6)	148 (77.9)	141 (73.8)	149 (78.0)	0.546
History of hyperlipidemia	41 (7.2)	18 (9.5)	14 (7.3)	9 (4.7)	0.196
History of diabetes mellitus	95 (16.6)	22 (11.6)	36 (18.9)	37 (19.4)	0.074
History of coronary heart disease	61 (10.7)	15 (7.9)	18 (9.4)	28 (14.7)	0.081
Family history of stroke	95 (16.6)	29 (15.3)	35 (18.3)	31 (16.2)	0.714
Ischemic stroke subtype					
Thrombotic	364 (63.6)	130 (68.4)	127 (66.5)	107 (56.0)	0.026
Embolic	23 (4.0)	3 (1.6)	10 (5.2)	10 (5.2)	0.111
Lacunar	194 (33.9)	59 (31.1)	58 (30.4)	77 (40.3)	0.072

Receiving immediate BP reduction	282 (49.3)	97 (51.1)	91 (47.6)	94 (49.2)	0.801

BP, blood pressure; NIHSS, National Institute of Health Stroke Scale; GDF-15, Growth Differentiation Factor 15.

*Continuous variables are expressed as the mean ± standard deviation or as the median (interquartile range). Categorical variables are expressed as frequencies (percentages).

Table S3. The OR and 95% CI of covariates.

Variables	Univariate		Multivariate Adjusted	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, years	1.02 (1.00-1.03)	0.039	1.02 (0.99-1.05)	0.167
Male	1.27 (0.88-1.84)	0.203	1.48 (0.77-2.84)	0.243
Education, years	0.96 (0.91-1.00)	0.070	0.99 (0.91-1.07)	0.701
Current cigarette smoking	1.30 (0.92-1.84)	0.131	1.66 (0.91-3.03)	0.098
Current alcohol drinking	1.03 (0.72-1.46)	0.879	1.32 (0.69-2.53)	0.400
Time from onset to randomization, h	1.01 (0.99-1.02)	0.504	1.00 (0.98-1.03)	0.683
Systolic BP, mm Hg	0.97 (0.96-0.98)	<0.001	0.98 (0.97-1.00)	0.061
Blood glucose, mmol/L	1.02 (0.96-1.08)	0.604	1.02 (0.94-1.12)	0.602
Galectin-3, ng/ml	0.94 (0.91-0.98)	0.003	1.00 (0.94-1.07)	0.993
Body mass index, kg/m^2	1.00 (0.95-1.06)	0.914	1.08 (0.98-1.18)	0.116
Baseline NIHSS score	1.33 (1.11-1.60)	0.002	1.85 (1.04-3.30)	0.036

History of hypertension	1.37 (0.93-2.03)	0.113	1.46 (0.80-2.68)	0.218
History of hyperlipidemia	1.50 (0.76-2.96)	0.243	1.85 (0.61-5.60)	0.276
History of coronary heart disease	1.23 (0.71-2.13)	0.468	1.53 (0.64-3.67)	0.339
Family history of stroke	2.27 (1.38-3.73)	<0.001	1.46 (0.80-2.68)	0.284
Ischemic stroke subtype	1.53 (1.28-1.84)	<0.001	1.14 (0.82-1.58)	0.448
Receiving immediate BP reduction	0.92 (0.66-1.28)	0.623	0.77 (0.47-1.26)	0.294
Clinical center*				
Center 2	1.68 (0.70-4.05)	0.857	2.20 (0.80-6.04)	0.126
Center 3	0.92 (0.31-2.70)	0.086	0.50 (0.14-1.76)	0.282
Center 4	38.88 (15.81-95.60)	<0.001	42.95 (14.18-130.12)	<0.001
Center 5	0.58 (0.25-1.33)	<0.001	0.54 (0.21-1.39)	0.205
Center 6	0.28 (0.08-0.97)	<0.001	0.29 (0.08-1.09)	0.068
Center 7	5.41 (2.29-12.76)	<0.001	4.41 (1.66-11.75)	0.003

*Taking Center 1 as the reference group.

Table S4. Reclassification and discrimination statistics (95% CI) for poststroke depression by serum GDF-15.

	Continuous NRI, %		IDI, %		C statistics		Likelihood
	Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value	ratio test, *P* value
HRSD score≥8							
Conventional model	Reference		Reference		0.740 (0.699–0.779)		Reference
Conventional model + GDF-15	28.21 (10.35-46.07)	0.002	1.86 (0.63-3.08)	0.003	0.754 (0.713–0.792)	0.109	<0.001

IDI, integrated discrimination index; NRI, net reclassification improvement; GDF-15, growth differentiation factor 15. The conventional model included age, sex, education level, time from onset to randomization, clinical center, current smoking, alcohol consumption, systolic BP, blood glucose, galectin-3, body mass index, baseline NIHSS scores, medical history (hypertension, hyperlipidemia, and coronary heart disease), family history of stroke, ischemic stroke subtype, and immediate BP reduction.

Table S5. Sensitivity analyses of the association between high serum GDF-15 and poststroke depression.

	GDF-15, ng/L			*P* value for trend
	< 792.94	792.94-1234.66	≥1234.66	
Events, n (%)	62 (32.6)	77 (40.3)	92 (48.17)	
Unadjusted	1.00	1.39 (0.92-2.12)	1.92 (1.27-2.91)	0.002
Model 1	1.00	1.63 (0.81-3.28)	2.92 (1.36-6.27)	0.006
Model 2	1.00	1.74 (0.85-3.58)	2.81 (1.27-6.23)	0.011
Model 3	1.00	1.69 (0.82-3.48)	3.26 (1.48-7.20)	0.003
Model 4	1.00	1.69 (0.84-3.40)	2.97 (1.36-6.46)	0.006
Model 5	1.00	1.68 (0.79-3.60)	3.33 (1.46-7.59)	0.004
Model 6	1.00	1.71 (0.85-3.44)	3.02 (1.40-6.52)	0.005

Model 1, adjusted for age, sex, education level, time from onset to randomization, clinical center, current smoking, alcohol consumption, systolic BP, blood glucose, galectin-3, body mass index, baseline NIHSS scores, medical history (hypertension, hyperlipidemia, and coronary heart disease), family history of stroke, ischemic stroke subtype, and immediate BP reduction.

Model 2, adjusted for Model 1 and further adjusted for the ratio of 12-hour systolic blood pressure to baseline systolic blood pressure.

Model 3, adjusted for Model 1 and further adjusted for the ratio of 24-hour systolic blood pressure to baseline systolic blood pressure.

Model 4, adjusted for Model 1 and further adjusted for the ratio of 3-day systolic blood pressure to baseline systolic blood pressure.

Model 5, adjusted for Model 1 and further adjusted for the ratio of 7-day systolic blood pressure to baseline systolic blood pressure.

Model 6, adjusted for Model 1 and further adjusted for the ratio of 3-month systolic blood pressure to baseline systolic blood pressure.

Figure S1. Flowchart of participants' selection.

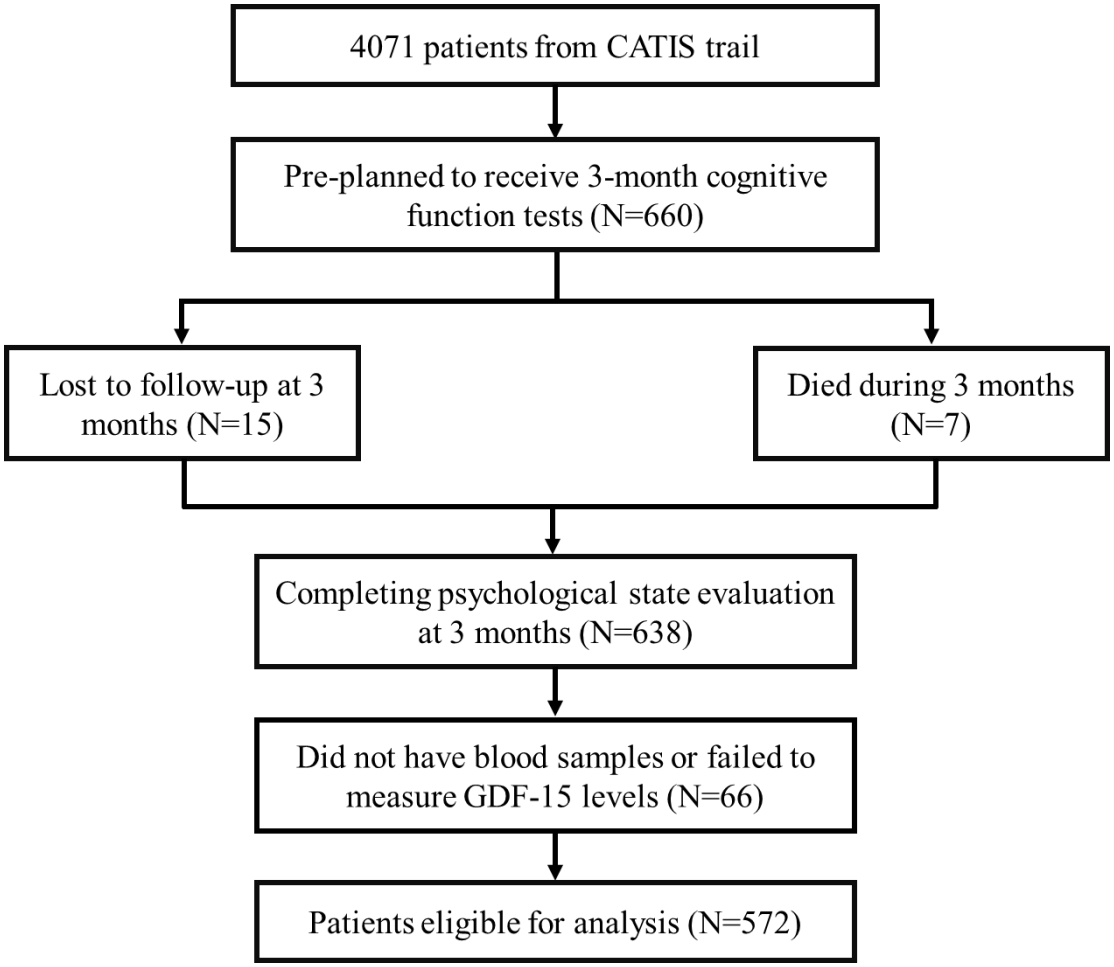
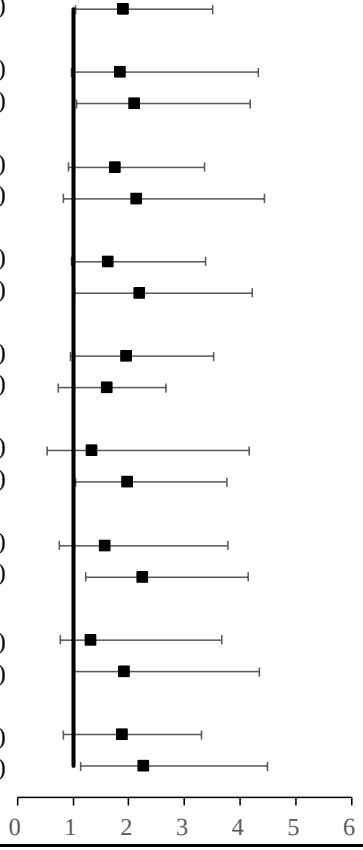


Figure S2. Subgroup analyses of the association between high serum GDF-15 and poststroke depression.

Subgroup	No. of PSD/patients (%) Low GDF-15	High GDF-15	OR (95% CI)	$P_{interaction}$
Overall	87/255 (34.1)	144/317 (45.4)	1.91 (1.04-3.51)	
Age, years				0.096
<65	72/207 (34.8)	62/162 (38.3)	1.84 (0.97-4.32)	
≥65	18/48 (37.5)	79/155 (51.0)	2.10 (1.06-4.18)	
Sex				0.550
Men	65/176 (36.9)	103/223 (46.2)	1.76 (0.92-3.36)	
Women	22/79 (27.9)	41/94 (43.6)	2.14 (0.82-4.43)	
Education				0.782
Primary	37/120 (30.8)	74/181 (40.9)	1.62 (0.97-3.38)	
Middle or high	50/135 (37.0)	70/136 (51.5)	2.19 (1.03-4.22)	
Time from onset to hospitalization				0.282
<12	40/121 (33.1)	80/167 (47.9)	1.96 (0.96-3.53)	
≥12	47/134 (35.1)	64/150 (42.7)	1.61 (0.73-2.67)	
History of hypertension				0.392
No	24/56 (42.9)	38/78 (48.7)	1.34 (0.53-4.17)	
Yes	63/199 (31.7)	106/239 (44.4)	1.97 (1.04-3.76)	
Baseline NIHSS score				0.836
<4	30/113 (26.6)	41/107 (38.3)	1.58 (0.76-3.78)	
≥4	57/142 (40.1)	103/210 (59.7)	2.25 (1.22-4.15)	
Body mass index, kg/m^2				0.473
<24	25/88 (28.4)	67/152 (44.1)	1.31 (0.78-3.67)	
≥24	62/167 (37.1)	77/165 (46.7)	1.92 (1.01-4.35)	
Receiving immediate blood pressure reduction				0.646
No	47/131 (35.9)	73/159 (45.9)	1.89 (0.82-3.31)	
Yes	40/124 (21.94)	71/158 (44.9)	2.26 (1.14-4.49)	



High serum GDF-15 was defined as ≥885.68 ng/L (optimal cut point obtained from the receiver operating characteristic curve). In the multivariate models, confounding factors, such as age, sex, education level, time from onset to randomization, current smoking, alcohol consumption, systolic BP, blood glucose, galectin-3, body mass index, baseline NIHSS scores, medical history (hypertension, hyperlipidemia, and coronary heart disease), family history of stroke, ischemic stroke subtype, and immediate BP reduction, were included unless the variable was used as a subgroup variable. OR indicates odds ratio.