

# Glial Fibrillary Acidic Protein Levels in Post-Stroke Depression: A Prospective Ischemic Stroke Cohort

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**Background and Purpose:** Increased glial fibrillary acidic protein (GFAP) levels were found in cerebrovascular disease patients. The pathogenesis of depression after ischemic stroke remains largely unknown. Here, we aim to determine whether GFAP concentrations were associated with post-stroke depression (PSD) at 3 months.

**Methods:** From March 2022 to September 2022, patients with first-ever ischemic stroke were prospectively recruited. GFAP concentrations were detected within 24 h using an enzyme-linked immunosorbent assay. The PSD was defined as a Hamilton Depression Rating Scale 24-Item score  $\geq 8$ .

**Results:** A total of 206 subjects with ischemic stroke (mean age: 63.6 years; 49.0% female) were enrolled. During the 90-day follow-up, 57 participants (27.7%) were observed in PSD. The median serum GFAP concentrations were 0.67 ng/mL. After adjustment for the covariates, higher increased GFAP levels were associated with increased risk of PSD (odds ratio [OR], 7.12; 95% confidence interval [CI], 3.29–15.44;  $P < 0.001$ ). Also, the multivariate-adjusted OR of PSD associated with the fourth quartile of GFAP was 10.89 (95% CI, 3.53–33.60;  $P < 0.001$ ) compared with the first quartile. Furthermore, the restricted cubic spline confirmed a linear association between GFAP and the risk of PSD ( $P$  for linearity  $< 0.001$ ).

**Conclusion:** Our results indicated that increased circulating GFAP concentrations were significantly correlated with the risk of PSD at 3 months. Measuring the GFAP levels after ischemic stroke may add some values for the risk stratifying of PSD.

**Keywords:** post-stroke depression, ischemic stroke, prognosis, glial fibrillary acidic protein, prospective study

## Introduction

Stroke is estimated to be the leading cause of acquired disability and mortality worldwide.<sup>1</sup> Post-stroke depression (PSD) is a common complication that affects approximately one-third of ischemic stroke survivors.<sup>2–4</sup> PSD may negatively affect the quality of life after ischemic stroke, and impair recovery of cognitive and motor function.<sup>5,6</sup> Also, a meta-analysis included 15 prospective cohort studies with 250,294 participants suggesting that PSD is significantly correlated with an increased risk of mortality in ischemic stroke patients.<sup>7</sup> Therefore, it is essential to identify the predictor and specific pathophysiology of PSD, in order to stratify the PSD risk and improve stroke prognosis.

Glial Fibrillary Acidic Protein (GFAP) is a cytoskeletal protein with a 50–52 KDa molecular mainly secreted by the astrocytes.<sup>8,9</sup> It plays an important role in the mediating shape and motility of astrocytic processes and contributes to blood-brain barrier (BBB) integrity and white matter architecture.<sup>10,11</sup> When astrocytes and the BBB are broken down, GFAP molecules may release into the blood and become detectable. Elevated GFAP levels in peripheral blood and cerebrospinal fluid have been found in several central nervous system diseases.<sup>12–14</sup> It has been reported that Alzheimer's disease dementia patients with increased GFAP levels show worse cognitive function.<sup>15</sup> Also, significant correlations were found between infarction size, stroke severity, and serum GFAP concentrations in ischemic stroke patients.<sup>16</sup> However, the correlation between circulating GFAP concentrations and depressive symptoms after ischemic stroke is still unclear.

We therefore prospectively recruited the ischemic stroke patients and evaluated whether the serum GFAP levels were correlated with the risk of 3-month PSD.

## Materials and Methods

### Study Patients and Design

Between March 2022 to September 2022, the first-ever ischemic stroke subjects with symptoms onset to hospitalization less than 7 days were consecutively enrolled at Suzhou Ninth People's Hospital. Ischemic stroke was confirmed by the World Health Organization criteria combined with brain computed tomography or magnetic resonance imaging results.<sup>17</sup> The exclusion standards were: 1) age less than 18 years; 2) unable to complete the psychological measurement; 3) had a history of psychiatric illness, Alzheimer's disease, Parkinson's disease, traumatic brain injury, central nervous system infection, hematological or immunological diseases, thyroid diseases, malignant tumor, and serious organ dysfunction. This study was approved by the Ethics Committee of Suzhou Ninth People's Hospital. Written consent was obtained from all participants before entering this study. All the participants were informed about the purpose of the study. All procedures were in accordance with the 1964 Helsinki Declaration and its later amendments.

### Baseline Data Collection

Baseline variables were recorded after admission, including demographic characteristics (age, gender, and educational background), traditional risk factors (hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, and smoking), clinical data (blood pressure, neurological deficits, side of infarction, and stroke subtypes) and laboratory data (total cholesterol, triglyceride, baseline glucose levels, and Hyper-sensitive C-reactive protein). Baseline neurological deficits were measured using the National Institutes of Health Stroke Scale (NIHSS).<sup>18</sup> Stroke subtypes were classified as large artery atherosclerosis, small artery occlusion, cardioembolism, and others according to the Trial of Org 10,172 in Acute Stroke Treatment (TOAST).<sup>19</sup>

### Measurements of GFAP Levels

Blood samples in all patients were collected within 24 hours after admission by trained nurses and tested by technicians who were blinded to clinical data. The blood was centrifuged, aliquoted, and kept at  $-80^{\circ}\text{C}$  for later analysis. Serum GFAP concentrations were detected by an enzyme-linked immunosorbent assay kit.

### Psychological Measurement

During the 3-month follow-up, the psychological measurement was performed using the validated version of the 24-item Hamilton Depression Rating Scale (HRSD-24).<sup>20</sup> According to previous studies, PSD was defined as a Hamilton Depression Rating Scale 24-Item score  $\geq 8$ .<sup>21–23</sup>

### Statistical Analysis

The continuous variables were expressed as means  $\pm$  standard deviation (SD) or medians with interquartile ranges (IQR). Univariate analysis for continuous variables was conducted using the Student's *t*-test or Mann–Whitney *U*-test. Categorical variables were shown as percentages and compared using the Fisher exact test or  $\chi^2$  test. Binary logistic regression analysis was performed to estimate the odds ratios (OR) and 95% confidence intervals (CI). Multivariate analyses were first controlled for demographic characteristics and educational status (Model 1) and additionally controlled for all variables (including demographic characteristics, educational status, and *P* value  $< 0.1$  in the univariate analysis).

Additionally, we utilized the restricted cubic splines to estimate and explore the shape of the correlation between GFAP levels and PSD, with 3 knots placed at the 5th, 50th, and 95th percentiles of GFAP, and the reference point was the median GFAP levels (0.67 ng/mL) among all patients. Furthermore, we used the receiver operating characteristic curve (ROC) to assess the overall predicted accuracy of GFAP. All statistical analyses were conducted with SPSS (version 24.0, SPSS Inc., Chicago, IL, USA) and R statistical software (version 4.0.0, R Foundation, Vienna, Austria). All analyses were two-tailed, and statistical significance was determined by  $P < 0.05$ .

## Results

### Baseline Data

In this study, 294 patients with ischemic stroke were screened for analysis. We excluded 62 patients unable to complete the psychological measurement, 19 patients previously diagnosed with psychiatric illness, Alzheimer's disease, Parkinson's disease, traumatic brain injury, central nervous system infection, hematological or immunological diseases, thyroid diseases, malignant tumor, and serious organ dysfunction, and 7 patients lost to follow-up. Finally, a total of 206 patients were finally included in the study. The average age was 63.6 years and 101 (49.0%) were male. Further details of baseline data are presented in Table 1. The median circulating GFAP concentrations were 0.67 ng/mL. According to the median GFAP levels, patients were divided into the higher GFAP levels group and the lower GFAP levels group. As shown in Table 1, as compared with patients with lower GFAP levels, those with higher GFAP levels had a higher prevalence of diabetes mellitus ( $P = 0.017$ ) and PSD ( $P < 0.001$ ) and had a higher Hs-CRP levels ( $P = 0.049$ ). However, there was no significant difference between the 2 groups in terms of age, sex, baseline NIHSS score, and stroke etiology.

**Table 1** Baseline Data of the Ischemic Stroke Patients According to the GFAP Levels

Variables	All Patients n=206	High GFAP Levels Group n=103	Low GFAP Levels Group n=103	P value
Demographic characteristics,				
Age, year	63.6 ± 9.2	63.9 ± 9.2	63.2 ± 9.3	0.575
Female, %	101 (49.0)	55 (53.4)	46 (44.7)	0.210
Education < 12 years, %	89 (43.2)	46 (44.7)	43 (41.7)	0.673
Live alone, %	57 (27.7)	30 (29.1)	27 (26.2)	0.640
Body mass index, kg/m <sup>2</sup>	24.1 ± 2.9	24.3 ± 3.6	23.9 ± 2.2	0.411
Traditional vascular risk factors, %				
Hypertension	150 (72.8)	73 (70.9)	77 (74.8)	0.531
Diabetes mellitus	53 (25.7)	34 (33.0)	19 (18.4)	0.017
Hyperlipidemia	35 (17.0)	18 (17.5)	17 (16.5)	0.853
Coronary heart disease	34 (16.5)	15 (14.6)	19 (18.4)	0.453
Current smoking	79 (38.3)	38 (36.9)	41 (39.8)	0.667
Clinical data				
Onset-to-blood drawing time, day	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)	2.0 (1.0, 3.0)	0.531
Systolic blood pressure, mmHg	136.8 ± 16.9	137.8 ± 16.2	135.7 ± 17.5	0.384
Diastolic blood pressure, mmHg	81.8 ± 10.0	82.0 ± 10.7	81.6 ± 9.2	0.743
Baseline NIHSS, score	5.0 (2.0, 8.0)	5.0 (3.0, 8.0)	5.0 (2.0, 8.0)	0.895
PSD, %	57 (27.7)	43 (41.7)	14 (13.6)	< 0.001
Infarction side				
Left	117 (56.8)	58 (56.3)	59 (57.3)	0.888
Right	97 (47.1)	50 (48.5)	47 (45.6)	0.675
Stroke etiology, %				
Large artery atherosclerosis	88 (42.7)	45 (43.7)	43 (41.7)	0.421
Cardioembolism	32 (15.5)	17 (16.5)	15 (14.6)	
Small vessel occlusion	69 (33.5)	30 (29.1)	39 (37.9)	
Others	17 (8.3)	11 (10.7)	6 (5.8)	
Laboratory data				
Total cholesterol, mmol/L	4.1 ± 1.1	4.1 ± 1.1	4.0 ± 1.1	0.566
Triglyceride, mmol/L	1.4 (1.1, 1.9)	1.5 (1.1, 1.9)	1.3 (1.0, 1.8)	0.103
Baseline glucose levels, mmol/L	5.5 ± 1.7	5.5 ± 1.7	5.5 ± 1.8	0.949
Glycated hemoglobin, %	6.4 ± 1.2	6.6 ± 1.3	6.2 ± 1.0	0.006
Hyper-sensitive C-reactive protein, mg/L	4.0 (1.0, 6.8)	5.0 (1.0, 7.2)	3.0 (1.0, 6.0)	0.049

**Abbreviations:** NIHSS, national institutes of health stroke scale; GFAP, Glial fibrillary acidic protein; PSD, post-stroke depression.

## Comparison of Baseline Data in Patients with or Without PSD

At the 3-month follow-up, PSD was observed in 57 patients (27.7%). The comparison of baseline data is shown in Table 2. The GFAP concentrations in subjects with PSD were higher than those in patients without PSD (median, 0.92 ng/mL versus 0.48 ng/mL;  $P = 0.001$ ). In addition, compared with patients without PSD, those with it were older ( $66.0 \pm 9.9$  versus  $62.7 \pm 8.7$  years,  $P = 0.018$ ), more likely to live alone (40.4% versus 22.8%,  $P = 0.012$ ), and have education <12 years (68.4% versus 52.3%,  $P = 0.037$ ) and diabetes mellitus (36.8% versus 21.5%,  $P = 0.024$ ), and have a higher NIHSS score (median, 5.0 versus 4.0,  $P = 0.011$ ), glucose levels ( $5.9 \pm 2.2$  mmol/L versus  $5.3 \pm 1.5$  mmol/L,  $P = 0.041$ ) and Hs-CRP levels (median, 6.0 mg/L versus 4.0 mg/L;  $P = 0.046$ ).

**Table 2** Clinical and Sociodemographic Characteristics of Patients Stratified by PSD at 3 Months

Variables	With PSD, n=57	Without PSD, n=149	P value
Demographic characteristics,			
Age, year	66.0 ± 9.9	62.7 ± 8.7	0.018
Female, %	28 (49.1)	73 (49.0)	0.987
Education <12 years, %	39 (68.4)	78 (52.3)	0.037
Live alone	23 (40.4)	34 (22.8)	0.012
Body mass index, kg/m <sup>2</sup>	24.1 ± 3.9	24.2 ± 2.5	0.986
Traditional vascular risk factors, %			
Hypertension	38 (66.7)	112 (75.2)	0.220
Diabetes mellitus	21 (36.8)	32 (21.5)	0.024
Hyperlipidemia	7 (12.3)	28 (18.8)	0.266
Coronary heart disease	13 (22.8)	21 (14.1)	0.132
Current smoking	22 (38.6)	57 (38.3)	0.963
Clinical data			
Onset-to-blood drawing time, day	3.0 (1.0, 4.0)	2.0 (1.0, 3.0)	0.458
Systolic blood pressure, mmHg	139.7 ± 18.7	135.7 ± 16.0	0.126
Diastolic blood pressure, mmHg	82.3 ± 9.7	81.6 ± 10.1	0.693
Baseline NIHSS, score	5.0 (4.0, 9.0)	4.0 (2.0, 8.0)	0.011
Infarction side			
Left	31 (54.4)	86 (57.7)	0.666
Right	31 (54.4)	66 (44.3)	0.194
Stroke etiology, %			
Large artery atherosclerosis	29 (50.9)	59 (39.6)	0.416
Cardioembolism	6 (10.5)	26 (17.4)	
Small vessel occlusion	17 (29.8)	52 (34.9)	
Others	5 (8.8)	12 (8.1)	
Blood laboratory findings			
Total cholesterol, mmol/L	4.0 ± 1.0	4.1 ± 1.1	0.474
Triglyceride, mmol/L	1.6 (1.1, 1.9)	1.4 (1.1, 1.9)	0.150
Baseline glucose levels, mmol/L	5.9 ± 2.2	5.3 ± 1.5	0.041
Glycated hemoglobin, %	6.6 ± 1.3	6.4 ± 1.1	0.148
Hyper-sensitive C-reactive protein, mg/L	6.0 (1.0, 7.2)	4.0 (1.0, 6.0)	0.046
GFAP, ng/mL	0.92 (0.65, 1.34)	0.48 (0.20, 0.87)	< 0.001
GFAP quartiles			< 0.001
1st quartile	6 (10.5)	45 (30.2)	
2nd quartile	8 (14.0)	44 (29.5)	
3rd quartile	15 (26.3)	37 (24.8)	
4th quartile	28 (49.1)	23 (15.4)	

**Abbreviations:** NIHSS, national institutes of health stroke scale; GFAP, glial fibrillary acidic protein; PSD, post-stroke depression.

## Association GFAP Levels and PSD

The cut-off values of the GFAP levels in the 4 quartiles were: (first quartile) < 0.23 ng/mL, (second quartile) 0.23–0.66 ng/mL, (third quartile) 0.67–1.00 ng/mL and (fourth quartile) >1.00 ng/mL. Patients in the fourth quartile of GFAP had the highest incidence of PSD (49.1%;  $P < 0.002$ ). After adjustment for potential confounders (including age, sex, education, and  $P$  value < 0.1 in the univariate analysis) in multivariate regression analysis, the OR of PSD associated with the fourth quartile of GFAP levels was 10.89 (compared with the first quartile; 95% CI, 3.53–33.60;  $P < 0.006$ ; Table 3). In continuous analysis, higher GFAP levels were confirmed to have an increased risk of PSD (OR, 7.12; 95% CI, 3.29–15.44;  $P < 0.001$ ). Furthermore, the results of restricted cubic spline regression analysis demonstrated that there was a linear relationship between GFAP levels and PSD ( $P < 0.001$ ; Figure 1) after adjustment for the covariates. In addition, the AUC of GFAP in predicting the presence of PSD was 0.735 (95% CI, 0.657–0.812,  $P = 0.001$ ). The optimal cutoff point of circulating GFAP levels was 0.45 ng/mL, with a sensitivity of 87.7% and a specificity of 51.7%.

## Discussion

This is the first prospective study to evaluate the predictive value of serum GFAP levels in 3-month PSD in ischemic stroke patients. The results found that even after controlling for demographic characteristics, stroke severity, and other potential confounders, patients with increased GFAP concentrations have a higher risk of PSD.

PSD is the most frequent and burdensome neuropsychiatric complication after ischemic stroke.<sup>24</sup> This discrepancy in the prevalence of PSD occurs because studies were performed in different settings, instruments assessing PSD, and the distinct time intervals between the PSD assessments and stroke symptoms onset. In this study, we found that 27.7% of ischemic stroke patients experience PSD at 90 days follow-up, which is similar to previous literature.<sup>2–4</sup> We found that age and educational background were predictors of PSD. Older patients with low educational status were more likely to have a depressive response when dealing with the stress of stroke, possibly due to a lack of sufficient social security.<sup>25</sup> The significant correlation between stroke severity and PSD was also consistent with earlier studies.<sup>26,27</sup> Due to the pathophysiology, prognosis, and clinical features of subcortical lacunar strokes being different from other acute cerebrovascular diseases,<sup>28</sup> some researchers might suppose that lacunar stroke is associated with the risk of PSD. However, our data did not confirm a significant correlation between stroke subtypes and PSD. Further studies are recommended to detect this association.

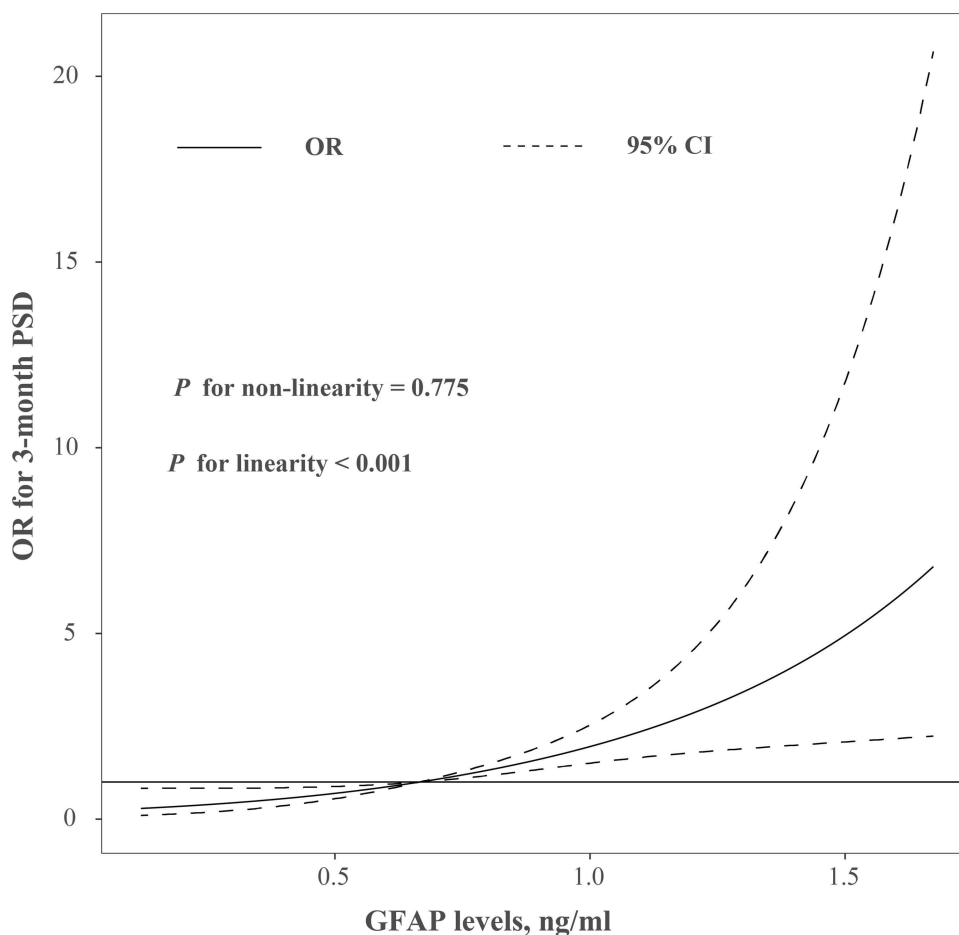
GFAP is a monomeric intermediate filament protein of the astroglia skeleton, which is considered brain-specific.<sup>8</sup> GFAP is involved in several cellular processes in astrocytes, such as vesicle trafficking, neuron-astrocyte interactions,

**Table 3** Multivariate Analysis for the Relationship Between GFAP Levels and PSD

Variables	Unadjusted Model		Adjusted Model		Adjusted Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.05 (1.01–1.08)	0.021	1.04 (1.00–1.08)	0.045	–	–
Female	1.01 (0.55–1.85)	0.987	–	–	–	–
Education <12 years	1.97 (1.04–3.76)	0.039	–	–	–	–
Live alone	2.29 (1.19–4.40)	0.013	–	–	–	–
Diabetes mellitus	2.13 (1.10–4.15)	0.026	–	–	–	–
Baseline NIHSS score	1.12 (1.03–1.22)	0.008	–	–	1.15 (1.04–1.28)	0.007
Baseline glucose levels	1.18 (1.00–1.40)	0.048	–	–	1.24 (1.04–1.55)	0.047
Hyper-sensitive C-reactive protein levels	1.03 (0.98–1.10)	0.332	–	–	–	–
GFAP quartile						
1st	Reference		Reference		Reference	
2nd	1.36 (0.44–4.25)	0.593	1.53 (0.48–4.86)	0.593	1.23 (0.34–4.25)	0.745
3rd	3.04 (1.07–8.62)	0.036	3.53 (1.21–10.33)	0.036	3.18 (1.01–10.05)	0.048
4th	9.13 (3.31–25.19)	< 0.001	10.12 (3.55–28.83)	< 0.001	10.89 (3.53–33.60)	< 0.001

**Notes:** Model 1 controlled for demographic characteristics and educational years; Model 2 controlled for demographic characteristics, educational years, and  $P$  value < 0.1 in the univariate analysis.

**Abbreviations:** CL, Confidence interval; GFAP, glial fibrillary acidic protein; NIHSS, national institutes of health stroke scale; OR, Odd ratio; PSD, post-stroke depression.



**Figure 1** Association of serum GFAP levels with risk of post-stroke depression. Odds ratios and 95% confidence intervals derived from restricted cubic spline regression, with knots placed at the 5th, 50th, and 95th percentiles of GFAP. Odds ratios were controlled for the same variables as model 2 in Table 3.

and blood-brain barrier integrity.<sup>29</sup> The GFAP molecules will be released into circulation through the damaged BBB in several central nervous system diseases. Circulating GFAP has recently been indicated as a promising biomarker for disease diagnosis.<sup>12–14</sup> Our data further extended the predictive value of GFAP in cerebrovascular diseases and showed that patients with increased serum GFAP levels have a higher PSD risk at 3 months after ischemic stroke.

PSD is a heterogeneous condition, and no individual pathophysiological processes can fully explain PSD. Recently, some processes have been confirmed to induce PSD including neuroinflammation, glutamate-mediated excitotoxicity, and abnormal neurotrophic response to stroke.<sup>2,24</sup> The precise mechanisms underlying the observed relationship between serum GFAP and PSD are unknown, but several pathophysiological processes may explain the association. Firstly, reactive astrocytes after central nervous system injury may induce the expression of GFAP and the release of several pro-inflammatory cytokines. Also, reactive astrocytes increase the excitotoxicity of glutamate to neurons and other brain cells by regulating the extracellular glutamate.<sup>30,31</sup> We, therefore, assume that GFAP may mediate the depressive symptoms after ischemic stroke by inducing neuroinflammation and glutamate excitotoxicity. Secondly, *GFAP*<sup>-/-</sup> mice display abnormalities of the BBB and endothelial function.<sup>11</sup> As the BBB plays a pivotal role in the pathogenesis of depression, GFAP is involved in the presence of PSD by mediating the integrity of the BBB. Thirdly, GFAP has also been reported to be correlated with small cerebral vessel disease, including lacunar infarction and white matter hyperintensity burden,<sup>15</sup> which might induce neuropsychological alterations.<sup>32</sup> Further basic experiments are needed to clarify the detailed mechanism of GFAP on depression after ischemic stroke.

The strengths of our study include prospective design, comprehensive assessment of PSD, and recruiting a homogeneous population of ischemic stroke patients. However, this study had some inevitable limitations. Firstly, this study was based on Asian ethnicity patients, it cannot be generalized to other populations. Secondly, GFAP levels were tested once at a time after admission.

We therefore could not assess the correlation between GFAP changes and PSD. Thirdly, ischemic stroke patients with severe neurological deficits, a history of psychiatric illness, and other serious illnesses were excluded, which might underestimate the incidence of PSD. Finally, several potential confounders were not recorded in this study, such as home care, medication compliance, and use of sedative and hypnotic drugs post-discharge. Therefore, these results should be interpreted with caution.

In conclusion, increased GFAP levels were associated with a significant augmentation of the proportion of patients with 3-month PSD after stroke. The results of the present report suggested that circulating GFAP levels could be a promising biomarker for PSD risk stratification. Further studies using more representative nationwide-based samples are needed to confirm our findings. Furthermore, whether the management of GFAP within the appropriate range could improve functional outcome after ischemic stroke is a possible future area of inquiry.

## Data Sharing Statement

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

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## Disclosure

The authors report no conflicts of interest in this work.

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