

# Increased Serum S100 $\beta$ Concentration is Associated with Depression in Parkinson's Disease

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**Purpose:** To explore the relationship between the serum level of S100 calcium-binding protein, beta chain (S100 $\beta$ ) and Parkinson's disease (PD) with depression.

**Patients and Methods:** A total of 145 patients with PD and 60 healthy controls matched for sex, age, and years of education in our hospital were selected. Fluorescence quantitative immunochromatography was used to quantify the level of S100 $\beta$  in serum. Clinical manifestations were assessed by Unified Parkinson's Disease Rating Scale part-III (UPDRS-III), Hoehn & Yahr (H-Y) stage and 17-item Hamilton Rating Scale for Depression (HAMD-17). According to the results of HAMD-17, PD patients were divided into PD with depression group and PD without depression group. The relationship between serum S100 $\beta$  and HAMD-17 scores in PD patients with depression was investigated through correlation analysis and multivariate regression analysis, and receiver operating characteristic (ROC) curve was used to evaluate the diagnostic value of serum S100 $\beta$ .

**Results:** The level of serum S100 $\beta$  in PD with depression group was significantly higher than that in PD without depression group and control group. In PD patients with depression, serum S100 $\beta$  level was positively correlated with UPDRS-III score, H-Y Scale and HAMD-17 score. The HAMD-17 score was positively correlated with the UPDRS-III and H-Y scales, and the increase in the HAMD-17 score was associated with women. Elevated serum S100 $\beta$  level and UPDRS-III score are independent risk factors for PD with depression. Analysis of receiver operating characteristic (ROC) curves showed that the serum S100 $\beta$  level with a cutoff of 0.28 ng/mL distinguished patients with PD with or without depression with an area under the ROC curve (AUC) of 0.742, sensitivity of 0.696, and specificity of 0.779.

**Conclusion:** The serum S100 $\beta$  level could be a biomarker of PD with depression.

**Keywords:** Parkinson's disease, depression, S100 $\beta$ , risk factors

## Introduction

Parkinson's disease (PD) is a common neurodegenerative disease in middle-aged and elderly people.<sup>1</sup> The typical clinical manifestations of PD include bradykinesia, rigidity, tremors, and postural balance disorders.<sup>2</sup> Non-motor symptoms of PD have attracted much attention in recent years. Depression is one of the common non-motor symptoms of PD and seriously affects the quality of life of patients.<sup>3-5</sup> The incidence of PD with depression is 2.7 ~ 90.0%,<sup>6</sup> which affects the quality of life of patients. In severe cases, this can lead to the aggravation of patients' movement disorders and cognitive disorders, and cause great burden to families and society.<sup>7,8</sup> Therefore, early screening and effective interventions for PD patients with depression are important to improve the quality of life and prognosis of patients.

S100 calcium-binding protein, beta chain (S100 $\beta$ ), also known as central nervous system-specific protein, is mainly expressed by astrocytes in the brain. It is considered to be a potential biomarker for blood-brain barrier (BBB) dysfunction, decreased neuronal activity and reduced neuroplasticity.<sup>9-11</sup> Damage to glial cell activity, BBB function and neuroplasticity is associated with various neurological and psychological disorders. Therefore, we believe that S100 $\beta$  protein may be involved in the pathophysiology of emotional disorders, and thus has some potential links with PD depression.

Previous studies have shown that there is a correlation between cerebrospinal fluid S100 $\beta$  concentration and depressive episodes.<sup>12</sup> The serum S100 $\beta$  level in patients with depression is significantly higher than that in patients without depression.<sup>13</sup> In PD patients, studies have shown that elevated serum S100 $\beta$  protein levels are associated with the severity of PD and motor symptoms.<sup>14</sup> However, the relationship between serum S100 $\beta$  levels and depressive symptoms in PD has not been studied. At present, the pathogenesis of depression in PD is not clear, which may be related to the loss of neurotransmitters such as 5-hydroxytryptamine (5-HT) and norepinephrine in the brain.<sup>15</sup> In patients with depression treated with 5-HT reuptake inhibitors, we found a decrease in S100 $\beta$  levels.<sup>16</sup> It is also believed that the occurrence of depression in PD may be related to the severity and motor symptoms of PD itself. Herein, the purpose of this study was to investigate whether serum S100 $\beta$  levels are associated with PD with depression.

## Materials and Methods

### Participants

All participants were recruited from the Affiliated Huai'an Hospital of Xuzhou Medical University. This study included 145 participants: 69 PD patients with depression, 76 PD patients without depression, and 60 healthy controls. All patients with PD met the following inclusion criteria: (a) Meeting the diagnostic criteria set by the UK Brain Bank for PD;<sup>17</sup> (b) Aged 40–80 years, Han Chinese. Exclusion criteria: (a) History of craniocerebral trauma, surgery, or cancer; (b) drug-induced secondary Parkinsonian syndrome, severe craniocerebral trauma, vascular and other secondary syndromes of PD; (c) Progressive supranuclear palsy, multiple-system atrophy or other syndromes of PD; (d) Patients using dopamine agonists, monoamine oxidase-B inhibitors and other anti-Parkinson's disease drugs, antidepressants and anti-anxiety drugs; (e) Severe cognitive impairment, Mini-Mental State Examination (MMSE) score<sup>18</sup> less than 24 points; (f) Serious systemic diseases of the heart, liver, or kidney; (g) Recent infection. The healthy control group was healthy volunteers in the physical examination center of the Affiliated Huai'an Hospital of Xuzhou Medical University. Their age, gender, and years of education were matched with PD patients, and there were no severe physical or mental illnesses.

The study protocol was approved by the Ethics Committee of the Second People's Hospital of Huai'an City (Huai'an, China).

### Clinical Assessment

All patients in the PD group were evaluated for severity of PD using H-Y Scale.<sup>19</sup> UPDRS-III<sup>20</sup> was used to assess the motor function of PD patients, and MMSE<sup>18</sup> was used to evaluate the cognitive function of patients. All clinical evaluations were performed during "on" condition.

### Depression Measure and Criteria

The screening or measuring the severity of such depressive symptoms in PD was measured by the HAMD-17,<sup>21</sup> it has been validated and traditionally recommended tool in individuals with PD. The scale includes 17 aspects: depression, guilt, suicidal ideation, sleep disorders (difficulty falling asleep, lack of sleep, early awakening), work and interest, block, agitation, mental anxiety, somatic anxiety, gastrointestinal symptoms, systemic symptoms, sexual symptoms, hypochondria, weight loss and insight. Among them, sleep disorders, gastrointestinal symptoms, systemic symptoms, sexual symptoms and weight loss were scored as follows: no abnormal 0 points, mild 1 points, severe 2 points; the remaining aspects were recorded as no abnormal 0 points, mild 1 point, moderate 2 points, severe 3 points, and extremely severe 4 points according to the severity; the full score of the scale was 54 points, and the higher the score, the more severe the depression.

According to the literature report,<sup>22</sup> the optimal threshold to utilize for maximum discrimination between depressed and non-depressed PD patients was reached at a cut-off score of 13/14 for the HAMD-17. Therefore, we divided PD patients into two groups according to the HAMD-17 score: PD without depression group (HAMD-17  $\leq$  13 points) and PD with depression group (HAMD-17  $\geq$  14 points). HAMD-17 assessment was also performed during "on" condition.

## Measurement of S100 $\beta$

Venous blood (5 mL) was collected on an empty stomach in people from both groups in the morning. The sample was allowed to stand at room temperature for 25 min. Then, the sample was centrifuged (4000 rpm, 15 min, room temperature) to separate and extract serum. Fluorescence quantitative immunochromatography was used to quantify the level of S100 $\beta$  in serum. This serum marker was detected by a fluorescence immunoassay analyzer (1600; Geteint Biotech; Nanjing, China).

## Acquisition of Remaining Risk Factors

Basic information such as gender, age, years of education and body mass index (BMI) were collected. The course of disease, hypertension history, diabetes history, smoking history and drinking history were recorded. Neutrophil ratio and high-sensitivity C-reactive protein (hs-CRP) were measured with an automatic biochemical analyzer (TBA 40FR, Toshiba, Tokyo, Japan).

## Statistical Analyses

Data were analyzed using SPSS 25.0 (IBM, Armonk, NY, USA). Graphs were created using Prism 9.0 (GraphPad, La Jolla, CA, USA). The normality test was carried out on measurement data. Data with a normal distribution are expressed as the mean  $\pm$  SD. Data with a non-normal distribution are expressed as median (interquartile range). The Student's *t*-test was employed to compare data between the two groups. Multiple groups of data were compared by ANOVA for those satisfying the conditions of a parametric test, and further two-by-two comparisons were made by the Bonferroni method. The Kruskal–Wallis test was used for data not satisfying the conditions of a parametric test, and further two-by-two comparisons were made by the Nemenyi method. Count data describe the number of cases, and the  $\chi^2$  test was used for comparison between groups. Correlations between variables were analyzed by applying Pearson or Spearman correlation coefficients. Multiple linear regression analysis was employed to explore independent risk factors for PD with depression. ROCs were used to the efficacy of serum S100 $\beta$  level in distinguishing PD with and without depression.  $P < 0.05$  (two-tailed) was deemed significant.

## Results

### Comparison of Baseline Characteristics of Participants

The demographic characteristics of PD patients and normal controls are shown in Table 1. There was no significant difference in gender, age, years of education, BMI, disease duration, smoking history, drinking history, hypertension, diabetes, neutrophil ratio and hs-CRP between PD with depression group, PD without depression group and normal control group (all  $p > 0.05$ ). However, compared with PD without depression group, the UPDRS-III score ( $p < 0.05$ ), H-Y Scale score ( $p < 0.05$ ) and HAMD-17 score ( $p < 0.05$ ) of PD with depression group were significantly higher (Table 1). There was no significant correlation between serum S100 $\beta$  level and age, sex, education years, BMI, course of disease, drinking and smoking history, hypertension and diabetes history, neutrophil ratio and hs-CRP level in each group.

### Serum S100 $\beta$ Level and Its Relationship with Clinical Features in PD Patients with and without Depression

The levels of serum S100 $\beta$  in PD with depression group ( $0.35 \pm 0.17$  ng/mL) and PD without depression group ( $0.21 \pm 0.11$  ng/mL) were higher than those in control group ( $0.12 \pm 0.05$  ng/mL) (Figure 1).

Correlation analysis showed that serum S100 $\beta$  level was positively correlated with UPDRS-III, H-Y grade and HAMD-17 score in PD patients with depression. HAMD-17 score was positively correlated with UPDRS-III and H-Y, and the increase of HAMD-17 score was related to women (Figure 2). In PD patients without depression, serum S100 $\beta$  level was positively correlated with UPDRS-III ( $r = 0.493$ ,  $p < 0.001$ ) and H-Y ( $r = 0.352$ ,  $p = 0.002$ ). The control group showed no significant correlation.

**Table 1** Comparison of Baseline Characteristics Between PD Patients with and without Depression and Healthy Controls

Variable	Normal Controls (N=60)	Patients with Depression (N=76)	Patients Without Depression (N=69)	P-value
Female, n (%)	32 (53.3%)	42 (54.5%)	33 (47.8%)	0.696
Age, years	63.80±7.72	64.64±7.04	65.78±7.51	0.311
Education, years	9.02±1.84	9.10±2.35	8.90±2.21	0.849
BMI, kg/m <sup>2</sup>	23.37 (20.81–25.65)	23.44 (20.58–24.68)	23.67 (20.21–25.27)	0.264
History of smoking, n (%)	16 (26.7)	22 (28.6)	10 (14.5)	0.102
History of alcohol consumption, n (%)	15 (25)	18 (23.4)	13 (18.8)	0.677
Hypertension, n (%)	18 (30)	20 (26)	25 (36.2)	0.403
Diabetes mellitus, n (%)	11 (18.3)	8 (10.4)	10 (14.5)	0.412
Neutrophil ratio, %	63.99±6.66	65.72±8.01	65.39±7.36	0.370
hs-CRP, mg/L	1.37 (0.67–1.96)	1.40 (0.73–2.77)	1.44 (0.65–3.00)	0.298
Disease duration, months	–	48.86±15.17	51.20±19.66	0.418
UPDRS-III	–	22.87±6.56	30.70±6.54	<0.001*
H-Y	–	1.5 (1.5–2)	2.5 (2.25–3)	<0.001*
HAMD-17	4.68±2.55	6.49±2.99	17.99±2.19	<0.001*
S100β, ng/mL	0.12±0.05	0.21±0.11	0.35±0.17	<0.001*

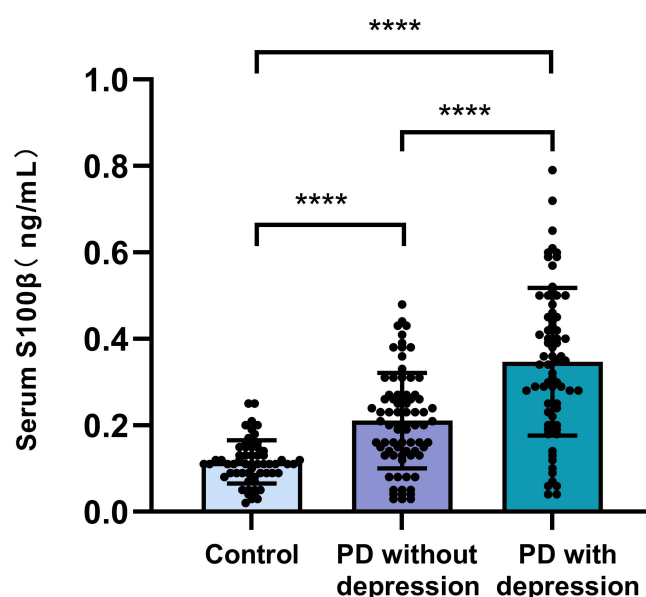
**Note:** \*Significant at  $p < 0.05$ .

**Abbreviations:** BMI, body mass index; hs-CRP, high sensitivity-C-reactive protein; UPDRS-III, Unified Parkinson's Disease Rating Scale part-III; H-Y, the Hoehn and Yahr stage; HAMD-17, 17-item Hamilton Rating Scale for Depression.

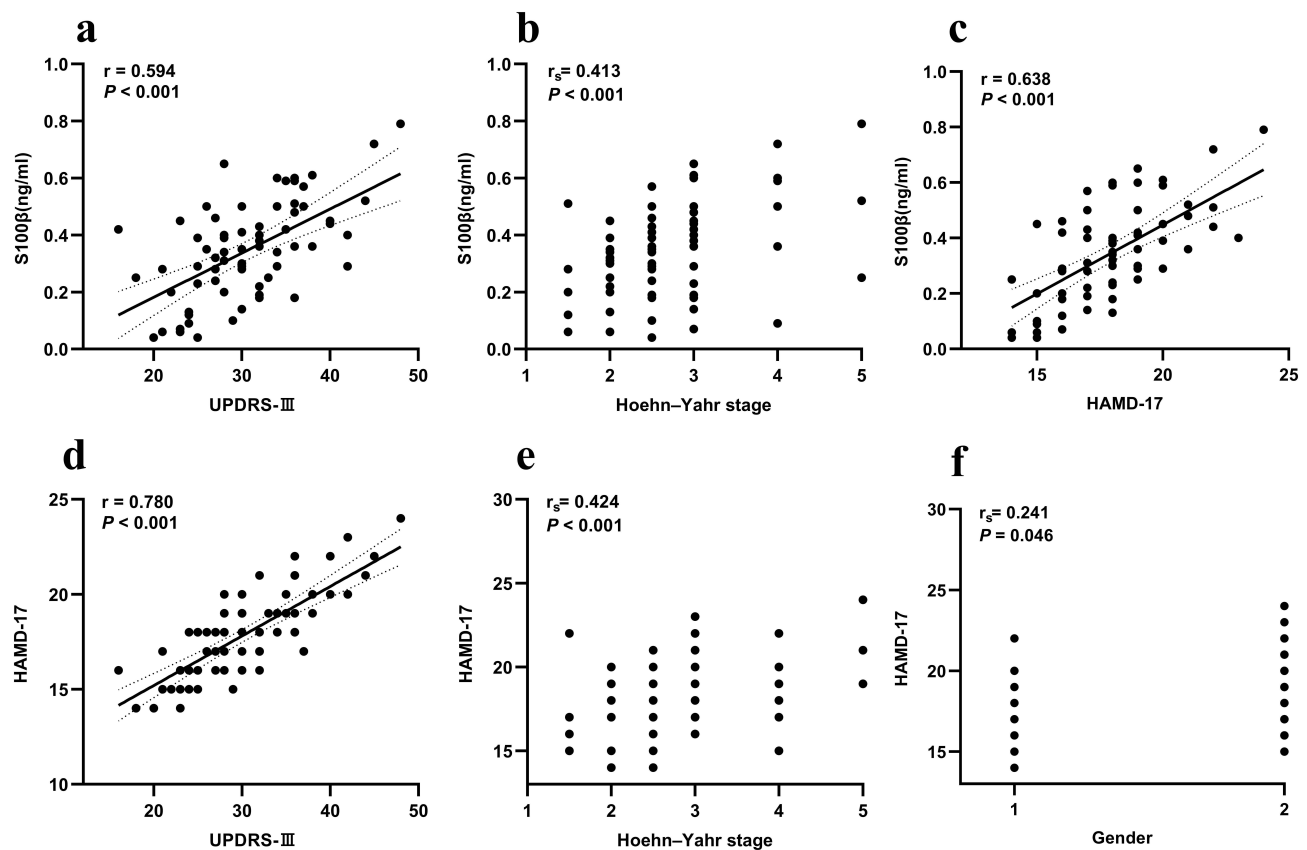
## Predictive Value of Serum S100β Level in PD with Depression

After collinearity diagnosis, we used UPDRS-III, H-Y Scale score, serum S100β level and gender as independent variables, and HAMD-17 score as dependent variable to perform multiple linear regression analysis. The results showed that serum S100β level ( $p = 0.002$ ), and UPDRS-III score ( $p < 0.001$ ) were independent risk factors for PD with depression (Table 2).

ROC curve analysis showed that serum S100β could distinguish PD patients with depression from those without depression with a cut-off value of 0.28 ng/mL. The area under the ROC curve (AUC) was 0.742, the sensitivity was 0.696, and the specificity was 0.779 (Figure 3).

**Figure 1** Comparison of serum S100β among PD with depression group, PD without depression group and normal control group.

**Note:** \*\*\*\* $p < 0.001$ .



**Figure 2** Correlation analysis of serum S100 $\beta$  levels according to UPDRS-III score (a), Hoehn and Yahr stage (b) and HAMD-17 score (c), and HAMD-17 score according to UPDRS-III score (d), Hoehn and Yahr stage (e) and Gender (f) in PD patients with depression. Gender 1 for male, 2 for female.

**Abbreviations:** UPDRS-III, Unified Parkinson's Disease Rating Scale Part-III; HAMD-17, 17-item Hamilton Rating Scale for Depression;  $r$ , Pearson's correlation coefficient,  $r_s$ , Spearman's rank correlation coefficient;  $P$ , level of significance of  $r$  or  $r_s$ .

## Discussion

In this study, we collected clinical data from 145 PD patients and 60 healthy controls, and analyzed the relationship between serum S100 $\beta$  levels and the results of clinical evaluation. The results showed that: (1) Serum S100 $\beta$  levels in PD with depression were significantly higher than that in PD without depression group and the control group. (2) Serum S100 $\beta$  levels in PD with depression group were positively correlated with UPDRS-III, H-Y scale and HAMD-17 scores. (3) Elevated serum S100 $\beta$  levels and UPDRS-III scores were independent risk factors for PD with depression. Serum S100 $\beta$  level has a high efficacy in distinguishing PD with depression and PD without depression.

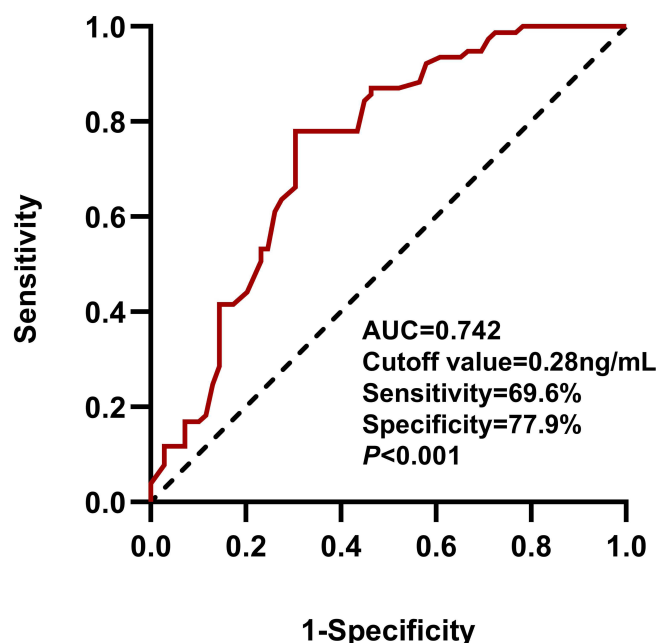
Consistent with previous studies,<sup>23</sup> we found that serum S100 $\beta$  levels in PD patients were higher than those in healthy controls, suggesting that S100 $\beta$  may play a role in the pathogenesis of PD. Human autopsy studies<sup>24</sup> also showed that compared with the control controls, the levels of S100 $\beta$  in substantia nigra and cerebrospinal fluid of PD patients

**Table 2** Multiple Linear Regression Analysis Result of HAMD-17 as the Dependent Variable

Independent Variable	Unstandardized Coefficients (B)	Standard Error (SE)	Standardized Regression Coefficient ( $\beta$ )	t value	p-value
Constant term	10.414	0.825	—	12.627	< 0.001*
S100 $\beta$ (ng/mL)	3.696	1.172	0.288	3.153	0.002*
UPDRS-III	0.214	0.034	0.640	6.245	< 0.001*

**Note:** \*Significant at  $p < 0.05$ .

**Abbreviations:** HAMD-17, 17-item Hamilton Rating Scale for Depression; UPDRS-III, Unified Parkinson's Disease Rating Scale part-III.



**Figure 3** ROC to evaluate the ability of serum S100 $\beta$  levels to differentiate PD patients with depression from PD without depression.

**Abbreviations:** ROC, Receiver operating characteristic curve; AUC, area under curve.

increased, and S100 $\beta$  may be a new mediator of PD neurodegeneration. The activation of astrocytes in PD patients will promote the release of S100 $\beta$ . S100 $\beta$  binds to advanced glycation end products (RAGE) and triggers the activation of downstream factors, leading to neuroinflammation amplification, oxidative damage and neurotransmitter metabolism disorder. The interaction with dopamine D2 receptor affects dopamine metabolism, which is a potential mechanism of PD pathogenesis.<sup>25–27</sup>

At the same time, we also found that serum S100 $\beta$  levels in PD patients with depression were significantly higher than that in PD patients without depression. The serum S100 $\beta$  level in PD patients with depression was significantly positively correlated with HAMD-17 score, indicating that S100 $\beta$  may play an essential role in the occurrence and development of PD depression. Studies<sup>28</sup> have shown that depression is related to the density of glial cells in the prefrontal cortex. The increase of S100 $\beta$  observed in this study may be closely related to the activation of astrocytes. The binding of extracellular 5-HT to 5-HT1A receptor on astrocytes in patients with depression can also cause S100 $\beta$  release.<sup>15</sup> In addition, this study showed that compared with PD patients without depression, PD patients with depression have higher motor symptoms and disease severity scores. UPDRS-III score was an independent risk factor for PD with depression. It is considered that there may be a common pathological basis with PD motor symptoms and depression. With the decline of motor dysfunction and the progressive decline of patients' daily living ability, they lose confidence in disease control and further aggravate depression. It may also be that depression has a greater impact on the motor symptoms of PD patients. In addition to the strong correlation in the correlation analysis of PD with depression, serum S100 $\beta$  also showed high sensitivity and specificity in distinguishing PD with depression from PD without depression. Therefore, serum S100 $\beta$  may be an effective biomarker for PD with depression.

In a previous study, Benitez et al<sup>29</sup> who found that S100 $\beta$  levels of participants with reported history of depression were higher than for those without such a history. In our study, the control group did not include patients with a history of reported depression. Therefore, it was not possible to verify the results of the previous study. In future studies, we will consider including such a population to further explore the relationship between S100 $\beta$  and depression. Riedel et al<sup>30</sup> found that women are more prone to depression than men, and the probability of depression in female PD patients is 1.3 times that of men. In our study, we did not find significant gender differences in the incidence of PD depression. However, the HAMD-17 score of PD patients with depression was correlated with women, but the correlation was not

strong. And women were not independent risk factors for PD depression. Further research is needed to explore the relationship between PD depression and gender.

However, the exact mechanism underlying the relationship between S100 $\beta$  and depression in PD is unclear. It may be related to the influence of the 5-HT function.<sup>31</sup> The disorder of 5-HT and norepinephrine signaling pathways in the brain is considered to be related to the pathophysiology of various psychiatric disorders.<sup>32</sup> 5-HT plays an essential role in the regulation of depression. However, S100 $\beta$  is the main neurotrophic factor of 5-HT neurons at physiological concentration, while elevated concentration will produce cytotoxic.<sup>33</sup> The binding of extracellular 5-HT to 5-HT1A receptor on astrocytes can trigger the release of S100 $\beta$ . Another possible explanation is based on the pathological mechanism of PD. It is currently believed that in addition to the metabolic imbalance of dopamine and acetylcholine in the brain of patients with Parkinson's disease, there is still a decrease in 5-HT.<sup>34</sup> The pathological changes of PD, that is, the aggregation of  $\alpha$ -synuclein, can activate astrocytes, increase the synthesis and secretion of S100 $\beta$ , and enter the blood through the damaged blood-brain barrier, eventually increasing the level of S100 $\beta$  protein in the blood. As an inflammatory factor, S100 $\beta$  can increase the release of pro-inflammatory cytokines by activating NF- $\kappa$ B and p38 MAPK, leading to neuroinflammation amplification, oxidative damage and neurotransmitter metabolism disorder, thus affecting the level of 5-HT and leading to depression.<sup>35</sup> In addition, the loss of dopaminergic neurons in the ventral tegmental area was found to be associated with depression in PD patients. We believe that the relationship between S100 $\beta$  and depression in PD patients deserves further study.

Chronic neuroinflammation is one of the characteristics of PD and may be involved in the beginning and progression of the disease. Considering that S100 $\beta$  is also elevated in other acute inflammatory diseases, this study also analyzed the levels of infection-related indicators such as neutrophil ratio and hs-CRP in each group of patients, and the results did not show significant differences (Table 1). At the same time, combined with the patient's clinical manifestations and other auxiliary examinations, the impact of other acute infectious diseases on the results of this study was excluded.

This study explored the clinical characteristics of PD patients with depression and its relationship with serum S100 $\beta$  levels, but there are still some limitations: First, our clinical data lack some information, such as employment information, family history and other data, which may also affect the depression of PD patients. Second, the sample size is relatively modest, and larger sample size studies are still needed in the future to further verify our results. Third, our study was entirely Han Chinese and lacked ethnic diversity. Fourth, this study is a cross-sectional study. In the future, longitudinal studies are still needed to determine whether serum S100 $\beta$  can be used as an effective biomarker for PD with depression.

## Conclusion

Elevated serum S100 $\beta$  level is an independent risk factors for PD with depression. Serum S100 $\beta$  is expected to be a biomarker for PD with depression. The detection of serum S100 $\beta$  level may be helpful for the early identification of PD with depression.

## Abbreviations

PD, Parkinson's disease; S100 $\beta$ , S100 calcium-binding protein, beta chain; UPDRS-III, part III of the Unified Parkinson Disease Rating Scale-III; H-Y, Hoehn-Yahr; HAMD-17, 17-item Hamilton Rating Scale for Depression; ROC, receiver operating characteristic; AUC, area under the ROC curve; MMSE, Mini-Mental State Examination; BMI, Body Mass Index; hs-CRP, high-sensitivity C-reactive protein; 5-HT, 5-hydroxytryptamine.

## Ethics Approval and Consent to Participate

The studies involving human participants were reviewed and approved by the Human Ethics Committees of The Affiliated Huai'an Hospital of Xuzhou Medical University. Informed consent was obtained for experimentation with human subjects. Every individual was informed about the aims of the study and provided written consent before participation. Written Informed consent was obtained from healthy controls and from the legal guardian/next of kin for Parkinson's Disease patients. All methods were carried out in accordance with relevant guidelines and regulations/Declaration of Helsinki.

## Author Contributions

Rui Chen and Ying Zhao are co-corresponding authors. All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

## Disclosure

The authors declare that they have no conflict of interest.

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