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Relationship between TIM3 Expression on Peripheral T Lymphocytes and Post-Stroke Depression

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ABSTRACT

Background: T cell immunoglobulin and mucin domain-containing protein 3 (TIM3) is a regulatory molecule expressed on a variety of cell types, including $CD3^+$ T cells. Few studies have been conducted to look into the correlation between TIM3 expression on peripheral T lymphocytes and post-stroke depression (PSD).

Objective: To investigate the relationship between TIM3 expressions on peripheral T lymphocytes in PSD patients.

Methods: Acute stroke patients without depression (NPSD) (n=65), PSD patients (n=23), and body mass index (BMI), age, and education-matched healthy controls (HC) (n=59) were enrolled. Using flow cytometry, TIM3 expression was examined in the peripheral $CD3^+CD4^+$ and $CD3^+CD8^+$ T lymphocytes. Evaluation of the depressive severity in PSD patients was assessed using a 17-item Hamilton Depression Rating Scale (HAM-D-17). We used enzyme-linked immunosorbent assay (ELISA) to determine the serum concentrations of IL-1β, IL-6, IL-10, and IL-18. We further assessed the relationships between TIM3 expression, serum cytokine levels, and the HAM-D-17 scores.

Results: $CD3^+CD4^+$ T cells reduced significantly in PSD patients compared with the NPSD patients and HC. Both NPSD patients and PSD patients had a significant increase in TIM3 expression in their peripheral $CD3^+CD4^+$ T lymphocytes, compared with HC. In PSD patients, a higher frequency of peripheral $CD3^+CD8^+$ T lymphocytes showed significant expression of TIM3 compared to NPSD patients and HC. High TIM3 level on peripheral $CD3^+CD8^+$ T lymphocytes was positively associated with the HAM-D score.

Conclusion: Patients with PSD exhibit immune dysfunction. TIM3 might contribute to the development and severity of PSD, making it a potential therapeutic target.

Keywords: Interleukin, Mucin Domain-Containing Protein 3, Post-Stroke Depression, Therapeutic Target, T Lymphocyte

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INTRODUCTION

Approximately 30% of stroke victims suffer from PSD, the most common neuropsychiatric complication, and it may lead to high mortality, poor recovery, serious cognitive impairment, and low quality of life, in addition, more than half of PSD patients are neither diagnosed nor treated (1). Risk factors of PSD include pre-stroke risk factors (such as higher neuroticism, psychological disorders-ridden family history, and female), risk factors for strokes (such as anterior/frontal strokes, basal ganglia strokes, and large and/or multiple strokes), and post-stroke risk factors (such as social isolation, disabilities of greater severity, pervasive white matter damage, the first year after stroke) (2). However, the pathophysiological mechanisms implicated in PSD are very complex and still poorly understood currently. The main pathophysiology of PSD involves reduced monoamine level, aberrant neurotrophic response to stroke, glutamate-mediated excitotoxicity, inflammatory response to the hypothalamic-pituitary-adrenal axis (HPA) dysfunction, imbalanced immunomodulation, among which a crucial role is played by an aberrant immune-inflammatory reaction in both the occurrence and development of PSD (3, 4).

Peripheral T cells can function as nerve monitors and repairmen in the brain after crossing the blood-brain barrier (5, 6). Besides, T cells can affect cellular and neuroendocrine functions by inducing the secretion of neurotrophic factors and cellular substances, which goes hand in hand with the prevalence and development of PSD. Whether T lymphocytes are beneficial or deleterious to PSD and whether they may affect different stages of PSD are still controversial. Therefore, investigating the T lymphocytes' role in PSD is extremely important for diagnosis in a timely manner and appropriate treatment of PSD.

TIM3, an immunomodulatory protein in the TIM family, is involved in a module composed of various co-inhibitory receptors that are expressed and regulated together on T cells that are dysfunctional or 'exhausted' in situations such as cancer and chronic viral infection. With a wide range of immune cells, TIM3 is expressed predominantly by $CD4^+$ and $CD8^+$ T lymphocytes that produce interferon-γ, dendritic cells, natural killer cells, macrophages, myeloid cells, and mast cells (7). TIM3 is able to function as an inhibitory receptor to induce T cell dysfunction in immune response, negatively regulating adaptive immune response and inducing peripheral immune tolerance. In addition, TIM3 is linked to functional disturbance of $CD8^+$ lymphocytes and disruption of immune homeostasis, leading to depression. LAG3 is another inhibitory checkpoint that negatively regulates the proliferation, activation, and homeostasis of T cells, and is also closely related to depression (8). There were a few studies, nevertheless, conducted to observe the relationship between TIM3 expression and PSD. This study's objective was to nail down the connection between TIM3 expression in peripheral T lymphocytes and PSD, which may shed light on TIM3's role in PSD.

MATERIALS AND METHODS

Study Population

In total, 88 patients who suffered from initial acute ischemic stroke (AIS) were enrolled in this study between September 2020 and February 2022. AIS was diagnosed according to the medical history and findings from neurological examinations, and confirmed by imaging with magnetic resonance or computerized tomography. One month after the stroke onset, AIS patients followed up in total. Experienced psychologists gauged depression symptoms with the HAM-D-17. According to the criteria from the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), the HAM-D score was greater than or equal to 7 in PSD's case. Among the 88 patients, 23 received PSD diagnosis, the remaining 65 were diagnosed with AIS alone (without depression; NPSD).

In addition, 59 individuals who received routine physical examinations during the same period were recruited as the healthy controls (HC). The followings were the criteria for the exclusion of all study subjects: intracranial hemorrhage history, severe acute infection, transient ischemic attack, surgery or trauma within 6 months, psychiatric or emotional disorders, dementia, Parkinson's disease, hematological disorders, malignancy, autoimmune disorders, chronic viral infection, and human immunodeficiency virus infection. The research plan (NO. 2020-K-120-01) was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang Chinese Medical University, and informed consent was obtained before the study.

Sample Collection, Flow Cytometry and Interleukin Measurement

Blood samples were collected from the periphery venous system in EDTA-containing tubes and CAT Serum Separation Clot Activator respectively within 24 h. after admission. Anticoagulated blood was processed for the flow cytometry, and pro-coagulant serum was processed for interleukin detection. The antibody mixture was prepared with APC-Cy7 anti-human CD3, BV510 anti-human CD4, PE-Cy7 anti-human CD8, and BB515 anti-human TIM3 (Clone: 7D3, BD Pharmingen, USA) in PBS at a volume ratio of 1:1:1:2 in compliance with the manufacturer's guidelines. Then, at 4°C in dark the antibodies solution was applied for 30 min. to 100 µl of whole blood, followed by red blood cell lysis using FACS lysis solution. After rinsing with PBS, TIM3 expression in T leukomonocytes was determined by the flow cytometric analysis. Serum contents of IL-1β, IL-6, IL-10, and IL-18 were detected by ELISA based on the reagent kit's instructions.

Statistical Analysis

Statistical analysis was engaged using SPSS version 25.0 and GraphPad Prism 8.0. One-way ANOVA was used to compare variables characterized as normal distribution by expressing mean±standard deviation (SD); when variables lacking normal distribution were represented as medians with interquartile ranges, then the Kruskal-Wallis H test was employed to evaluate the data. Categorical variables were represented as frequencies or percentages, and then the Chi-square test was applied to analyze the results. The correlations of the HAM-D score and interleukin contents with TIM3 expression were analyzed through the Spearman correlation analysis. *P*-values less than 0.05 were considered statistically significant.

RESULTS

Characteristics of Subjects in the Study

The average age was 60.11±5.96 years, 61.17±3.35 years, and 58.73±5.36 years in the NPSD, PSD, and HC groups respectively. The NPSD, PSD, and HC groups each had a BMI of 23.85±2.16 kg/m^2, 24.33±2.14 kg/m^2, and 23.42±2.10 kg/m^2 respectively. Age, BMI, and education level among the three groups did not differ significantly; however, the PSD patients had a higher proportion of females than the NPSD and HC groups (Table 1).

Peripheral T Lymphocytes in PSD Patients

To investigate the T lymphocytes'

Table 1. Baseline demographics of subjects in this study

Variables	NPSD (n=65)	PSD (n=23)	HC (n=59)	*P*
Male, % (n)	56.9% (37)	34.8% (8)	55.9% (33)	0.1596
Age, years	60.11±5.96	61.17±3.35	58.73±5.36	0.1389
BMI, kg/m^2	23.85±2.16	24.23±2.14	23.42±2.10	0.2648
Education, years	13.83±3.58	13.26±4.34	15.10±4.01	0.0817

BMI, Body Mass Index; NPSD, acute ischemic stroke without depression; PSD, post-stroke depression; HC, the healthy controls

immune status in PSD, total $CD3^+$, $CD3^+CD4^+$, and $CD3^+CD8^+$ T lymphocytes from periphery blood were counted among the three groups by the flow cytometry. Results showed total $CD3^+$ T cell count was significantly lower in the PSD patients (64.09±8.28% $CD45^+$ cells) compared with the HC (69.93±9.04% $CD45^+$ cells). However, there was no marked difference in the $CD3^+$ T cell count between the NPSD patients (66.78±9.29 %$CD45^+$ cells) and the HC (Fig. 1A). The $CD3^+CD4^+$ T cell count in the PSD group (43.92±7.06% $CD3^+$ cells) was lower than in the NPSD group (48.60±8.13% $CD3^+$ cells) and the HC group (50.10±8.60% $CD3^+$ cells) (Fig. 1B). In addition, $CD3^+CD8^+$ T cell count was significantly higher in the NPSD group (26.49±7.75% $CD3^+$ cells) and PSD group (29.94±6.40% $CD3^+$ cells) than in the HC group (23.25±6.76% $CD3^+$ cells); $CD3^+CD8^+$ T cell count in the PSD group was higher than in the NPSD group (Fig. 1C). $CD3^+CD4^+$ T lymphocytes were found to reduce, whereas $CD3^+CD8^+$ T lymphocytes elevated in the PSD patients, as indicated by these findings.

TIM3 Expression of Peripheral $CD4^+$ and $CD8^+$ T Lymphocytes in PSD

TIM3 Levels in periphery blood's $CD3^+CD4^+$ and $CD3^+CD8^+$ T lymphocytes were detected by means of the flow cytometric technique in three groups (Fig. 2). The results showed the percentage of TIM3-positive T leukomonocytes among peripheral $CD3^+CD4^+$ T lymphocytes in the NPSD patients and PSD patients was 9.01±3.38% and 8.97±2.71%, respectively, but it was 6.06±2.20% in the HC group. The NPSD and PSD patients had a greater proportion of TIM3-positive $CD3^+CD4^+$ T lymphocytes than in the HC. However, no significant difference

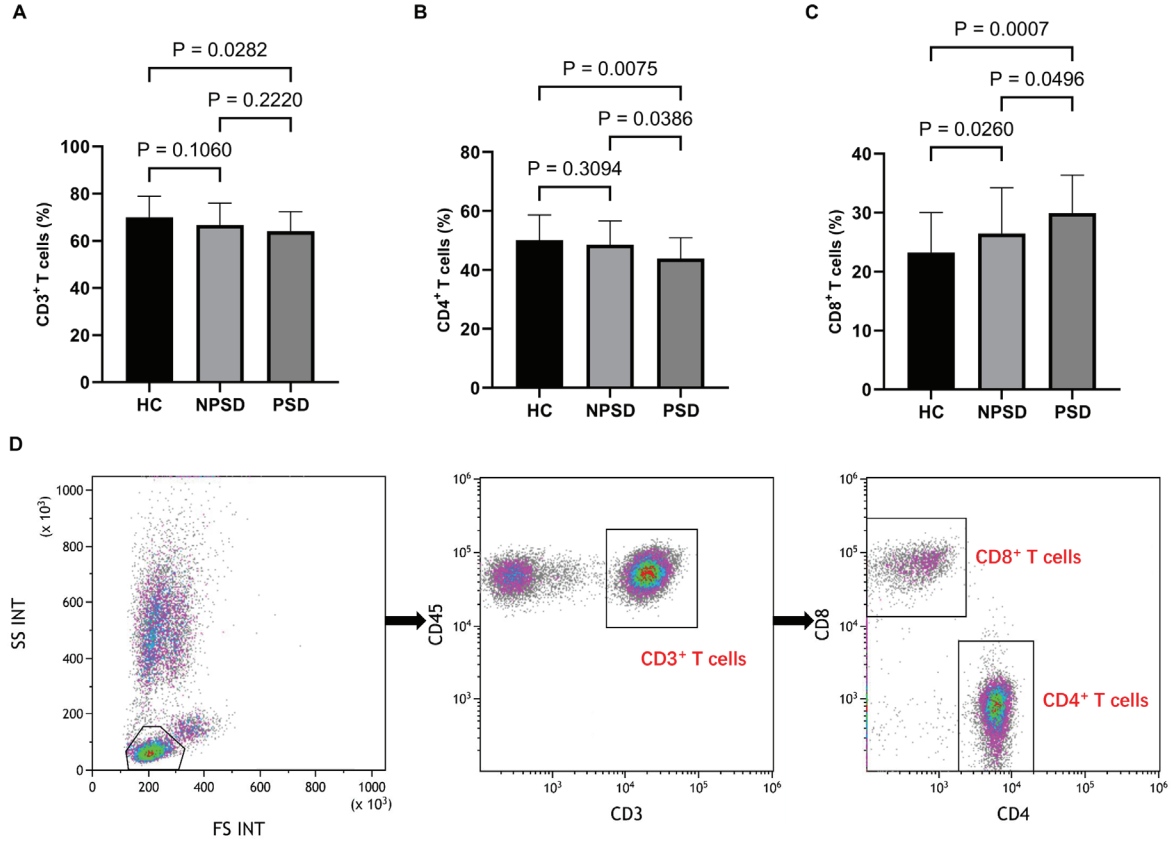

Fig. 1. Amounts of peripheral T cells in HC, NPSD patients and PSD patients. A Counts of $CD3^+$ T cells in HC, NPSD patients and PSD patients. B Counts of $CD4^+$ T cells in HC, NPSD patients and PSD patients. C Counts of $CD8^+$ T cells in HC, NPSD patients and PSD patients. D Amounts of $CD3^+$, $CD4^+$, and $CD8^+$ T cells in peripheral blood (the flow cytometry). NPSD, acute ischemic stroke without depression; PSD, post-stroke depression; HC, the healthy controls

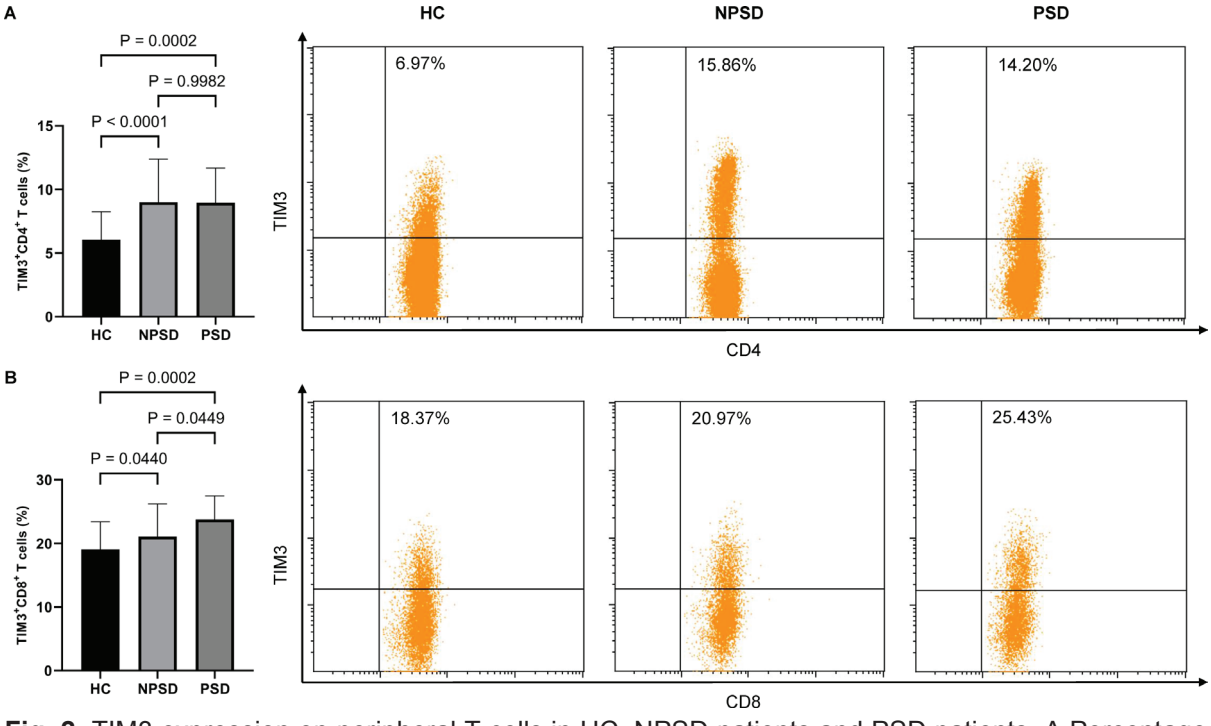

Fig. 2. TIM3 expression on peripheral T cells in HC, NPSD patients and PSD patients. A Percentage of TIM3-positive $CD4^+$ T cells in HC, NPSD patients and PSD patients. B Percentage of TIM3-positive $CD8^+$ T cells in HC, NPSD patients and PSD patients. TIM3, T cell immunoglobulin and mucin domain-containing protein 3; NPSD, acute ischemic stroke without depression; PSD, post-stroke depression; HC, the healthy controls

was observed between the NPSD patients and the PSD patients in the proportion of TIM3-positive $CD3^+CD4^+$ T cells. The percentage of TIM3-positive $CD3^+CD8^+$ T cells in the PSD patients (23.78±3.68%) was higher than in the NPSD patients (21.08±5.10%) and the HC (19.08±4.34%). Moreover, TIM3 expression on $CD3^+CD8^+$ cells was evaluated by mean fluorescence intensity (MFI) among the groups. The results showed the proportion of TIM3 positive $CD3^+CD8^+$ T leukomonocytes increased obviously in the PSD patients (Fig. 3). These results indicated that TIM3 expression may be involved in T lymphocyte dysfunction in PSD.

Serum Contents of Interleukins in Patients with PSD

To investigate the changes in immune-related inflammatory factors after stroke, the serum interleukin contents including IL-10, IL-1β, IL-6, and IL-18 were tested by ELISA. As shown in Table 2, the NPSD and PSD patients had a visibly greater

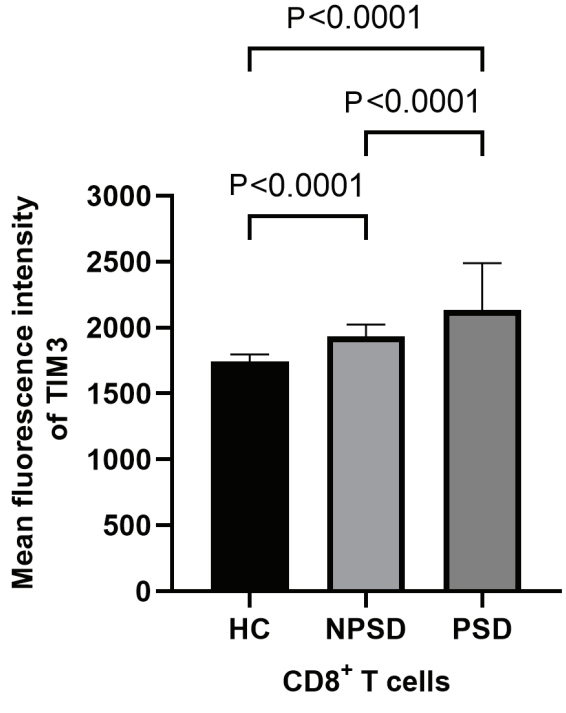

Fig. 3. MFI of TIM3 expression on $CD8^+$ T cells among the three groups. MFI, Mean fluorescence intensity; TIM3, T cell immunoglobulin and mucin domain-containing protein 3; NPSD, acute ischemic stroke without depression; PSD, post-stroke depression; HC, the healthy controls

Table 2. Serum interleukin contents in three groups (pg/mL)

Interleukins	HC (n=59)	NPSD (n=65)	PSD (n=23)
IL-1β	2.44±1.14	3.23±1.57	4.05±1.61
IL-6	7.01±3.07	12.68±3.27	13.96±3.18
IL-10	1.61 (0.82-2.32)	0.97 (0.69-1.65)	0.68 (0.58-1.01)
IL-18	142.5 (103.3-150.4)	223.9 (197.9-252.7)	279.6 (262.6-303.9)

IL-1β, Interleukin-1 beta; NPSD, acute ischemic stroke without depression; PSD, post-stroke depression; HC, the healthy controls

amount of IL-1β than the HC. Additionally, the PSD patients had a greater amount of IL-1β than the NPSD patients (Fig. 4A). The IL-6 content in the NPSD patients and PSD patients was markedly higher than in the HC, but patients with NPSD and PSD did not differ significantly (Fig. 4B). In the PSD patients, a lower serum IL-10 level was observed in comparison with the NPSD patients, and the HC had a lower IL-10 content compared with the NPSD patients (Fig. 4C). Furthermore, serum IL-18 content increased in HC, NPSD patients, and PSD patients sequentially (Fig. 4D). These findings point to the involvement of activated peripheral immuno-inflammatory in the PSD pathogenesis.

TIM3 Expression and PSD Relationship

To investigate the correlation between the TIM3 expression of peripheral $CD3^+CD8^+$ T lymphocytes and PSD, PSD patients were grouped according to the HAM-D score. In the present study, only 3 patients had the

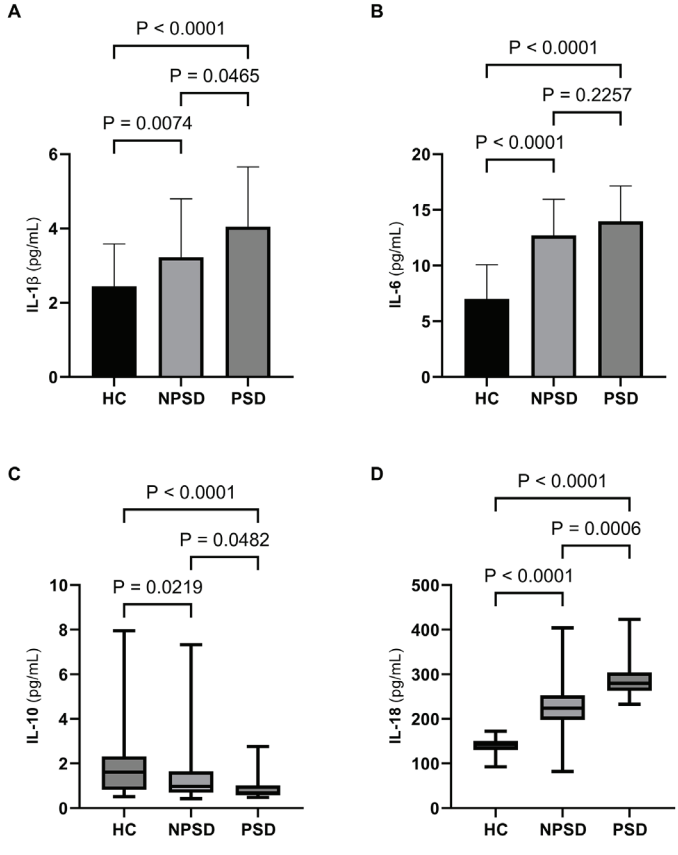

Fig. 4. Serum interleukin contents in HC, NPSD patients and PSD patients. A IL-1β content in HC, NPSD patients and PSD patients. B IL-6 content in HC, NPSD patients and PSD patients. C IL-10 content in HC, NPSD patients and PSD patients. D IL-18 content in HC, NPSD patients and PSD patients. IL, Interleukin; NPSD, acute ischemic stroke without depression; PSD, post-stroke depression; HC, the healthy controls

Table 3. Data comparison between the mild and severe PSD patients

Variables	Mild (n=13)	Severe (n=10)	*P*
$TIM3^+$ $CD8^+$, %	21.63±2.45	26.56±3.14	0.0004
IL-1β, pg/mL	3.87±1.64	4.28±1.62	0.5571
IL-10, pg/mL	1.19±0.65	0.57±0.08	0.0067
IL-18, pg/mL	276.1±24.36	313.5±52.56	0.0330

TIM3, T cell immunoglobulin and mucin domain-containing protein 3; IL-1β, Interleukin-1 beta; PSD, post-stroke depression

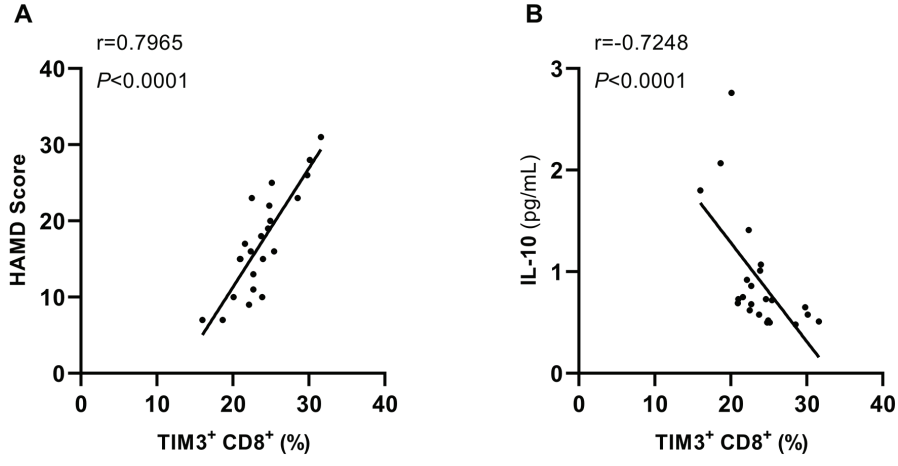

Fig. 5. Correlation of TIM3 expression on $CD8^+$ T cells with the HAM-D scores and serum IL-10 content. A TIM3 expression positively correlated with the HAM-D score. B TIM3 level negatively correlated with serum IL-10 content. The HAM-D, Hamilton Depression Rating Scale; IL, Interleukin; TIM3, T cell immunoglobulin and mucin domain-containing protein 3

HAM-D score ≥24; 7 had the HAM-D score higher than 17, but lower than 24; 13 had the HAM-D scores higher than 7 but lower than 17. Then, 23 PSD patients were divided into a mild PSD group (7≤ HAM-D score <17) and a severe PSD group (the HAM-D score ≥17). As shown in Table 3, significant differences were observed in the TIM3 content and serum contents of IL-1β, IL-10, and IL-18 between the mild PSD group and the severe PSD group. Further analysis showed the TIM3 expression on $CD3^+CD8^+$ lympohcytes was positively correlated with the HAM-D score with the r-value of 0.7965 and *p*-value below 0.0001 (Fig. 5A). The correlation of theTIM3 expression with serum interleukin contents was further assessed. As shown in Fig. 4, the TIM3 expression negatively related to serum IL-10 content with an r-value of -0.7248 and a *p*-value below 0.0001 (Fig. 5B). However, the TIM3 expression and IL-18 content were not associated with the r-value being 0.3034 and *p*-value being 0.1580. These findings revealed that the progression of PSD is linked to $CD3^+CD8^+$ T lymphocytes expressing TIM3.

DISCUSSION

Sustained activation of the immune system after stroke is across post-stroke stages due to immune inflammation of the cross-regulation of the peripheral and central nervous systems, temporally and spatially (9). The excessive neuroimmune responses in the CNS may recruit a large amount of periphery immune cells into the injured site, which disrupt the homeostasis of peripheral immunity in turn, leading to immune dysfunction following stroke, although there are relatively a few lymphocytes infiltrating into the CNS, unlike innate immune cells. In general, $CD3^+CD4^+$ T cells tend to transiently increase in the acute phase of stroke and then fluctuate down,

while the changes in $CD3^+$ T lymphocytes and $CD3^+CD8^+$ T lymphocytes are complicated and controversial in different phases of stroke (10, 11). In the peripheral blood of PSD patients soon after admission, $CD3^+CD8^+$ T cells increased while total $CD3^+$ and $CD3^+CD4^+$ T cells decreased compared with the HC as shown in our results. The change in the quantity of peripheral lymphocytes not only contributes to the immune inflammation, but also some of their subsets are related to the outcomes and complications after stroke such as PSD (12). Furthermore, the dysfunction of peripheral T lymphocytes, mainly including $CD3^+CD4^+$ T cells secreting complex immune cytokines and $CD3^+CD8^+$ T cells with cytotoxic capability, is the main cause of mental disorder (13-15). Different disease-associated depressions exhibit unique immune abnormalities. Compared with the controls, healthy postpartum women have significantly more $CD3^+$ T lymphocytes, as well as $CD3^+CD4^+$ and $CD3^+CD8^+$ T lymphocytes reportedly, but not in postpartum depression women. In the postpartum depression women, by contrast, the amounts of Th1 and Th17 leukomonocytes reduced. In the postpartum period, T-cell activity is enhanced in healthy women, but the T cell activity remains unchanged in postpartum depression women (16). Psoriasis and depression have the same neuro-dermatological association reportedly along with elevated $CD3^+CD4^+$ and $CD3^+CD8^+$ lymphocyte levels (17). Our findings indicated that immune inflammation plays a significant role in the pathophysiology of PSD.

The causes of peripheral T lymphocyte dysregulation in PSD are complex and remain poorly understood. The expression of TIM3, acting as a 'co-inhibitory' or 'checkpoint' receptor, may regulate lymphocytic function in mood disorders, thereby regulating the adaptive immune system (18, 19). Chronic antigen stimulation leads to T cell dysfunction, called T cell exhaustion, and TIM3, similar to CTLA4 and PD1, is a novel marker for it. TIM3 is a novel marker of T cell exhaustion which refers to T cell dysfunction caused by chronic antigen stimulation, and high expression of TIM3 may disrupt T cell activation (20). Currently, studies on T cell exhaustion focus mainly on tumor immunity, immunity after virus infection, and autoimmunity. In general, TIM3 inhibits Th1 and Th17 immune reactions, attenuates the cytotoxic effect of $CD3^+CD8^+$ T lymphocytes, and enhances the inhibitory effect of Treg cells, negatively regulating adaptive immune responses. However, there is evidence showing that reactive oxygen species may be produced more easily when TIM3 is highly expressed, which may enhance innate immunity to kill pathogens during pregnancy (21). TIM3 on antigen-presenting cells may induce monocytes and dendritic cells to secrete pro-inflammatory cytokines (TNF-α) (22). Of note, the specific mechanisms underlying the effect of TIM3 on T cell activity remain to be elucidated. It has been revealed that peripheral $CD16^+CD56^+$ NK cells and $CD4^+CD25^+$ Treg cells decrease along with raised TIM3 expression on CD4 cells in depression patients in contrast to the healthy controls (23). In addition, the percentage of $CD3^+CD8^+$ T lymphocytes significantly reduced with marked increased TIM3 expression, whereas the amount of $CD16^+CD56^+$ NK cells remained unchanged in bipolar II disorder depression patients compared with the major depression patients and the healthy controls (24). Our study showed that both $CD3^+CD4^+$ and $CD3^+CD8^+$ T leukomonocytes of PSD and NPSD patients had elevated TIM3 expression in comparison with the HC. However, in PSD patients, there was a significant increase in the expression of TIM3 on $CD3^+CD8^+$ T cells compared with the NPSD patients. This implies that the immune modulation becomes abnormal in PSD patients. Interestingly, contrary to most previous findings, the proportion of cytotoxic T lymphocytes in depression patients' blood decreased along with increased TIM3 expression on cytotoxic T lymphocytes, the proportion of $CD3^+CD8^+$ cells and TIM3 level

on it in PSD patients were simultaneously higher than in the NPSD patients and HC of the present study. Mature T cell apoptosis could be induced, in several reports, through elevated TIM3 expression, which causes a decreased number of T cells (25). We speculate that the decreased $CD3^+CD4^+$ leukomonocytes and increased $CD3^+CD8^+$ leukomonocytes are ascribed to the increased TIM3 level and subsequent dysregulation of the immune inflammatory response.

The pathogenesis of PSD has not yet been thoroughly clarified to date. The pathogenesis of depression is also influenced by some inflammatory-related cytokines such as IL-1β, IL-6, IL-10, and IL-18, implicated in stroke (26, 27). The inflammatory-related cytokines' role in the pathogenesis of depression is complex and still controversial (28). Therefore, serum levels of IL-1β, IL-6, IL-10, and IL-18 were detected in the HC, PSD patients, and NPSD patients. Our results showed the serum contents of IL-1β, IL-6, and IL-18 significantly increased, but the PSD patients had a noticeable decreased IL-10 content in contrast with the HC. In addition, significant differences were observed in the concentration of IL-1β, IL-10, and IL-18 (but not IL-6 level) between the PSD patients and the NPSD ones.

It has been reported that IL-1β may reduce the concentration of 5-hydroxytryptamine (5-TH) by acting on the Bcl-2 protein, boosting the HPA axis effect to promote the development of depression (29, 30). $CD8^+$ T cells can also synthesize 5-HT and enhance their activity by binding to 5-HT receptors on their surfaces (31). However, T cells with high TIM3 expression have elevated expression of MAO-A, a flavoenzyme that degrades amine neurotransmitters including 5-HT, and negatively regulates T cell function (32). TIM3 deletion increased antitumor immunity, but blocking either inflammasomes or the downstream effectors reversed that protection according to Dixon et al. (33). Furthermore, monoamines have been reported to be important mood-relevant neurotransmitters, and IL-1β, IL-6, and IFN-α are involved in monoamine synthesis and reuptake (34). IL-6 is a potent stimulator of the HPA axis and contributes to HPA dysregulation in depressed patients. Depressed patients have higher levels of serum IL-18 than the healthy individuals, and depressive symptoms are positively correlated with serum IL-18 levels (35). In addition, IL-18 may facilitate tryptophan metabolism which reduces serotonin availability and increases neurotoxic metabolites via the kynurenine pathway, conversely, up-regulates indoleamine 2,3-dioxygenase expression (36). This study has reported that reduced serotonin is positively correlated with PSD (37). As well as its role in AIS pathophysiology, IL-10 is also associated with mood disorders (38). According to reports, predicting PSD may be possible with a lower IL-10 level (39). The protective effect of increased B cells after stroke was found to be mediated by IL-10, and depletion of B cells delayed the recovery of motor function, adversely affected spatial memory, and promoted anxiety in a post-stroke study. The relationship of TIM3 expression with IL-1β, IL-10, and IL-18 in PSD patients remains to be elucidated. Our results showed serum contents of IL-10 and IL-18 (but not IL-1β) were associated with the severity of the PSD. Moreover, serum contents of IL-18 and IL-10 were both positively and negatively related to the TIM3 expression on CD8+ T cells, respectively. These findings indicate the intimate relationship between the dysfunction of $CD8^+$ T cells induced by TIM3 and IL-10 levels.

Studies have reported that TIM3 is connected to poor prognosis in cancer patients. Nevertheless, the relationship between TIM3 expression and the outcomes of PSD has been explored in a few studies. In our study, depression severity was estimated by employing the HAM-D-17, and the association of the HAM-D-17 score with TIM3 was further evaluated. Our results showed that TIM3 expression on $CD3^+CD8^+$ T cells was positively associated with the HAM-D score. A critical role for $CD3^+CD8^+$

T cell's dysfunction in PSD development is demonstrated by these findings, and TIM3 could become a prognostic marker of PSD. However, more studies are warranted to confirm our findings.

CONCLUSION

Our results indicate that TIM3 is involved in PSD pathophysiology and therapy targeting TIM3 may become a viable option for preventing and treating PSD. However, there were still limitations in the presented study. Firstly, the study began with a single center and a small sample size. Secondly, cytokines secreted by T lymphocytes play a significant role in immune regulation, but the specific mechanism was not deeply discussed in this study. Ultimately, the molecular mechanism underlying TIM3's involvement in PSD is still unknown, and it is necessary to conduct more research to elucidate the potential mechanism by which TIM3 contributes to PSD.

AUTHORS' CONTRIBUTIONS

QM and PZ performed the experiment and drafted the manuscript; ZS, WQ, YX, TC, and XL performed the experiment; ZZ, SX, and ZS analyzed the data; QM and ZZ revised the manuscript; ZS and ZZ proposed research ideas and designed experiments. Manuscript approval was obtained from all the authors.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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