

## RESEARCH ARTICLE

# Blood Th17 cells and IL-17A as candidate biomarkers estimating the progression of cognitive impairment in stroke patients

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**Abstract**

**Background:** T helper (Th) cells regulate immunity and inflammation to engage in cognitive impairment in several neurological diseases, while their clinical relevance in stroke patients is not clear. The current study intended to assess the relationship of Th1 cells, Th17 cells, interferon-gamma (IFN- $\gamma$ ), and interleukin (IL)-17A with cognitive function in stroke patients.

**Methods:** One hundred twenty stroke patients and 40 controls were enrolled in this multicenter study. Th1 and Th17 cells in peripheral blood were assessed by flow cytometry; meanwhile, IFN- $\gamma$  and IL-17A in serum were detected by enzyme-linked immunosorbent assay. Cognitive function of stroke patients was evaluated by Mini-Mental State Examination (MMSE) score at enrollment (baseline), year 1, year 2, and year 3.

**Results:** Th1 cells ( $p = 0.037$ ) and IFN- $\gamma$  ( $p = 0.048$ ) were slightly increased, while Th17 cells ( $p < 0.001$ ) and IL-17A ( $p < 0.001$ ) were greatly elevated in stroke patients compared with controls. Th17 cells ( $r_s = -0.374$ ,  $p < 0.001$ ) and IL-17A ( $r_s = -0.267$ ,  $p = 0.003$ ) were negatively correlated with MMSE score at baseline, but Th1 cells and IFN- $\gamma$  were not. Meanwhile, Th17 cells ( $p = 0.001$ ) and IL-17A ( $p = 0.024$ ) were increased in patients with cognitive impairment compared to those without cognitive impairment. Notably, Th17 cells were positively associated with 1-year ( $r_s = 0.331$ ,  $p < 0.001$ ), 2-year ( $r_s = 0.261$ ,  $p = 0.006$ ), and 3-year ( $r_s = 0.256$ ,  $p = 0.011$ ) MMSE decline; IL-17A was positively correlated with 1-year ( $r_s = 0.262$ ,  $p = 0.005$ ), 2-year ( $r_s = 0.193$ ,  $p = 0.045$ ), but not 3-year MMSE decline. However, both Th1 cells and IFN- $\gamma$  were not linked with MMSE decline.

**Conclusion:** Th17 cells and IL-17A estimate the progression of cognitive impairment in stroke patients.

**KEYWORDS**

cognitive impairment, MMSE, stroke, Th1 cells and IFN- $\gamma$ , Th17 cells and IL-17A

Tianming Lu and Le Ma contributed equally to this work.

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## 1 | INTRODUCTION

Stroke, a common cerebrovascular disease, causes the third top mortality rate and the first top long-term disability rate worldwide.<sup>1-4</sup> Apart from stroke itself, cognitive impairment after stroke also receives high attention for it causes motor function disorders, dementia, aphasia, and depression,<sup>5-8</sup> which reduces their life quality,<sup>9</sup> increases the cost burden for their caregivers,<sup>10</sup> and even causes caregiver depression.<sup>11</sup> Moreover, cognitive impairment serves as an independent risk factor for stroke recurrence and prognosis.<sup>12</sup> Therefore, predicting the risk of cognitive decline is crucial for the management of stroke patients, thus improving their outcomes. A possible solution to solve this issue is to identify new biomarkers that reflect poststroke cognitive decline.<sup>13</sup>

During stroke, a series of inflammatory responses are activated because the necrotic neurons promote macrophages activation to release pro-inflammatory cytokines and subsequently T cells are recruited to elevate the inflammatory reaction.<sup>14</sup> Among these, T helper (Th) 1 and Th17 cells, subtypes of CD4<sup>+</sup> T cells, exhibit vital roles in exacerbating the brain injury following stroke.<sup>15</sup> For instance, interferon-gamma (IFN- $\gamma$ ) and interleukin (IL)-17A (mainly generated from Th1 and Th17 cells) can elevate the permeability of the blood-brain barrier (BBB),<sup>16</sup> and reinforce neuroinflammation in stroke; IL-17A in infarct hemisphere amplifies the inflammation and aggravates ischemic neuron injury<sup>17</sup>; IL-17A extends infarct size in ischemic stroke model.<sup>18</sup> However, the association of Th1 cells, Th17

cells, and their mainly related cytokines (including IFN- $\gamma$  and IL-17A) with cognitive impairment in stroke patients remain obscure.

Thus, the study intended to evaluate the relationship of Th1 cells, Th17 cells, and their secreted cytokines with cognitive impairment progression during 3 years in stroke patients.

## 2 | METHODS

### 2.1 | Participants

From March 2018 to February 2019, a total of 120 stroke patients were recruited in this multicenter study. The eligibility criteria: (1) the diagnosis of stroke confirmed by brain and vascular imaging,<sup>19</sup> (2) accompanied with ischemic symptoms, (3) older than 18 years old, and (4) willing to provide blood samples after enrollment. The exclusion criteria are: (1) diagnosed with intracerebral hemorrhage (ICH) or had a history of ICH, (2) accompanied with autoimmune disease or received immunotherapy in the past 6 months, (3) presented with malignancies or cancers, (4) had active infections in the past 6 months, and (5) women who were lactating or having a positive pregnancy test. Besides, 40 age-/gender-matched subjects with stroke risk factors and without presence or history of cerebrovascular disease were enrolled as controls. The age of controls was  $66.1 \pm 7.8$  years, with 52.5% males and 47.5% females. The study was permitted by the Research Ethics Committee of Inner Mongolia

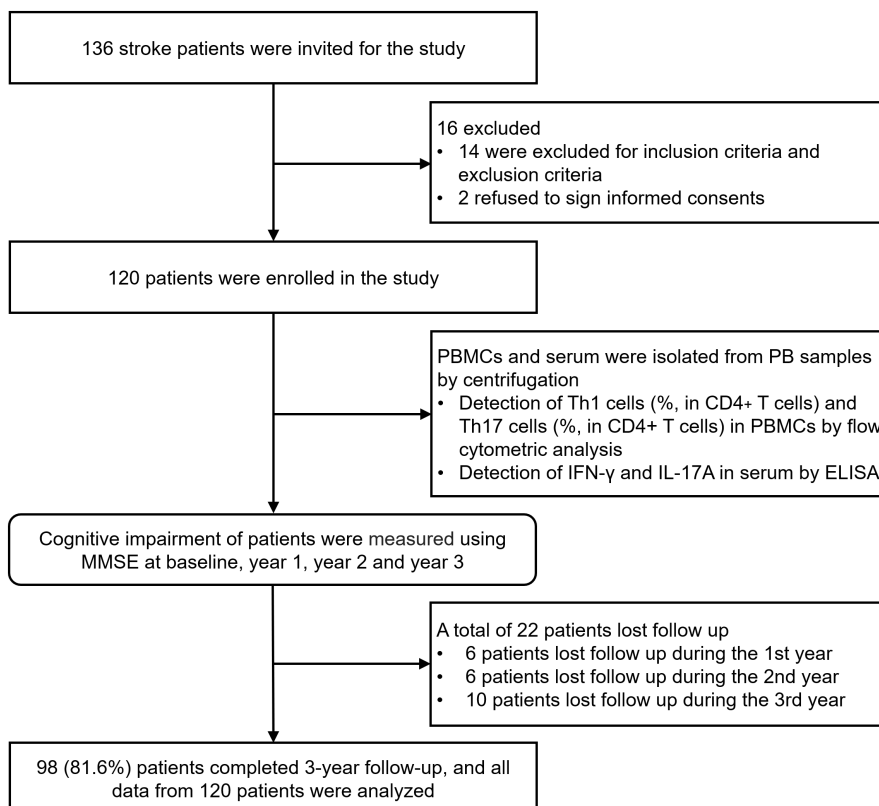


FIGURE 1 Flow of current research

TABLE 1 Characteristics of stroke patients

Variables	Stroke patients (N = 120)
Age (years), mean $\pm$ SD	67.4 $\pm$ 7.9
Gender, n (%)	
Female	48 (40.0)
Male	72 (60.0)
Smoke status, n (%)	
Never	54 (45.0)
Former	63 (52.5)
Current	3 (2.5)
Education duration (years), median (IQR)	7.0 (5.0–10.0)
Marry status, n (%)	
Married	44 (36.7)
Divorced/widowed/single	76 (63.3)
Location, n (%)	
Urban	18 (15.0)
Rural	102 (85.0)
Hypertension, n (%)	101 (84.2)
Hyperlipidemia, n (%)	60 (50.0)
Diabetes, n (%)	42 (35.0)
CKD, n (%)	18 (15.0)
CVD, n (%)	46 (38.3)
Lesion location, n (%)	
Left	43 (35.8)
Right	43 (35.8)
Bilateral/brainstem/unknown	34 (28.3)
Recurrence experience, n (%)	35 (29.2)
MMSE score, mean $\pm$ SD	26.4 $\pm$ 1.9
Cognition impairment, n (%)	57 (47.5)

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; IQR, interquartile range; MMSE, Mini-mental State Examination; SD, standard deviation.

Forestry General Hospital. Participants provided their informed consent.

## 2.2 | Clinical data collection and follow-up

The baseline clinical data of the stroke patients were documented after participation, including demographics, concomitant disease, and disease features. At the same time, the Mini-Mental State Examination (MMSE) scale was applied to evaluate cognitive functions.<sup>20</sup> MMSE score  $\leq$  26 was considered a cognitive impairment. The follow-up visits of this study were scheduled for year 1, year 2, and year 3 after enrollment. All the follow-ups included an MMSE test. The MMSE decline of each visit was calculated by using baseline MMSE score minus each visit's follow-up MMSE score.

## 2.3 | Collection of blood samples and determination of biochemical indexes

The peripheral blood (PB) sample was collected from each stroke patient immediately after enrollment. Within 24 h after collection, the PB sample was separated into two parts. Half of the PB sample was analyzed using flow cytometry to detect Th1 cells (% in CD4<sup>+</sup> T cells) and Th17 cells (% in CD4<sup>+</sup> T cells) with the employment of eBioscience™ Essential Human Th1/Th17 Phenotyping Kit (Life Technologies Corporation, Carlsbad, California, United States). Another half of the PB sample was centrifuged (1200g, 10 min, 25°C) to separate the serum sample. The IFN- $\gamma$  and IL-17 in serum were quantitatively measured with enzyme-linked immunosorbent assay (ELISA) by using Human IFN- $\gamma$  ELISA<sup>PRO</sup> kit (Sensitivity: 1.5 pg/ml; Mabtech, Inc.) and Human IL-17A ELISA Kit (Sensitivity: 2 pg/ml; Cell Sciences®), respectively. All procedures were strictly implemented according to the product protocol. Meanwhile, Th1 cells, Th17 cells, IFN- $\gamma$ , and IL-17A were also detected in controls.

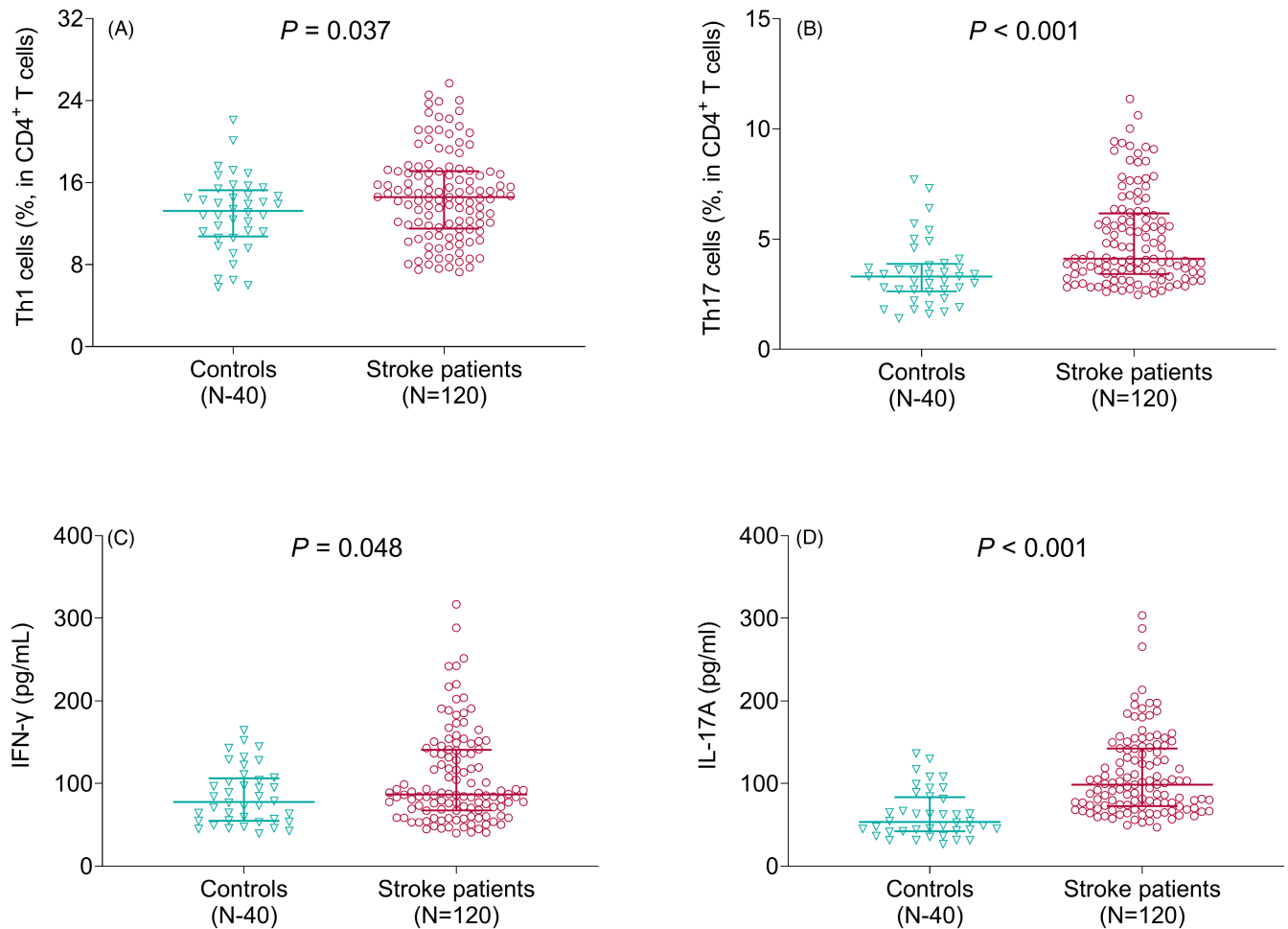
## 2.4 | Statistical analysis

The statistical analyses were performed by SPSS 26.0 (IBM Corporate., Armonk, New York, USA). The figures were plotted by GraphPad Prism 7.01 software (GraphPad Software Inc.). The differences in Th1 cells, Th17 cells, and cytokines between the two groups were evaluated by the Mann-Whitney U test, then the receiver operator characteristic (ROC) curve was performed. The associations of Th1 cells, Th17 cells, and cytokines with MMSE score or MMSE decline were analyzed by the Spearman's rank correlation test. The differences in MMSE score between patients with recurrence experience and patients without recurrence experience were evaluated by the Mann-Whitney U test. At each time point, the MMSE data of patients lost-follow-up were not included in the analysis. *p* value  $<$ 0.05 was concluded as statistical significance.

## 3 | RESULTS

### 3.1 | Study flow

Totally, 136 stroke patients were invited to participate in the study, among them 16 patients were excluded by the screening criteria. Subsequently, 120 patients were included. The levels of Th1 and Th17 cells from PBMCs were assessed by flow cytometric. The levels of IFN- $\gamma$  and IL-17A from serum were detected by ELISA. Then, the cognitive function of patients was measured using MMSE at baseline, year 1, year 2, and year 3. Besides, 22 patients including 6 patients, 6 patients, and 10 patients lost follow-up in the 1st year, 2nd year, and 3rd year, respectively. All 120 patients were included in the final analysis according to intention-to-treat (ITT) principle (Figure 1).



**FIGURE 2** The levels of Th1 cells, Th17 cells, IFN- $\gamma$ , and IL-17A in stroke patients and controls. Comparison of the levels of Th1 cells (A), Th17 cells (B), IFN- $\gamma$  (C), IL-17A (D) between stroke patients and controls

### 3.2 | Characteristics of stroke patients

The stroke patients had a mean age of  $67.4 \pm 7.9$  with 48 (40.0%) females and 72 (60.0%) males. 84.2%, 50.0%, 35.0%, 15.0%, and 38.3% patients had history of hypertension, hyperlipidemia, diabetes, CKD, and CVD, respectively. Moreover, it was presented that the mean MMSE score was  $26.4 \pm 1.9$  and the cognitive impairment rate was 47.5% in stroke patients. The detailed characteristics of stroke patients are displayed in [Table 1](#).

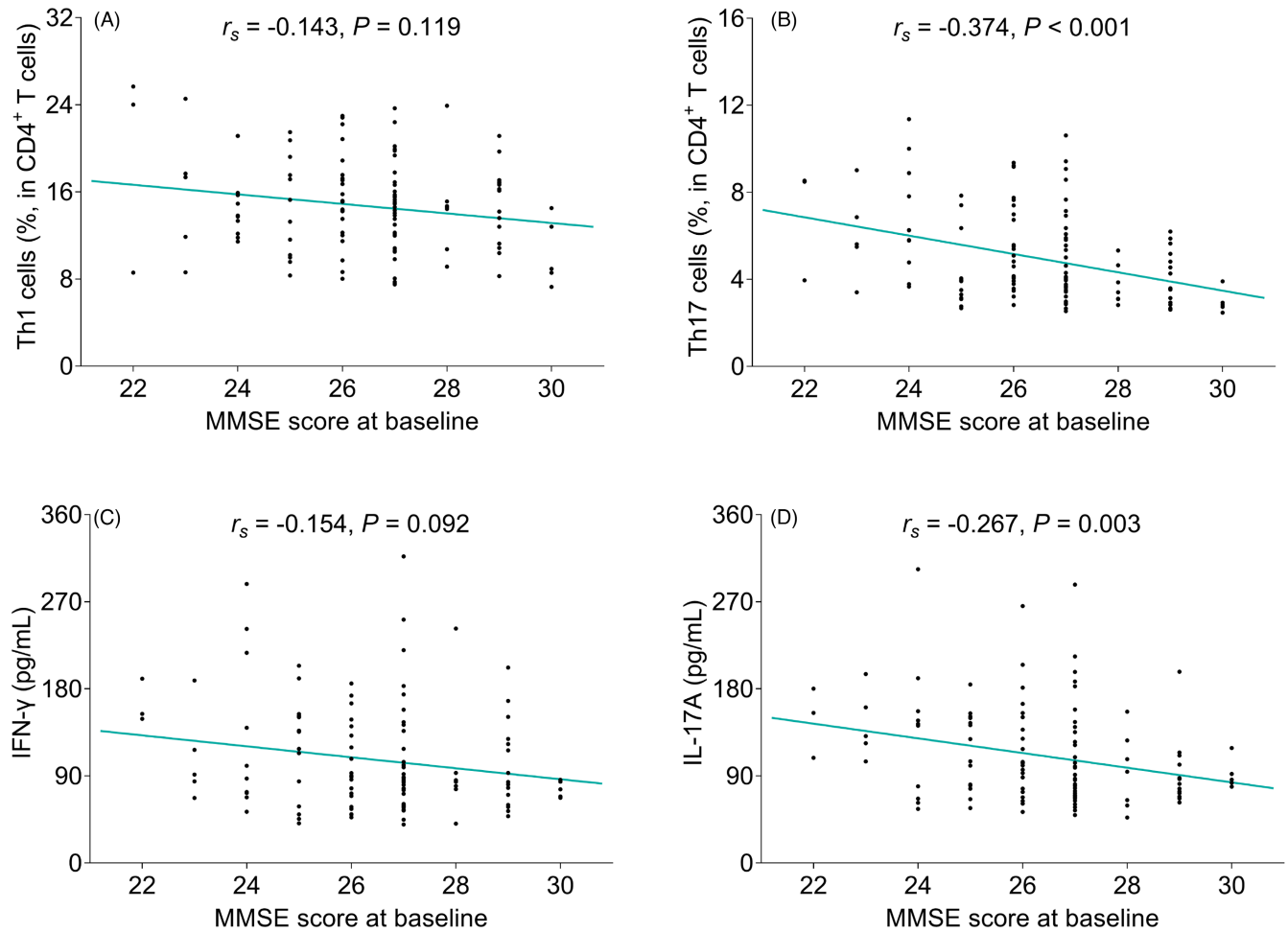
### 3.3 | Levels of Th1 cells, Th17 cells, IFN- $\gamma$ , and IL-17A

Levels of Th1 cells (median (interquartile range): 14.6 (11.5–17.1) % vs. 13.3 (10.8–15.3) %,  $p = 0.037$ ) and IFN- $\gamma$  (median (interquartile range): 86.8 (67.5–140.8) pg/ml vs. 77.7 (54.9–106.4) pg/ml,  $p = 0.048$ ) were slightly increased in stroke patients compared to controls ([Figure 2A,C](#)). Notably, levels of Th17 cells (median (interquartile range): 4.1 (3.4–6.2) % vs. 3.3 (2.6–3.9) %,  $p < 0.001$ ) and IL-17A (median (interquartile range): 98.7 (72.6–142.5) pg/ml vs. 53.5 (42.4–83.5) pg/ml,  $p < 0.001$ ) were greatly higher in stroke patients compared with controls ([Figure 2B,D](#)). In addition, ROC curves exhibited that Th1 cells, Th17 cells, IFN- $\gamma$ , and IL-17A could distinguish stroke patients from controls, among which Th17 cells and IL-17A had relatively higher ability ([Figure S2](#)).

$p < 0.001$ ) and IL-17A (median (interquartile range): 98.7 (72.6–142.5) pg/ml vs. 53.5 (42.4–83.5) pg/ml,  $p < 0.001$ ) were greatly higher in stroke patients compared with controls ([Figure 2B,D](#)). In addition, ROC curves exhibited that Th1 cells, Th17 cells, IFN- $\gamma$ , and IL-17A could distinguish stroke patients from controls, among which Th17 cells and IL-17A had relatively higher ability ([Figure S2](#)).

### 3.4 | Correlations of Th1 cells, Th17 cells, IFN- $\gamma$ , and IL-17A with MMSE score at baseline

The level of Th1 cells was not associated with MMSE score at baseline ( $r_s = -0.143$ ,  $p = 0.119$ ), while the level of Th17 cells was negatively correlated with MMSE score at baseline ( $r_s = -0.374$ ,  $p < 0.001$ ) in stroke patients ([Figure 3A,B](#)). In addition, no correlation had been found between the level of IFN- $\gamma$  and MMSE score at baseline ( $r_s = -0.154$ ,  $p = 0.092$ ). However, a higher level of IL-17A was associated with a lower MMSE score at baseline ( $r_s = -0.267$ ,  $p = 0.003$ ) in stroke patients ([Figure 3C,D](#)).



**FIGURE 3** The association of Th1 cells, Th17 cells, IFN- $\gamma$ , and IL-17A with MMSE score in stroke patients. The correlation of Th1 cells (A), Th17 cells (B), IFN- $\gamma$  (C), and IL-17A (D) with MMSE score at baseline

### 3.5 | Comparisons of Th1 cells, Th17 cells, IFN- $\gamma$ , and IL-17A in stroke patients with or without cognitive impairment at baseline

The levels of Th17 cells ( $p = 0.001$ ) and IL-17A ( $p = 0.024$ ) were enhanced in cognitive impairment stroke patients compared to non-cognitive impairment stroke patients at baseline, whereas both Th1 cells and IFN- $\gamma$  levels remained unchanged between these patients at baseline (both  $p > 0.05$ ; Figure 4A-D).

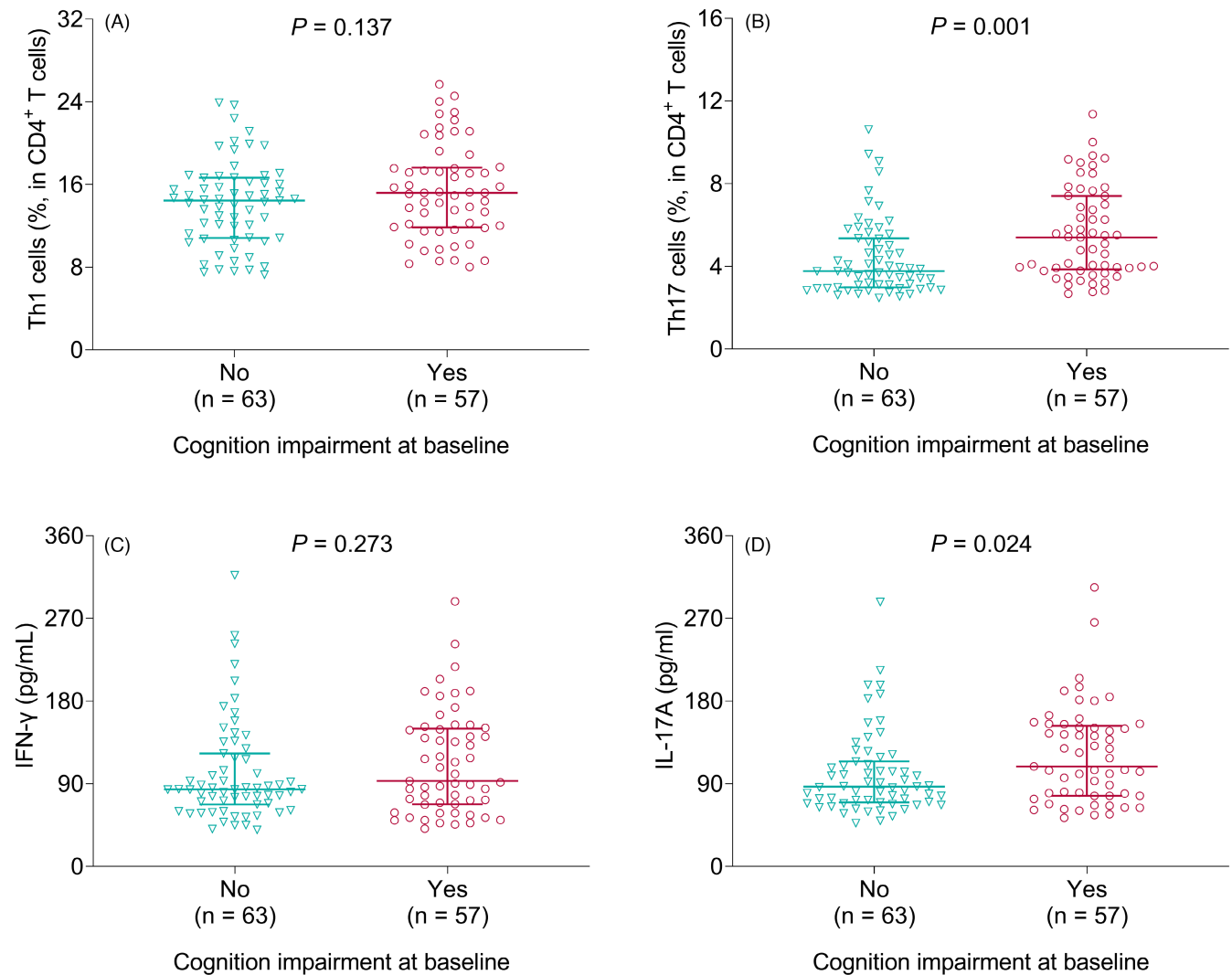
### 3.6 | Correlations of Th1 cells, Th17 cells, IFN- $\gamma$ , and IL-17A with MMSE decline during 3-year follow-up

The cognitive decline was assessed by MMSE score at baseline minus that at year 1, year 2, and year 3 visit points in stroke patients, respectively. 57.0% (65/114), 69.4% (75/108), and 72.4% (71/98) stroke patients had MMSE  $\leq 26$  at 1st year, 2nd year, and 3rd year, respectively. Positive associations were observed in the levels of Th17 cells ( $r_s = 0.331$ ,  $p < 0.001$ ) and IL-17A ( $r_s = 0.262$ ,  $p = 0.005$ )

with 1-year MMSE decline, while no correlation was identified in the levels of Th1 cells and IFN- $\gamma$  with 1-year MMSE decline (both  $p > 0.05$ ) in stroke patients (Figure 5A-D). Meanwhile, the levels of Th17 cells ( $r_s = 0.261$ ,  $p = 0.006$ ) and IL-17A ( $r_s = 0.193$ ,  $p = 0.045$ ) were also positively related to 2-year MMSE decline. Nevertheless, the levels of Th1 cells and IFN- $\gamma$  were not correlated with 2-year MMSE decline (both  $p > 0.05$ ) (Figure 5E-H). Moreover, only the level of Th17 cells was associated with more 3-year MMSE decline ( $r_s = 0.256$ ,  $p = 0.011$ ), but there was no correlation in the levels of Th1 cells, IFN- $\gamma$ , and IL-17A with 3-year MMSE decline (all  $p > 0.05$ ) (Figure 5I-L). Besides, the MMSE score was increased in stroke patients without recurrence experience compared to those with recurrence experience during 3 years (all  $p < 0.01$ ; Figure S1).

## 4 | DISCUSSION

Neuroinflammation is the major driver for cognitive impairment in neurological diseases including: stroke, Parkinson's disease (PD), and Alzheimer's disease (AD).<sup>21-26</sup> For instance, in stroke with cognitive impairment model, inflammasome pyrin-domain-containing protein

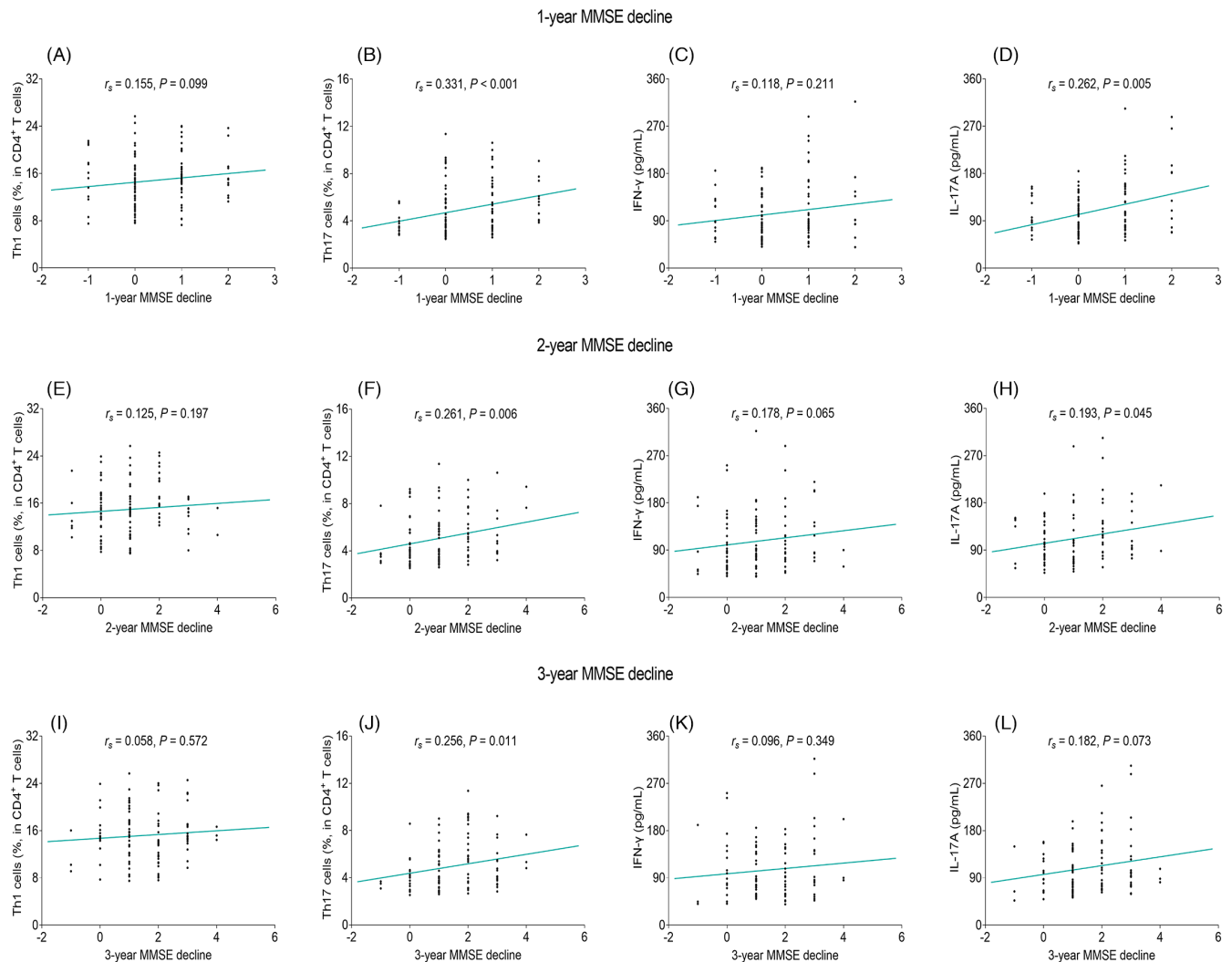


**FIGURE 4** Comparison of Th1 cells, Th17 cells, IFN- $\gamma$ , and IL-17A levels in stroke patients with/without cognitive impairment. Correlation of the levels of Th1 cells (A), Th17 cells (B), IFN- $\gamma$  (C), and IL-17A (D) with cognitive impairment at baseline in stroke patients

3 (NLRP3) is activated, which increases microglial activation, reduces neuronal cell number, damages hippocampal neurogenesis, and ultimately leads to neurological dysfunction<sup>21</sup>; in animal models of Parkinson's disease,  $\alpha$ -synuclein activates microglia and promotes the secretion of inflammatory factors like IL-1 $\beta$  that adversely affect neurons and subsequently cause cognitive impairment<sup>23</sup>; in AD model, microglia is activated and releases pro-inflammatory cytokines, among which IL-1 mediates astrocytes and neurons to generate amyloid  $\beta$ -protein (A $\beta$ ), leading to amyloid protein deposition, ultimately resulting in cognitive impairment.<sup>22</sup>

Previous researches report that a high number of circulating lymphocytes are correlated with cognitive impairment in a wide variety of neurological diseases.<sup>27,28</sup> For instance, Th1 cells display a higher percentage in PD patients with cognitive impairment,<sup>27</sup> while Th1 cells are not related to cognitive impairment progression in AD patients.<sup>28</sup> In addition, high levels of Th17 cells and IL-17 are associated with cognitive impairment in multiple sclerosis patients and AD patients.<sup>29,30</sup> Considering that cognitive impairment presents a high

prevalence in poststroke patients, the association of Th1 and Th17 cells with cognitive function in stroke is worth noting. In our study, the levels of Th17 cells and IL-17A were increased in stroke patients with cognitive impairment at baseline, while the relationships of Th1 and IFN- $\gamma$  levels with cognitive impairment at baseline were not observed. We suspected that the reasons might be: (1) after stroke, Th17 cell and IL-17A might enhance the penetrability of BBB<sup>16</sup> and aggravated pro-inflammatory cytokines release in the brain, which led to neuronal damage and cognitive impairment; (2) IL-17A might promote glia to secrete numerous chemokine1, which could induce neutrophils infiltration in brain<sup>31</sup> and subsequently might cause the cognitive impairment in stroke patients; and (3) Th1 cells might not involve in regulating cognitive impairment in stroke patients, which was consistent with previous research in AD patients.<sup>28</sup> Besides, IL-17A is commonly used to identify Th17 cells. However, in circulating blood, the contribution of IL-17A is not only from Th17 cells, but also from neutrophils. Therefore, it could be seen that Th17 and IL-17A exhibit a little different utility in this study.



**FIGURE 5** The association of Th1 cells, Th17 cells, IFN- $\gamma$ , and IL-17A levels with cognitive decline at each year in stroke patients. The correlation of Th1 cells (A), Th17 cells (B), IFN- $\gamma$  (C), and IL-17A (D) with 1-year MMSE decline; the association of Th1 cells (E), Th17 cells (F), IFN- $\gamma$  (G), and IL-17A (H) with 2-year MMSE decline; the relationship of Th1 cells (I), Th17 cells (J), IFN- $\gamma$  (K), and IL-17A (L) with 3-year MMSE decline. At each time point, the MMSE data of patients lost-follow-up were not included in the analysis

The levels of Th1 and Th17 cells predicting the cognitive decline have been illustrated recently.<sup>27,30,32</sup> For instance, massive IL-17 level in the central nervous system is positively correlated with short-term memory deficits at the early stage of AD, while anti-IL-17 prevents cognitive decline in AD<sup>30</sup>; high level of IFN- $\gamma$  is associated with the decline of executive function in vascular dementia patients.<sup>32</sup> While the association of Th1 and Th17 cells with cognitive decline in stroke patients need to explore. Thus, our findings presented that (1) the levels of Th17 cells and IL-17A were correlated with 1-year cognitive decline and 2-year cognitive decline, possibly because Th17 cells and IL-17A might be main mediators to cause chronic inflammation, resulting in long-term cognitive decline in poststroke patients; (2) the correlation of IL-17A with 3-year cognitive decline was not marked. We guessed that the long-term prediction effect of IL-17A is not obvious, which might be interfered by other factors, and these influence factors could be further explored in subsequent studies; (3) the

association of Th1 cells and IFN- $\gamma$  with cognitive decline was not observed, the explanation might be Th1 and Th2 cells present a synergistic effect on the regulation of inflammation,<sup>33</sup> while the level of Th2 cells and the Th1/Th2 balance were not detected in this study, which need to be verified in further study. Apart from these, cognitive impairment was more obvious in stroke patients with recurrence experience during 3 years after stroke.

Some limitations still existed in this study: (1) Our study only included patients with ischemic stroke, so our conclusions were not suitable for hemorrhage stroke patients, we needed to enroll more typical patients in our future study; (2) during the follow-up, we did not evaluate the levels of Th1 cells, Th17 cells, IFN- $\gamma$ , and IL-17A; hence, their subsequent changes were not clear; (3) the detailed mechanism between Th cells and their cytokines with cognitive impairment needed further investigation. (4) MoCA is a better and more precise scale than MMSE; however, it consists of much more questions than MMSE, which is hard to execute at

multiple time points in our clinics; therefore, MMSE was chosen in this study, and further study using MoCA validation was the next topic.

In summary, Th17 cells and IL-17A estimate the progression of cognitive impairment in stroke patients, which may provide information for monitoring or preventing cognitive impairment of stroke.

#### ACKNOWLEDGMENTS

None.

#### CONFLICT OF INTEREST

The authors declare that they have no competing interests.

#### DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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