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Longitudinal change of Th1, Th2, and Th17 cells and their relationship between cognitive impairment, stroke recurrence, and mortality among acute ischemic stroke patients

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Abstract

Background: T-helper (Th) cells regulate immunity and inflammation, and modulate cognitive impairment in both cardio-cerebrovascular and neurological diseases. This study aimed to explore the correlation of longitudinal change of Th1/2/17 cells with cognitive impairment and prognosis in acute ischemic stroke (AIS).

Methods: Th1/2/17 cells were detected by flow cytometry in peripheral blood samples from 150 AIS patients at admission (baseline), Day (D)1, D3, and D7 after admission, and from 30 controls. Mini-Mental State Examination (MMSE) score among AIS patients at discharge was assessed. Stroke recurrence and mortality were evaluated.

Results: Th1 ($p = 0.013$) and Th17 cells ($p < 0.001$) but not Th2 cells ($p = 0.105$) were elevated in AIS patients versus controls. Th1 cells ($p = 0.027$) and Th17 cells ($p < 0.001$) but not Th2 cells ($p = 0.227$) were positively correlated with NIHSS score in AIS patients. Furthermore, Th1 and Th17 cells elevated from baseline to D3 and then decreased on D7 after AIS onset, while Th2 cells illustrated an opposite trend (all $p < 0.001$). Th17 cells on D1 ($p = 0.011$), D3 ($p = 0.014$), and D7 ($p < 0.001$) were correlated with lower MMSE score, and their levels on D3 ($p = 0.033$) and D7 ($p = 0.004$) were related to elevated cognitive impairment. Th1 and Th2 cells were not related to cognitive function (all $p > 0.05$). Additionally, Th17 cells at baseline, D1, D3, and D7 (all $p < 0.05$) were increased in recurrent patients versus non-recurrent patients, and in survived patients versus dead patients, but Th1 or Th2 cells did not vary (all $p > 0.05$).

Conclusion: Th17 cells correlate with increased cognitive impairment, stroke recurrence, and mortality among AIS patients.

KEYWORDS
acute ischemic stroke, cognitive impairment, mortality, recurrence, Th1/Th2/Th17 cells

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Shijian Yu and Wei Cui contributed equally to this work.

1 | INTRODUCTION

Acute ischemic stroke (AIS) is a cerebrovascular disorder caused by arterial stenosis or occlusion, which is one of the major causes of neurological deaths globally.[1,2] Currently, great progress has been made in treatments of AIS (including thrombolytic treatment, revascularization therapy, and neuroprotective treatment), while there exist a proportion of AIS patients facing long-term adverse outcomes.[3–5] Cognitive impairment is a common undesirable outcome of AIS patients that is correlated with permanent disability and even death, which results in a huge economical and humanistic burden.[5–7] In view of the challenge in the management of AIS, the exploration of factors affecting cognitive impairment and prognosis of AIS is an urgent issue.

The dysregulation of T-helper (Th) cells plays an important role in the development of cardio-cerebrovascular diseases. For instance, it has been reported that the imbalance of Th1 and Th2 cells promote atherosclerotic plaque formation in atherosclerosis model mice[8]; furthermore, suppressed Th2 cells and increased Th17 cells are able to accelerate ischemic brain injury in middle cerebral artery occlusion mice.[9] In addition, the measurement of Th cells also has a crucial clinical value in cardio-cerebrovascular disease supervision. For example, Th2 and Th17 cells are varied between ischemic stroke patients and healthy populations[10,11]; moreover, Th17 cells are positively correlated with the atherosclerosis severity in coronary artery disease patients[12]; furthermore, increased Th17 cells but not Th1 cells are related to higher recurrence-free survival among AIS patients.[13] Apart from that, Th cells are involved in the progression of cognitive impairment in neurological diseases[14,15]; meanwhile, Th17 cells are also negatively correlated with cognitive impairment among patients with Alzheimer's disease and Parkinson's disease.[16,17] However, few studies have explored the clinical implication of longitudinal change of Th1, Th2, and Th17 cells in AIS.

Thus, the current study aimed to explore the longitudinal change of Th1, Th2, and Th17 cells, and their correlation between cognitive impairment and prognosis in AIS patients, aiming to promote the management of AIS.

2 | METHODS

2.1 | Participants

This study consecutively recruited 150 first-ever stroke AIS patients hospitalized and was registered at Jing'an District Central Hospital between March 2018 and July 2021. The inclusion criteria for AIS patients were as follows: (1) Newly diagnosed as AIS according to the American Stroke Association Guideline[18]; (2) aged ≥18 years; and (3) admitted to the hospital within 24 hours after the episode of symptoms. The exclusion criteria for AIS patients were as follows: (1) had intracranial hemorrhage; (2) history of stroke; (3) history of head surgery; (4) accompanied by inflammatory disease or immune system disease; (5) history of cancers or malignancies; and (6) pregnancy or lactation. Besides, the study enrolled 30 subjects during the same period as controls. The inclusion criteria for controls were as follows: (1) with ≥2 risk factors of stroke[19] and (2) aged ≥18 years. The exclusion criteria for controls were the same as the AIS patients. The Ethical Committee of Jing'an District Central Hospital approved the study. Each subject or corresponding guardian provided written informed consent.

2.2 | Clinical data and blood sample collection

After enrollment, the demographics, medical history, disease features, and treatment were recorded by case report form. The demographics included the following: Age; gender (female or male); body mass index (BMI); and smoke history (yes/no). The medical history included the following: hypertension (yes/no); hyperlipidemia (yes/no); diabetes mellitus (yes/no); and chronic kidney disease (CKD) (yes/no). The disease features included the following: National Institutes of Health Stroke Scale (NIHSS) score; and Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification.[20] Treatment included thrombolysis and mechanical thrombectomy. The peripheral blood (PB) samples of AIS patients were collected at the following time points: at admission (baseline), D1, D3, and D7. The PB samples of controls were also collected after enrollment. The PB samples were used to detect Th cells.

2.3 | Assessment of cognitive function

The patient's cognitive function was assessed by the Mini-Mental State Examination (MMSE) at discharge from the hospital. MMSE includes 11 items and five facets (space and time, registration, attention and calculation, recall, and language). The total score of MMSE ranged from 0 to 30. Lower scores represent a worse cognitive function. The MMSE score ≤26 was considered cognitive impairment.[21]

2.4 | Th cell determination

Within 24 h after collection, fresh PB samples were analyzed using flow cytometry to detect Th1 cells (%, in $CD4^+$ T cells), Th2 cells (%, in $CD4^+$ T cells), and Th17 cells (%, in $CD4^+$ T cells) with the employment of Human Th1/Th2/Th17 staining kit (MultiSciences). The flow cytometry used was FACSCanto™ II (BD Biosciences). Then, FlowJo (Tree Star, Ashland, Oregon, United States) was used for analyzing flow cytometry data. All procedures were strictly implemented according to the product protocol.

2.5 | Follow-up

AIS patients were closely followed up according to the AIS Guideline.[18] The last follow-up date was October 31, 2021. Then,

the recurrence of stroke and patient's death were recorded. The median follow-up duration was 18.0 months with a range from 2.0 to 41.0 months. The recurrence and death of patients were processed as censored data if lost to follow-up. Seventeen AIS patients were lost to follow-up during the study.

2.6 | Statistics

The statistical analyses were performed by SPSS V.26.0 (IBM Corp.). The figures were plotted by GraphPad Prism V.7.02 (GraphPad Software Inc.). The comparison of Th cells between the two groups was evaluated using the Mann–Whitney U test. The repeated-measures analysis of Th cells was assessed using the Friedman test. The correlation between two variables was analyzed by Spearman's rank correlation test. The $p < 0.05$ was considered statistical significance.

3 | RESULTS

3.1 | Study flow

Between March 2018 and July 2021, 167 patients with first-onset AIS were screened for eligibility; then, 17 patients were excluded (including 12 patients who did not meet inclusion criteria or met exclusion criteria, and 5 patients who disagreed with informed consent). Thus, 150 patients were eligible for recruitment. Then, PB samples of 150 patients were collected at baseline, D1, D3, and D7; meanwhile, Th1, Th2, and Th17 cells from PB samples were detected by flow cytometry. Besides, cognitive function was assessed by MMSE at discharge from the hospital. The follow-up was managed until October 2021 (the last follow-up date was October 31, 2021). During the follow-up period, 17 patients experienced AIS recurrence and 7 patients died. Finally, all 150 patients were included in the analysis according to the intention to treat principle (Figure 1).

3.2 | Characteristics of AIS patients

Among 150 patients, the mean age was 63.8 ± 9.2 years; meanwhile, there exited 47 (31.3%) females and 103 (68.7%) males. Furthermore, there were 79 (52.7%) patients with smoke history, 129 (86.0%) patients with hypertension, 73 (48.7%) patients with hyperlipidemia, 27 (18.0%) patients with diabetes mellitus, and 28 (18.7%) patients with CKD. According to the TOAST classification, 62 (41.3%), 38 (25.3%), 24 (16.0%), 16 (10.7%), and 10 (6.7%) patients were classified into large artery atherosclerosis (LAA), small artery occlusion (SAA), cardioembolism (CE), stroke of undetermined etiology (SUE), and stroke of other determined etiology (SOE), respectively. In addition, the median (interquartile range [IQR]) of the NIHSS score on
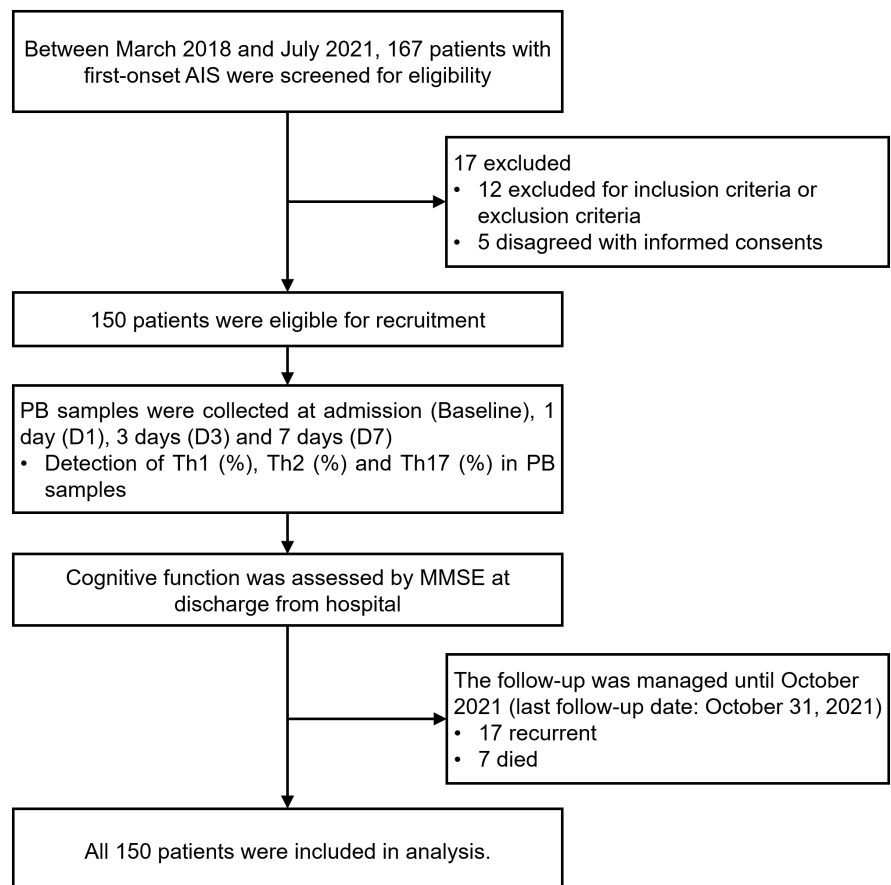

FIGURE 1 Study flowchart. AIS, acute ischemic stroke; MMSE, Mini-Mental State Examination; PB, peripheral blood; Th, T helper

the first day was 6.0 (4.0–9.0). Besides, 121 (80.7%) and 29 (19.3%) patients received thrombolysis and mechanical embolectomy, respectively (Table 1).

3.3 | Comparison of Th cells between AIS patients and controls

Th1 cells (median (IQR): 15.4 (12.7–20.1) % vs. 13.8 (10.9–16.1) %) were elevated in AIS patients compared with controls ($p = 0.013$) (Figure 2A). However, no difference was found in Th2 cells (median

TABLE 1 Characteristics of AIS patients

Items	AIS patients (N = 150)
Age (years), mean ± SD	63.8 ± 9.2
Gender, n (%)	
Female	47 (31.3)
Male	103 (68.7)
BMI (kg/m^2), mean ± SD	24.4 ± 2.7
Smoke history, n (%)	
No	71 (47.3)
Yes	79 (52.7)
Hypertension, n (%)	
No	21 (14.0)
Yes	129 (86.0)
Hyperlipidemia, n (%)	
No	77 (51.3)
Yes	73 (48.7)
Diabetes mellitus, n (%)	
No	123 (82.0)
Yes	27 (18.0)
CKD, n (%)	
No	122 (81.3)
Yes	28 (18.7)
TOAST classification, n (%)	
LAA	62 (41.3)
SAA	38 (25.3)
CE	24 (16.0)
SUE	16 (10.7)
SOE	10 (6.7)
NIHSS score, median (IQR)	6.0 (4.0–9.0)
Treatment, n (%)	
Thrombolysis	121 (80.7)
Mechanical embolectomy	29 (19.3)

Abbreviations: AIS, acute ischemic stroke; BMI, body mass index; CE, cardioembolism; CKD, chronic kidney disease; IQR, interquartile range; LAA, large artery atherosclerosis; NIHSS, National Institute Health of Stroke Scale; SAA, small artery occlusion; SD, standard deviation; SOE, stroke of other determined etiology; SUE, stroke of undetermined etiology; TOAST, Trial of Org 10172 in acute stroke treatment.
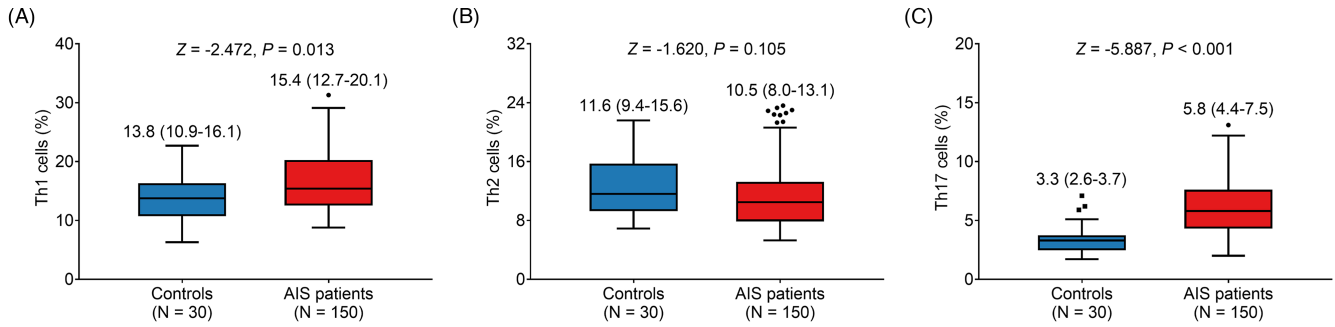
(IQR): 10.5 (8.0–13.1) % vs. 11.6 (9.4–15.6) %) between AIS patients and controls ($p = 0.105$) (Figure 2B). In addition, Th17 cells (median (IQR): 5.8 (4.4–7.5) % vs. 3.3 (2.6–3.7) %) were increased in AIS patients compared with controls ($p < 0.001$) (Figure 2C).

3.4 | Correlation of Th cells with NIHSS score and treatment in AIS patients

Th1 cells were positively linked with NIHSS score ($r_s = 0.181$, $p = 0.027$) (Figure 3A). However, no correlation was found in Th2 cells with NIHSS score ($r_s = -0.099$, $p = 0.227$) (Figure 3B). Additionally, Th17 cells were positively related to NIHSS score ($r_s = 0.282$, $p < 0.001$) (Figure 3C). In addition, Th1 cells (Figure S1A), Th2 cells (Figure S1B), and Th17 cells (Figure S1C) from baseline to D7 were not linked with treatment options (thrombolysis or mechanical embolectomy) (all $p > 0.05$).

3.5 | Change of Th cells from baseline to D7 in AIS patients

Th1, Th2, and Th17 cells all varied from baseline to D7 (all $p < 0.001$). In specific, Th1 cells presented an elevated trend from baseline to D3, but were declined at D7 (Figure 4A). Th2 cells illustrated a decreased trend from baseline to D3, but were elevated at D7 (Figure 4B). Additionally, Th17 cells showed a rising trend from baseline to D3, but were decreased at D7 (Figure 4C).

3.6 | Association of Th cells at different time points with cognitive function in AIS patients

Th1 and Th2 cells at baseline, D1, D3, and D7 were not associated with MMSE score (all $p > 0.05$). Moreover, Th17 cells at baseline were not linked to MMSE score ($r_s = -0.144$, $p = 0.079$), while Th17 cells at D1 ($r_s = -0.206$, $p = 0.011$), D3 ($r_s = -0.211$, $p = 0.014$), and D7 ($r_s = -0.304$, $p < 0.001$) were negatively correlated with MMSE score (Table 2).

Then, cognitive impairment was assessed by MMSE score ≤26, which illustrated that Th1 and Th2 cells at baseline, D1, D3, and D7 were not linked to cognitive impairment (all $p > 0.05$). In addition, Th17 cells at baseline ($p = 0.114$) and D1 ($p = 0.066$) were not related to cognitive impairment, while Th17 cells at D3 ($p = 0.033$) and D7 ($p = 0.004$) were related to elevated cognitive impairment (Table 3).

3.7 | Correlation of Th cells at different time points with AIS recurrence and mortality in AIS patients

Th1 cells on D3 were elevated in recurrent patients compared with non-recurrent patients ($p = 0.048$), but did not vary at baseline, D1,

FIGURE 2 Th cells in AIS patients and controls. Comparison between Th1 cells (A), Th2 cells (B), and Th17 cells (C) between AIS patients and controls. AIS, acute ischemic stroke; Th, T helper
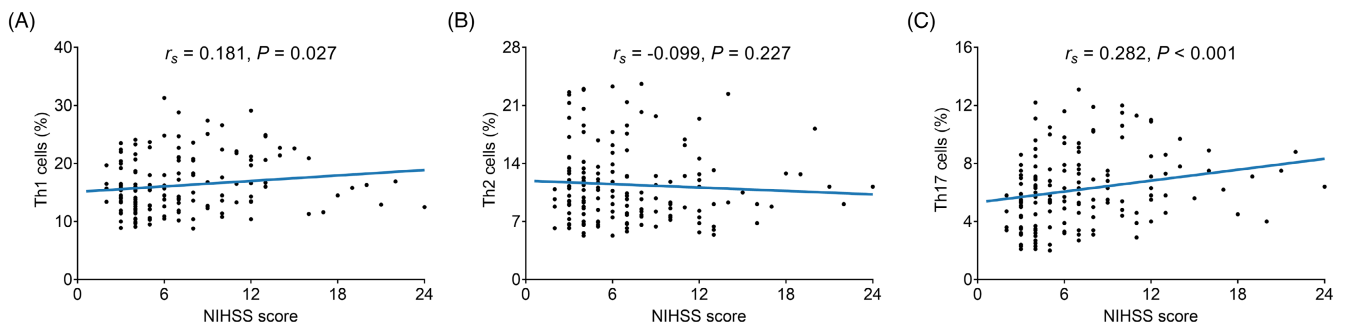

FIGURE 3 Association of Th cells with NIHSS score in AIS patients. Association of Th1 cells (A), Th2 cells (B), and Th17 cells (C) with NIHSS score. NIHSS, National Institutes of Health Stroke Scale; Th, T helper
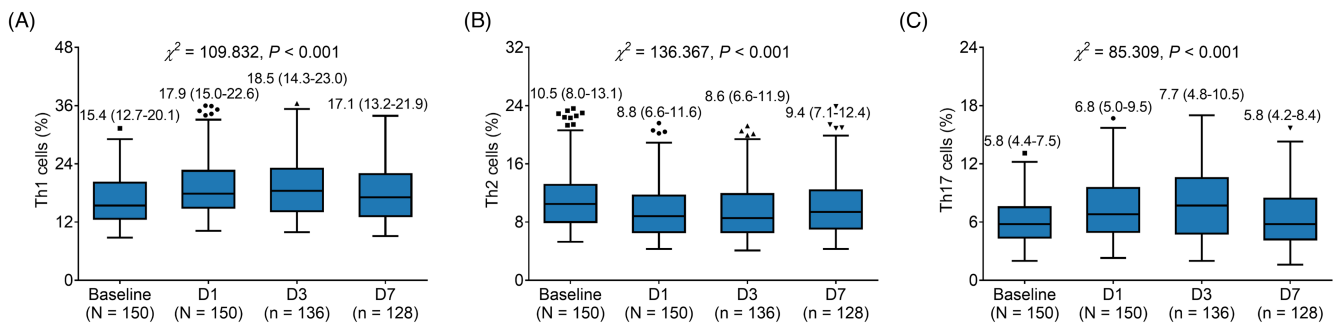

FIGURE 4 Th cells at different time points in AIS patients after onset. Change of Th1 cells (A), Th2 cells (B), and Th17 cells (C) at baseline, D1, D3, and D7. D, day; Th, T helper

or D7 (all $p > 0.05$) (Figure 5A). No difference was found in Th2 cells at each time point between recurrent patients and non-recurrent patients (all $p > 0.05$) (Figure 5B). Inspiringly, Th17 cells at baseline ($p = 0.002$), D1 ($p = 0.015$), D3 ($p = 0.006$), and D7 ($p = 0.002$) were all increased in recurrent patients compared with non-recurrent patients (Figure 5C).

In addition, Th1 cells (Figure 5D) and Th2 cells (Figure 5E) at baseline, D1, D3, and D7 did not vary between survived patients and dead patients (all $p > 0.05$). It is important that Th17 cells at baseline ($p = 0.009$), D1 ($p = 0.022$), D3 ($p = 0.008$), and D7 ($p = 0.030$) were all elevated in dead patients compared with survived patients (Figure 5F).

4 | DISCUSSION

The dysregulation of Th cells in cardio-cerebrovascular diseases is of interest. For instance, it has been reported that Th17 cells are increased in ischemic stroke patients compared with healthy populations[10]; moreover, an increment of Th17 cells is found in patients with atherosclerosis compared to healthy controls[22]; furthermore, Th1 cells and Th17 cells are elevated, while Th2 cells are declined in aortic dissection patients compared with controls.[23] In the current study, we found that Th1 and Th17 cells but not Th2 cells were elevated in AIS patients compared with controls; meanwhile, Th1 and Th17 cells but not Th2 cells were positively correlated with disease

TABLE 2 Correlation of Th cells with MMSE score in AIS patients

	MMSE score at discharge	
Items	**Statistic (r_s)**	**p value**
Baseline		
Th1 cells (%)	0.015	0.856
Th2 cells (%)	−0.033	0.688
Th17 cells (%)	−0.144	0.079
D1		
Th1 cells (%)	0.003	0.970
Th2 cells (%)	<0.001	0.998
Th17 cells (%)	−0.206	**0.011**
D3		
Th1 cells (%)	−0.015	0.864
Th2 cells (%)	0.076	0.380
Th17 cells (%)	−0.211	**0.014**
D7		
Th1 cells (%)	−0.011	0.900
Th2 cells (%)	0.050	0.576
Th17 cells (%)	−0.304	**<0.001**

Abbreviations: AIS, acute ischemic stroke; MMSE, Mini-Mental State Examination; Th, T helper; Th1, T helper 1; Th17, T helper 17; Th2, T helper 2.

Bold value means it has statistical significance.

severity of AIS. The potential explanation might be that Th1 and Th17 cells could secret pro-inflammatory cytokines to increase neuroinflammation, which accelerated the pathogenesis and severity of AIS.[24,25] However, Th2 cells might be not involved in the development of AIS; thus, they were not varied between AIS patients and controls, as well as did not correlate with disease severity among AIS patients.

Apart from that, we also explored the longitudinal change of Th1, Th2, and Th17 cells in AIS, which showed that Th1 and Th17 cells presented an elevated trend from baseline to D3, and they were decreased at D7, while Th2 cells illustrated an opposite trend. The potential explanation might be that Th1 and Th17 cells were able to secret pro-inflammatory cytokines, while Th2 could secret anti-inflammation cytokines, indicating their expressions could reflect inflammation levels[24,25]; meanwhile, from admission to D3, the neuroinflammation was elevated among AIS patients; thus, Th1 and Th17 cells were increased, while Th2 cells were decreased from admission to D3 among AIS patients. In addition, the neuroinflammation was alleviated along with the treatment at D7; thus, Th1 and Th17 cells were declined, while Th2 cells were elevated at D7 among AIS patients.

It has been presented that Th cells take part in cognitive impairment in neurological diseases. For instance, Th1, Th2, and Th17 cells are able to modulate cognitive impairment in Alzheimer's disease and Parkinson's disease model mice[14,26]; moreover, it has been reported that Th17 cells are negatively correlated with 1-year,

TABLE 3 Correlation of Th cells with cognitive impairment in AIS patients

	Cognitive impairment at discharge, median (IQR)			
Items	**No (n = 112)**	**Yes (n = 38)**	**Statistic (Z)**	**p Value**
Baseline				
Th1 cells (%)	15.7 (12.7–20.5)	14.3 (12.6–18.1)	−0.756	0.449
Th2 cells (%)	10.1 (7.9–13.0)	10.8 (8.2–14.6)	−0.506	0.613
Th17 cells (%)	5.8 (3.9–7.5)	6.3 (4.9–8.8)	−1.582	0.114
D1				
Th1 cells (%)	18.8 (15.2–22.7)	17.5 (14.3–20.5)	−0.694	0.488
Th2 cells (%)	8.8 (6.6–11.2)	9.4 (6.7–12.0)	−0.523	0.601
Th17 cells (%)	6.7 (4.7–9.3)	7.5 (5.4–10.3)	−1.839	0.066
D3				
Th1 cells (%)	18.6 (14.5–23.1)	17.9 (13.5–22.0)	−0.632	0.527
Th2 cells (%)	8.8 (6.6–11.7)	8.0 (6.1–12.4)	−0.541	0.589
Th17 cells (%)	7.0 (4.5–9.9)	8.8 (5.4–12.9)	−2.137	**0.033**
D7				
Th1 cells (%)	17.8 (13.3–22.1)	15.8 (12.8–21.4)	−0.626	0.532
Th2 cells (%)	9.5 (7.2–12.0)	9.2 (7.1–13.0)	−0.032	0.974
Th17 cells (%)	5.5 (3.8–7.9)	7.5 (5.3–10.9)	−2.890	**0.004**

Abbreviations: AIS, acute ischemic stroke; IQR, interquartile range; Th, T helper; Th1, T helper 1; Th17, T helper 17; Th2, T helper 2.

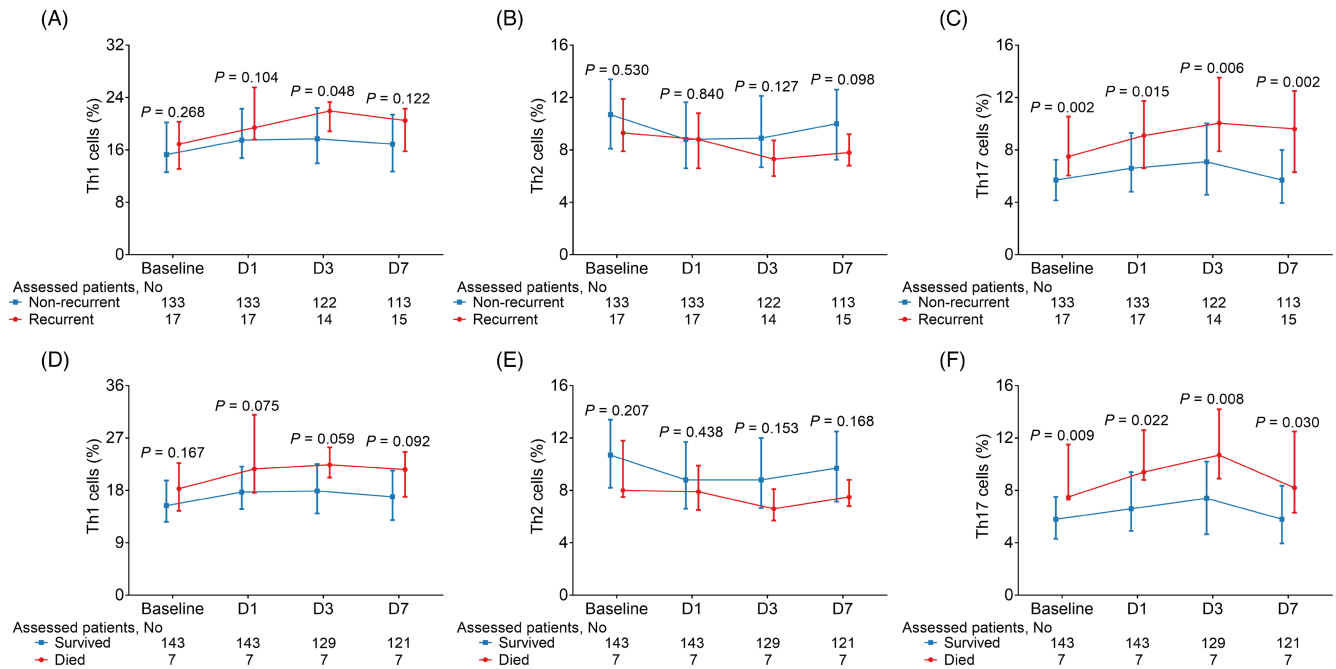Bold value means it has statistical significance.

FIGURE 5 Th cells in recurrent and non-recurrent AIS patients, and survived and dead AIS patients. Comparison of Th1 cells (A), Th2 cells (B), and Th17 cells (C) at baseline, D1, D3, and D7 between recurrent patients and non-recurrent patients; comparison of Th1 cells (D), Th2 cells (E), and Th17 cells (F) at baseline, D1, D3, and D7 between survived patients and dead patients. D, day; Th, T helper

2-year, and 3-year MMSE scores in Alzheimer's disease patients.[16] However, the correlation of Th1, Th2, and Th17 cells with cognitive impairment in AIS is unclear. In the current study, we discovered that Th1 and Th2 cells at any time point were not related to cognitive function. However, Th17 cells on D1, D3, and D7 were negatively associated with MMSE score; meanwhile, Th17 cells on D3 and D7 were also related to increased cognitive impairment (MMSE score <26) among AIS patients. The potential explanation might be that Th17 cells might modulate cognitive function through several methods, including regulating hippocampal neurogenesis, brain tissue integrity, and neuroinflammation[24,27,28]; thus, Th17 cells were associated with cognitive impairment among AIS patients.

The correlation of Th cells with long-term clinical outcomes in patients with the cardio-cerebrovascular disease has been explored. For example, the ratio of Th1 to Th2 cells is correlated with shorter event-free survival among acute myocardial infarction patients[29]; moreover, interleukin-17A (the main secreted cytokines of Th17 cells) is related to declined recurrence-free survival among AIS patients.[13] However, the data about the correlation of longitudinal change of Th cells with prognosis among AIS patients are scarce. In the current study, Th17 cells but not Th1 and Th2 cells at baseline, D1, D3, and D7 were positively correlated with AIS recurrence and mortality. The potential explanations might be that: (1) Th17 cells were able to promote immune dysregulation and neuroinflammation, as well as accelerate atherosclerosis[24,25,30]; therefore, AIS patients with increased Th17 cells might face more risk of recurrence and death; (2) Th17 cells could promote brain injury through regulating neurovascular dysfunction and blood–brain barrier disruption, which lead to poor prognosis in AIS patients[5,31]; (3) Th1 cells might be weakly correlated

with neuroinflammation in AIS[24]; thus, they were not correlated with prognosis among AIS patients, which needed further exploration; and (4) Th2 cells were not related to disease severity and cognitive impairment (above-mentioned); therefore, they were not associated with prognosis among AIS patients. Thus, Th17 cells but not Th1 or Th2 cells were elevated in recurrent and dead AIS patients.

According to our discovery, Th17 might be a potential biomarker among Th cells for stroke cognitive impairment prediction, as well as stroke recurrence and mortality estimation among AIS patients. However, there were some limitations in the current study: (1) The underlying mechanism of Th17 cells in the progression of AIS could be explored in the future; (2) the enrolled patients were first-episode AIS patients; hence, the correlation of Th cells with cognitive impairment and prognosis in recurrent AIS could be further explored; (3) the variation of Th1/2/17 cells in longer time could be explored in the forthcoming study; and (4) the follow-up duration was relatively short, which could be prolonged in the future.

To be conclusive, Th1/2/17 cells are varied within 7 days after AIS onset, among which Th17 cells are related to increased cognitive impairment, stroke recurrence, and mortality among AIS patients, indicating their monitoring may help promote the management of AIS.

CONFLICT OF INTEREST

The authors have no relevant financial or non-financial interests to disclose.

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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