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RESEARCH ARTICLE

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# JNK pathway-associated phosphatase in acute ischemic stroke patients: Its correlation with T helper cells, clinical properties, and recurrence risk

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## Abstract

**Objective:** JKAP modifies T-cell immune response and inflammation, also involves in cardia-cerebrovascular disease etiology. This study intended to explore JKAP's relation with T-helper 1 (Th1), T-helper 17 (Th17) cell levels, clinical properties, and recurrence-free survival (RFS) in acute ischemic stroke (AIS) patients.

**Methods:** A total of 155 AIS patients were analyzed. Serum JKAP, interferon-gamma (IFN-γ), and interleukin-17A (IL-17A) were detected by ELISA; then blood Th1 and Th17 cells were quantified by flow cytometry. Besides, 30 healthy subjects were enrolled as controls to detect JKAP, Th1, and Th17 cells.

**Results:** JKAP level was lower ($p < 0.001$), Th1 cells were not differed ($p = 0.068$), but Th17 cells were elevated in AIS patients versus controls ($p < 0.001$). Meanwhile, JKAP was negatively correlated with Th1 cells ($p = 0.038$), Th17 cells ($P < 0.001$), IFN-γ ($p = 0.002$), and IL-17A ($p < 0.001$) in AIS patients. JKAP was negatively associated with the National Institutes of Health Stroke Scale (NIHSS) score ($p < 0.001$), but Th17 cells ($p = 0.001$), IFN-γ ($p = 0.035$), and IL-17A ($p = 0.008$) levels were positively associated with NIHSS score. Additionally, accumulating RFS was numerically longer in patients with JKAP Quantile (Q) 4 than patients with JKAP Q1–Q3 ($p = 0.068$), and numerically better in patients with JKAP Q3–Q4 than patients with JKAP Q1–Q2 ($p = 0.069$), but without statistical significance.

**Conclusion:** JKAP correlates with lower Th1 and Th17 cell percentages as well as milder disease severity.

KEYWORDS
acute ischemic stroke, $CD4^+$ T cells, disease severity, JKAP, prognosis

Ping Zhao and Huiyong Huo contributed to this work equally.

## 1 | INTRODUCTION

Acute ischemic stroke (AIS) serves as the most common cause of disability and mortality, that accounts for 5.5 million deaths annually.[1,2] Many AIS patients have one or more comorbidities, including hypertension, diabetes mellitus, hyperlipidemia, etc., which increase the mortality rate of AIS.[3,4] In addition, due to the narrow therapeutic time window that limits the therapeutic application, only a minority of AIS patients benefit from the timely effective AIS treatment methods.[5,6] In order to extend treatment application and improve AIS management, there is a need to find out novel biomarkers to assist identify early and monitoring of the prognosis of AIS patients.[7–9]

C-Jun N-terminal kinase (JNK) pathway-associated phosphatase (JKAP), also known as Dual-specificity phosphatase 22 or JNK Stimulatory Phosphatase-1, is a dual-specificity phosphatase that activates the JNK.[10] JKAP is observed to regulate autoimmunity and inflammation via several means.[11,12] What's more, JKAP also participates in the progression of immune/inflammation diseases by altering T-helper 1 (Th1) and T-helper 17 (Th17) cells.[13–16] For instance, through inactivating $CD4^+$ T cells, postponing Th1 and Th17 cell differentiation, JKAP is linked with lower risk, inflammation, and activity of inflammatory bowel disease (IBD).[14] Furthermore, inflammation is greatly involved in the whole course of AIS.[17] For example, the cytokines interferon-gamma (IFN-γ) and interleukin-17A (IL-17A), two main secretions of Th1 and Th17 cells respectively, migrate into the brain and aggravate inflammation in AIS patients[18]; whereas, suppression of inflammatory responses reduces tissue damage and improves treatment outcome in AIS patients.[17,19] In addition, it's reported that JKAP regulates lipid metabolism to involve in atherosclerosis.[20] Gathering the aforementioned observations, we assumed that JKAP might be related to the prognosis of AIS. However, no investigation has been conducted before.

In this study, we attempted to evaluate JKAP's linkage with Th1 and Th17 cells, then further explore its relationship with clinical properties and recurrence-free survival (RFS) in AIS patients.

## 2 | METHODS

### 2.1 | Subjects

From May 2017 to Dec 2018, 155 AIS patients were consecutively enrolled in this prospective, cohort study. The inclusion criteria included: (a) first-episode AIS, which was diagnosed in accordance with the American Stroke Association Guideline[21]; (b) age more than 18 years; (c) absent of intracranial hemorrhage; (d) ability to follow up regularly. The exclusion criteria included: (a) complicated with immune/inflammatory disease; (b) presented with active infections; (c) treated with an immunosuppressive agent within 3 months; (d) had a history of malignancies; (e) lactating or pregnant patients. Besides, 30 healthy subjects were also enrolled (controls). This study was permitted by the Ethics Committee of our hospital. The informed consent was signed from each subject or the guardian.

### 2.2 | Disease severity assessment and samples

AIS patients' characteristics were documented. The disease severity was assessed within 24 h after hospitalization using the National Institutes of Health Stroke Scale (NIHSS). Patients were treated by thrombolytic therapy, or mechanical thrombectomy, and/or other supportive therapies according to the disease conditions. For sample collection, peripheral venous blood samples were acquired from AIS patients (on 1st day of admission), then from controls on enrollment using vacuum tubes in sterile conditions. Then, the peripheral venous blood samples were separated to mononuclear cells and serum.

### 2.3 | JKAP and cytokines detection

Serum JKAP, IFN-γ, and IL-17A were detected using enzyme-linked immunosorbent assay (ELISA) kits (Shanghai Enzyme-linked Biotechnology Co., Ltd.). The sensitivity of JKAP, IFN-γ, and IL-17A ELISA kits was 0.5, 1.5 and 0.57 pg/ml, respectively. In brief, samples and standards were added in a 96-well microtiter plate and incubated with polyclonal according antibody at 25°C for 1 h. Subsequently, secondary antibody was added in each well, then 3,3′-5,5′-tetramethylbenzidin was added for development, which was incubated at 25°C for 20 min. Finally, stop solution was used, then the plate was read with an absorbance microplate reader at 450 nm.

### 2.4 | Th1 and Th17 cells detection

Blood Th1 and Th17 cells were quantified using Human Th1/Th17 Phenotyping Kit (Becton, Dickinson and Company) in terms of the protocol recommended by the manufacturer. The Th1 and Th17 cell percentage in $CD4^+$ T cells was calculated by flow cytometry. The FCM instrument was Attune (Thermo Fisher), the processing software was FlowJo 7.6 (Acresso Software Inc.).

### 2.5 | Recurrence-free survival (RFS) assessment

All patients were followed up regularly and lasted up to 36 months, and it was discontinued when stroke recurred or death occurred. The last follow-up date was Jan 31, 2022. Totally, 22 patients lost follow-up who were censored for RFS analysis, and 32 patients had stroke recurrence. The median follow-up time is 36 months, with range from 0 to 36 months. Based on follow-up data, RFS was assessed between the time of hospitalization and the time of stroke recurrence, death or last follow-up (censored).

### 2.6 | Statistical analysis

Data were analyzed by SPSS 22.0 (IBM Corp.) and graphs were made by GraphPad Prism 7.01 software (GraphPad Software Inc.).

Comparison analysis was determined by the Mann–Whitney *U* test. Correlation analysis was completed by Spearman's rank correlation test. Kaplan–Meier curve was made to exhibit the RFS; the log-rank test was applied to check the RFS difference. Statistical significance was concluded if $p$ value $< 0.05$.

## 3 | RESULTS

### 3.1 | Study flow and characteristics of AIS patients

A total of 166 first-episode AIS patients were invited, and 11 of them were excluded, consisting of three cases who did not meet the inclusion criteria, two cases who met the exclusion criteria, and six patients whose guardians refused the participation. The remaining 155 AIS patients were enrolled in this study. For them, assessment of NIHSS score was recorded, JKAP, IFN-γ, IL-17A, Th1 cells, and Th17 cells were detected. Besides, during 36 months of follow-up, 22 cases lost follow-up, 30 cases had disease recurrence, and ten cases died. All 155 patients were analyzed finally, and the patients who lost follow-up were censored at the last visit date for RFS analysis (Figure 1).

AIS patients' age was 67.6 ± 9.8 years, including 64.5% males and 35.5% females. The BMI was 24.4 ± 2.3 kg/m.$^2$ Besides, there were 75 (48.4%) patients with current smoking. Additionally, the NIHSS score was 9.0 (IQR: 7.0–12.0). The detailed characteristics of AIS patients are summarized in Table 1.

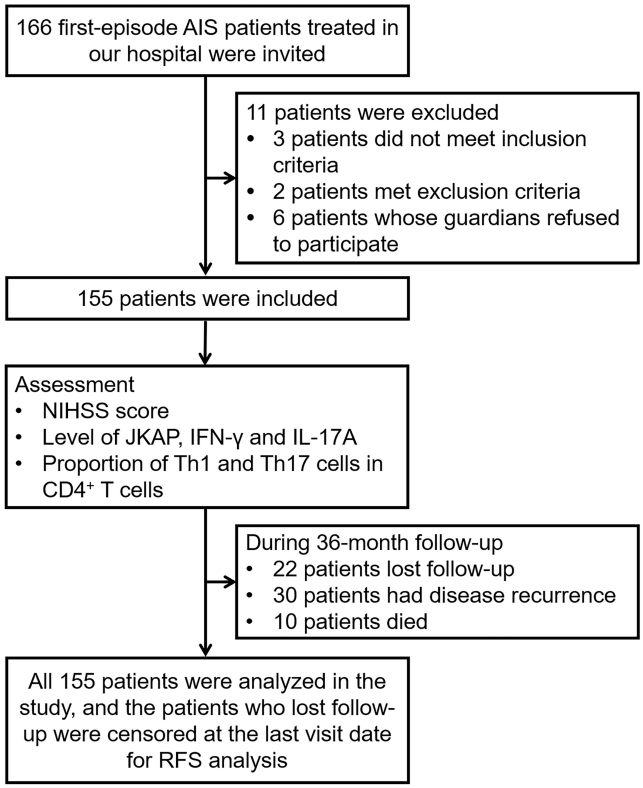


**FIGURE 1** Research flow chart

**TABLE 1** Baseline characteristics of AIS patients

| Items | AIS patients ($N = 155$) |
|---|---|
| Age (years), mean ± SD | 67.6 ± 9.8 |
| Gender, No. (%) | |
| Male | 100 (64.5) |
| Female | 55 (35.5) |
| BMI (kg/m$^2$), mean ± SD | 24.4 ± 2.3 |
| Current smoke, No. (%) | 75 (48.4) |
| Comorbidities, No. (%) | |
| Hypertension | 135 (87.1) |
| Hyperlipidemia | 78 (50.3) |
| hyperuricemia | 63 (40.6) |
| Diabetes mellitus | 36 (23.2) |
| Chronic kidney disease | 26 (16.8) |
| NIHSS score, median (IQR) | 9.0 (7.0–12.0) |

Abbreviations: AIS, acute ischemic stroke; BMI, body mass indexes; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation.

### 3.2 | Level of JKAP, Th1 cells, and Th17 cells

JKAP level was decreased in AIS patients versus controls (median (IQR): 38.6 (28.3–56.0) vs. 83.6 (59.2–109.8) pg/ml, $p < 0.001$), but the Th17 cells were elevated in AIS patients versus controls (median (IQR): 7.5 (5.5–10.2) % vs. 3.0 (2.2–4.1) %, $p < 0.001$) (Figure 2). However, no difference was found in the Th1 cells between the AIS patients and controls ($p = 0.068$).

It was of note that JKAP was associated with decreased Th1 cells ($r = -0.166$, $p = 0.038$) and Th17 cells ($r = -0.342$, $p < 0.001$) (Figure 3A,B) in AIS patients, as well as their main secreted cytokines: IFN-γ ($r = -0.252$, $p = 0.002$) and IL-17A ($r = -0.278$, $p < 0.001$) (Figure 3C,D).

### 3.3 | Correlation of JKAP, Th1, and Th17 cells with clinical features in AIS patients

JKAP was negatively related to NIHSS score in AIS patients ($r = -0.312$, $p < 0.001$) (Figure 4). Besides, JKAP was connected with diabetes mellitus presence ($p = 0.010$), whereas it was not related to the presence of hypertension, hyperlipidemia, hyperuricemia, or chronic kidney disease (CKD) (all $p > 0.05$) (Figure S1A–E).

Moreover, no association was found in the Th1 cells with NIHSS score ($r = 0.135$, $p = 0.093$) (Figure S2A**).** However, Th17 cells ($r = 0.255$, $p = 0.001$), IFN-γ ($r = 0.170$, $p = 0.035$) and IL-17A ($r = 0.211$, $p = 0.008$) were associated with higher NIHSS score (Figure S2B–D).

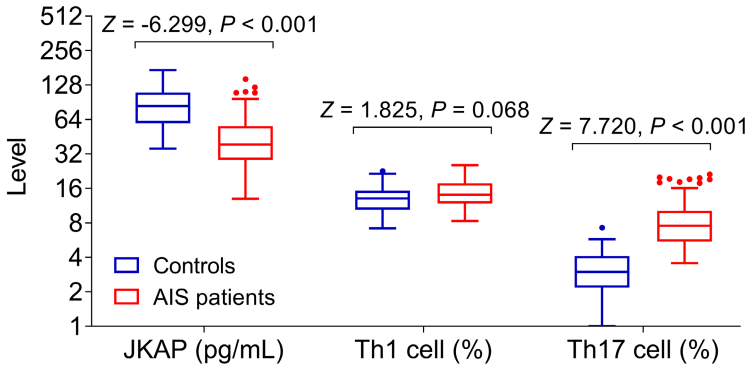


FIGURE 2 JKAP, Th1 and Th17 cell levels in AIS patients and controls

| | JKAP (pg/mL) | | Th1 cell (%) | | Th17 cell (%) | |
|---|---|---|---|---|---|---|
| | Controls | AIS patients | Controls | AIS patients | Controls | AIS patients |
| Mean | 88.4 | 44.8 | 13.4 | 14.9 | 3.3 | 8.5 |
| SD | 35.1 | 24.5 | 3.9 | 4.0 | 1.5 | 3.8 |
| Median | 83.6 | 38.6 | 13.1 | 14.1 | 3.0 | 7.5 |
| IQR | 59.2-109.8 | 28.3-56.0 | 10.4-15.3 | 11.8-17.7 | 2.2-4.1 | 5.5-10.2 |
| Range | 35.6-172.6 | 13.0-144.3 | 7.2-22.7 | 8.3-25.5 | 0.9-7.3 | 3.6-21.2 |

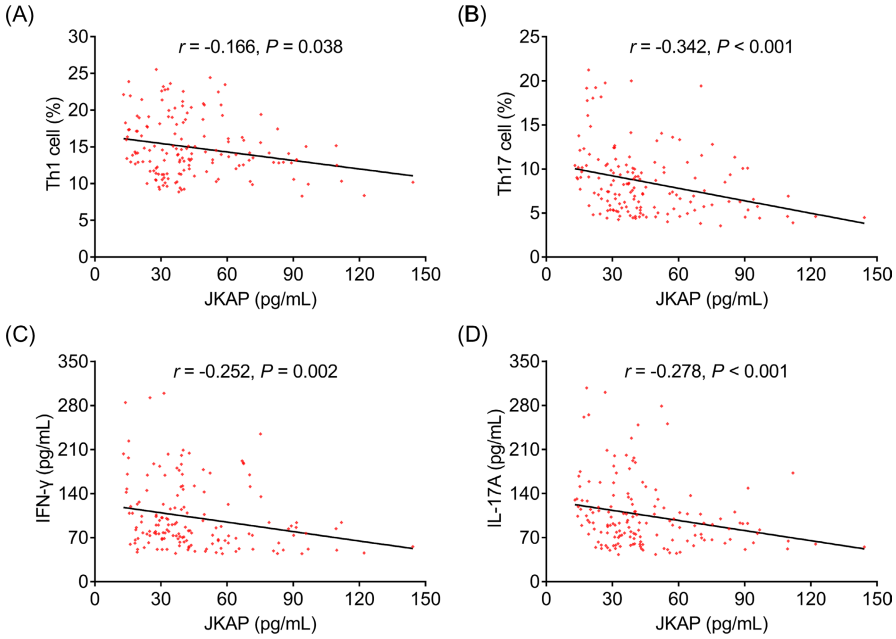


FIGURE 3 Association of JKAP with Th1 and Th17 cell levels in AIS patients. Correlation of JKAP with the Th1 cell level (A), Th17 cell level (B), IFN-γ (C), and IL-17A (D)

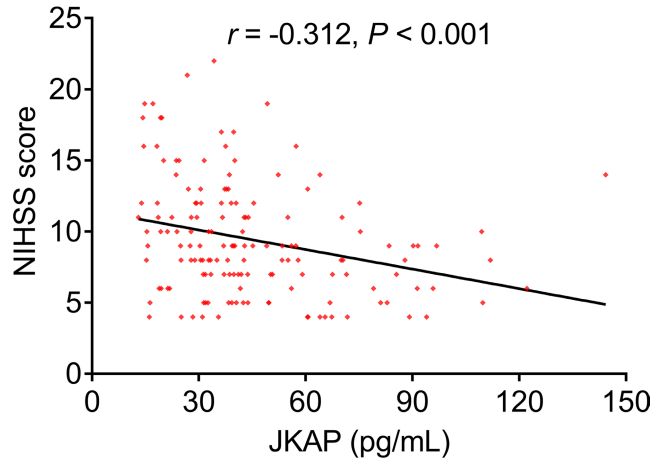


FIGURE 4 Association of JKAP with NIHSS score in AIS patients

### 3.4 | Correlation between JKAP quantiles and RFS

JKAP was classified into four quantiles in AIS patients for RFS analysis: quantile 1 (Q1): 0%–25%; quantile 2 (Q2): 26%–50%; quantile 3 (Q3): 51%–75%; quantile 4 (Q4): 76%–100%. Accumulating RFS was numerically prolonged in patients with JKAP Q4 than in patients with JKAP Q1-Q3 ($p = 0.068$), and also numerically better in patients with JKAP Q3-Q4 than in patients with JKAP Q1-Q2 ($p = 0.069$), however, no statistical significance was found (Figure 5A,B). No difference of accumulating RFS was found between patients with JKAP Q1 and patients with JKAP Q2-Q4 ($p = 0.451$) (Figure 5C). In addition, Th1 high was not related to RFS in AIS patients ($p = 0.816$) (Figure 6A), while Th17 high was correlated with shorter RFS in AIS patients ($p = 0.008$) (Figure 6B).

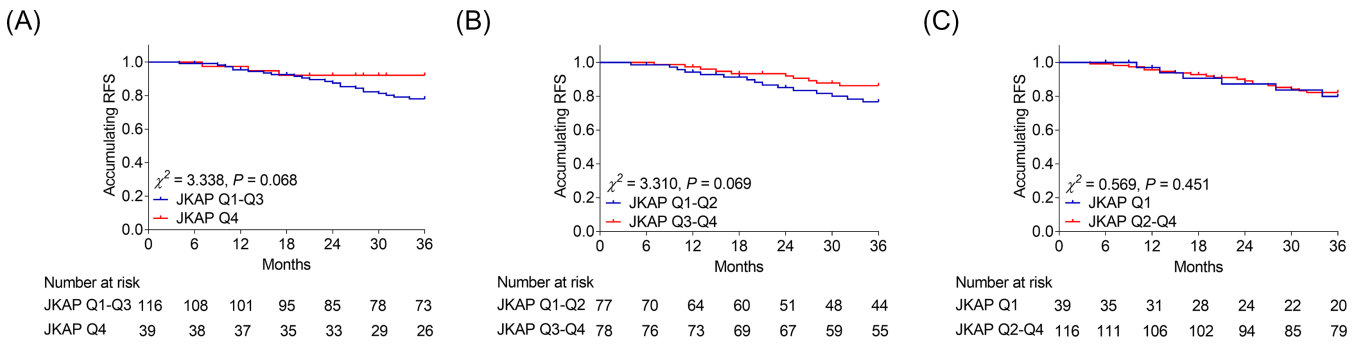


**FIGURE 5** Correlation of JKAP with RFS in AIS patients. Comparison of accumulating RFS between patients with JKAP Q4 and patients with JKAP Q1-Q3 (A), between patients with JKAP Q3-Q4 and patients with JKAP Q1-Q2 (B), between patients with JKAP Q2-Q4 and patients with JKAP Q1 (C)

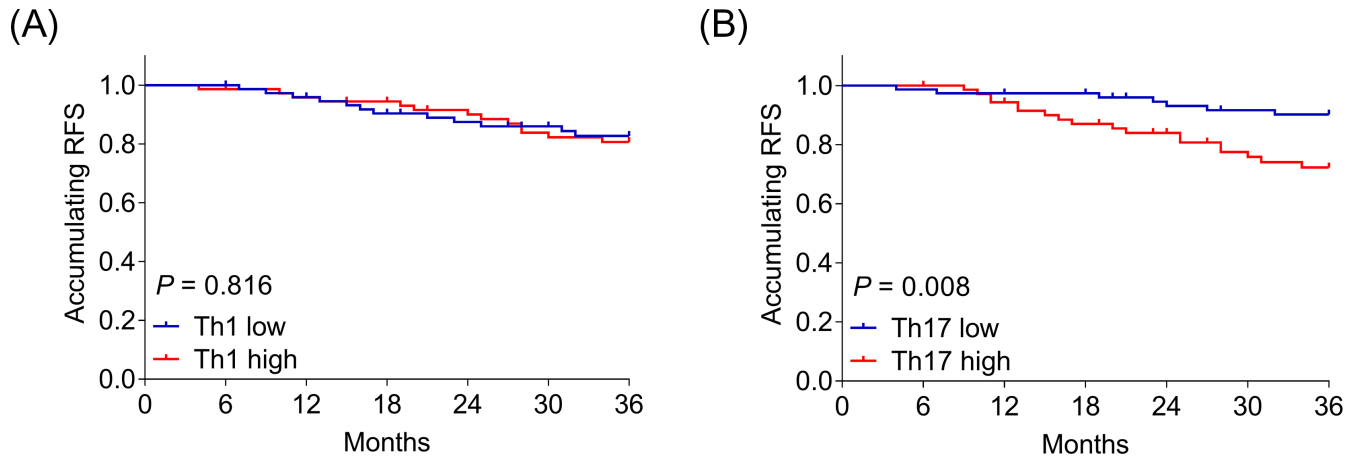


**FIGURE 6** Correlation of Th1 and Th17 cells with RFS in AIS patients. Comparison of accumulating RFS between patients with Th1 high and patients with Th1 low (A), between patients with Th17 high and patients with Th17 low (B)

## 4 | DISCUSSION

JKAP, widely exists in various human tissues,[22] regulating the inhibition of T-cell mediated inflammation or T cell activation. For example, it's suggested that the knockout of JKAP promotes cell proliferation and increases the expression of inflammation cytokines in T cells.[14] Additionally, JKAP has been discovered to modify T cell activation and participate in inflammation-related disease progression.[22] According to another recent study, JKAP inhibits T cell activation, which plays a vital role in systemic lupus erythematosus (SLE) pathology.[11] As mentioned above, inflammation is regulated by JKAP, furthermore, it also contributes to neural injury and blood–brain barrier dysfunction, which occurs during and after AIS.[23] Thus, it could be deduced that JKAP might take part in the pathogenesis of AIS through regulating T cell activity as shown by these previous studies. Interestingly, a recent study reports JKAP possess the potency as a biomarker for AIS, while its sample size is relatively small, and it neither detects Th1 and Th17 cell percentage in blood, nor evaluates the RFS in AIS patients.[24] Therefore, our current study enrolled a relatively larger sample-size AIS patients, evaluated their JKAP, Th1 and TH17 cells, then assess their correlation with RFS.

In the aspect of JKAP' relation to $CD4^+$ T cells in patients with inflammation-related disease: JKAP level negatively associates with Th1 and Th17 cells in sepsis patients.[13] Moreover, JKAP relates to decreased level of Th1 secreted cytokine (IFN-γ) and Th17 secreted cytokine (IL-17A) in IBD patients.[14] The current study discovered that JKAP was negatively correlated with Th1 cells, Th17 cells, IFN-γ, and IL-17A in AIS patients, which showed similar correlation trend with previous studies focusing other diseases. A possible explanation for our data might be that: JKAP regulates Lck and further blocks T-cell receptor (TCR) pathway, so as to repress $CD4^+$ T cell's differentiation into Th1/Th17 cells.[10]

JKAP's relationship with clinical characteristics in patients with inflammation-related disease is also observed. A study suggests that JKAP is linked with better lung function indexes in asthmatic exacerbation children.[25] Another study shows that JKAP level negatively associates with inflammation and organ injuries in sepsis patients.[13] The present study observed that JKAP was associated with milder disease severity of AIS, which could be explained: JKAP might activate JNK signaling pathways and further inhibit the inflammatory cytokine production, then leads to the inactivation of inflammatory cytokine-induced immune responses, therefore, resulting in favorable disease severity in patients with AIS.[23] Besides, we also found

that Th17 cells, IFN-γ, and IL-17A were correlated with higher disease severity. The reason for this could be that: Th17 cells, IFN-γ and IL-17A are hallmarks of inflammation, thus their high expression means increasing inflammation, which causes more severe brain damage and acute disease condition, subsequently correlates with higher disease severity. Meanwhile, it could also be mentioned that regulatory T cells (Tregs) are closely involved in AIS etiology.[26]

Interestingly, a study observes that the downregulation of JKAP may be used as a potential prognostic biomarker for SLE nephritis.[11] Another study finds that JKAP level is reduced in septic deaths versus septic survivors.[13] Similar with previous studies, our study discovered that JKAP showed a positive trend of associating with longer RFS, while without statistical significance. Possible reasons might be that: (a) JKAP represses T-cell mediated immune responses by modulating TCR signaling, which then causes reduced inflammatory levels[27] and improves neurological outcome,[17] thus bringing in longer RFS; (b) JKAP is correlated with milder disease conditions, which might indirectly result in a better prognosis. However, these data need further validation.

Some limitations were noted: Firstly, this study had relatively short follow-up duration so that long-term prognostic impact of JKAP in AIS patients could be explored. Secondly, to minimize the interference, we enrolled patients with first-episode AIS. Therefore, the prognostic role of JKAP for recurrent AIS patients was to be further explored. Thirdly, this study did not investigate the molecular mechanism of JKAP in the regulation of AIS recurrence, which could be performed. Fourthly, the blood samples were collected only one time, while they could be collected more times to monitor the change of JKAP. Fifthly, the gene variation of JKAP was not detected in our study, which could be explored in the future. Sixthly, there are many factors that may relate to the prognosis of AIS, which may affect our findings.

In conclusion, JKAP correlates with lower Th1 and Th17 cell levels as well as milder disease severity, which may have potency to serve as a biomarker for AIS patients management, but further studies are needed for validation.

## ACKNOWLEDGEMENTS

None.

## CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

## DATA AVAILABILITY STATEMENT

The datasets used and analysed 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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