



Profiles of Proinflammatory Cytokines and T Cells in Patients With Tourette Syndrome: A Meta-Analysis

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Background: Tic disorder is a neurodevelopmental disorder characterized by motor and phonic tic symptoms. Tourette syndrome (TS) is a subtype of tic disorder that shows more persistent tic symptoms. The etiological mechanism of TS concerning immune dysfunction remains unclear due to limited evidence, especially for pediatric TS patients.

Method: In the present study, a meta-analysis was performed to confirm the identified changes in proinflammatory cytokines and T cells of pediatric TS patients. A total of five databases, including PubMed, Web of Science, PsycINFO, Google Scholar and the China National Knowledge Infrastructure (CNKI), were used for the literature search. The standardized mean difference (SMD) and mean difference (MD) with a 95% confidence interval (CI) were used to present the effect size of each type of proinflammatory cytokine and T cell. Sensitivity analysis, subgroup analysis and meta-regression analysis were used to explore the heterogeneity of the meta-analysis. This meta-analysis was registered in the International Platform of Registered Systematic Review and Meta-analysis Protocols (number: INPLASY2021110079).

Results: In the 25 studies included in this meta-analysis, thirteen studies focused on the levels of T cells, and twelve studies focused on the levels of proinflammatory cytokines. Based on the random-effects model, the pooled MDs are -1.45 (95% CI: -3.44, 0.54) for CD3 cells, -4.44 (95% CI: -6.80, -2.08) for CD4 cells, and 1.94 (95% CI: -0.08, 3.97) for CD8 cells. The pooled SMDs are 1.36 for IL-6 (95% CI: 0.00, 2.72) and 2.39 for tumor necrosis factor alpha (TNF- α) (95% CI: 0.93, 3.84).

Conclusion: We provided evidence of immune dysfunction in pediatric TS patients, with elevated levels of particular proinflammatory cytokines and disproportionate changes in T-cell subpopulations. Small to large effect sizes were identified for increased IL-6 levels as well as a reduced number of T helper cells, while a large effect size was identified for increased TNF- α levels. These results indicate a close association between peripheral immune activation and TS. However, the most direct and meaningful interaction between

peripheral immune status and microglial activation in the central nervous system in TS patients requires further exploration.

Keywords: Tourette syndrome, proinflammatory cytokines, T cell, immunological dysfunction, meta-analysis

INTRODUCTION

Tic disorders (TDs) are common neurodevelopmental disorders in children and adolescents. According to the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), Tourette's syndrome (TS), chronic motor tic disorder (CMTD), chronic vocal tic disorder (CVTD), and transient tic disorder (TTD) are the main diagnostic types of TDs (1). Of them, TS shows more persistent tic symptoms (2), and patients with TS commonly have poorer prognosis than those with other types of tic disorders (3). According to a previous investigation, TS affects approximately 4 to 8 per 1000 children and is associated with hyperactivity, impulsiveness, inattention and emotional problems (4). Despite numerous attempts to clarify the pathophysiology of TS from behavioral and brain imaging levels (5, 6) to genetic and immunological levels (7, 8), the etiology of TS is still not well established (9). It is worth noting that immune dysfunction has been regarded as one of the most important factors involved in the onset and development of TS (10).

Tic symptoms generally start at the age of 7-8 years and reach their utmost severity at approximately 8-12 years old (11, 12), with occasional reoccurrences throughout the lifespan in many cases (13). Accumulated evidence has suggested that relapse of tic symptoms during the long pathophysiological course of TS might be triggered by improper immune activation and inflammation (14, 15). A larger number of TS patients were identified to have group A streptococcal (GAS) infection that was not in the healthy group (16). Moreover, a group of TS patients have also been proven to have streptococcal infection (17). Other infections, such as mycoplasma and enterovirus (EV), are also reported to be associated with tic symptoms (10, 18, 19). Infections commonly trigger immune activation and proinflammatory reactions. For instance, it has been documented that GAS infection in TS patients induced an increased serum antistreptolysin O (ASO) level (7). However, the most recent study by the European multicenter tics in children identified that GAS exposure is not associated with the development of tics in children with a chronic tic disorder (20). CD69⁺ B lymphocytes and CD95⁺ T lymphocytes have been revealed to be markedly increased in adult TS patients (21). It has been commonly believed that a skewed increase in particular proinflammatory cytokines as well as a deviated change in a particular T-cell component are closely associated with TS (10).

Recently, only a narrative review (10) and a meta-analysis on proinflammatory cytokines in TS have been reported (7). Notably, most present studies on the inflammatory environment in TS are limited by small sample sizes (10). However, the conclusion of that meta-analysis is limited by the very small number of enrolled studies (only 2-3 studies were

included in each meta-analysis). Therefore, a comprehensive meta-analysis with more exhaustive inclusion of TS-related studies is warranted to determine the relationship between immune dysfunction and the disease progression of TS. To achieve this aim, we conducted a meta-analysis to delineate the profiles of immune cells and proinflammatory cytokines in patients with TS. Our analysis based on the results of previous studies indicated that deviation in the T-cell compartment and proinflammatory cytokines in peripheral circulation are featured in TS patients.

MATERIALS AND METHODS

Literature Search

A systematic search was performed in the PubMed, Elsevier, and China National Knowledge Infrastructure (CNKI) databases. The keywords used to identify studies are as follows: ('tic' or 'Tourette' or 'TD' or 'TS' or 'Tourette syndrome') and ('cytokines' or 'TNF- α ' or 'IL-2' or 'IL-4' or 'IL-6' or 'IL-8' or 'IL-12' or 'IFN- γ ' or 'CD3' or 'CD4' or 'CD8' or 'CD4/CD8' or 'T-cell'). When searching the CNKI database, we used the corresponding formal translation terms (in Chinese) mentioned above. The included studies (up to 31 October 2021) subjected to our meta-analysis were independently cross-checked by two researchers to verify their relevance to the topic. This study is registered in the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY, number: INPLASY2021110079).

Inclusion and Exclusion Criteria

To identify relevant studies for our meta-analysis, we developed the following inclusion and exclusion criteria:

The inclusion criteria are as follows:

- (1) English or Chinese studies from peer-reviewed journals.
- (2) The included patients are diagnosed with Tourette syndrome-related disorders.
- (3) T cells and cytokines are assessed in the serum or plasma of peripheral blood.

The exclusion criteria are as follows:

- (1) Case reports, reviews, or meta-analyses.
- (2) Studies with a sample size less than 5.
- (3) Studies involving rats or mice, rather than humans.
- (4) Studies that included the same participants in the included studies.

Quality Assessment for the Included Studies

The quality of each study is assessed by the modified Critical Appraisal Skills Programme (CASP) scale. The CASP tool is widely used for appraising the limitations and strengths of any qualitative research methodology (22, 23). This tool included 11 items such as ‘Item 1: Did the study address a clearly focused issue?’ or ‘Item 4: Were the controls selected in an acceptable way?’. Studies were chosen or discarded until a consensus was reached after independent assessment from two authors. Studies are excluded when less than 6 ‘Yes’ responses after CASP scale processing.

Data Extraction

The following information was extracted from the included studies: authors, publication years, countries, sample sizes (patients/controls), mean ages (years), types of proinflammatory cytokines and T cells, Yale Global Tic Severity Scale (YGTSS) scores (mean \pm standard deviation), and techniques for measuring the T cells/proinflammatory cytokines.

Statistical Analysis

I^2 statistics and forest plots are used to identify the heterogeneity of the meta-analysis. Provided that I^2 was greater than 50%, a random-effects model is applied (24). Egger’s test is employed to judge whether there is publication bias. A sensitivity analysis is also performed to identify the study with high heterogeneity (omitting one study at a time and tracking the change in I^2 to identify the contribution of each study to the heterogeneity) (25). The standardized mean difference (SMD) is calculated to

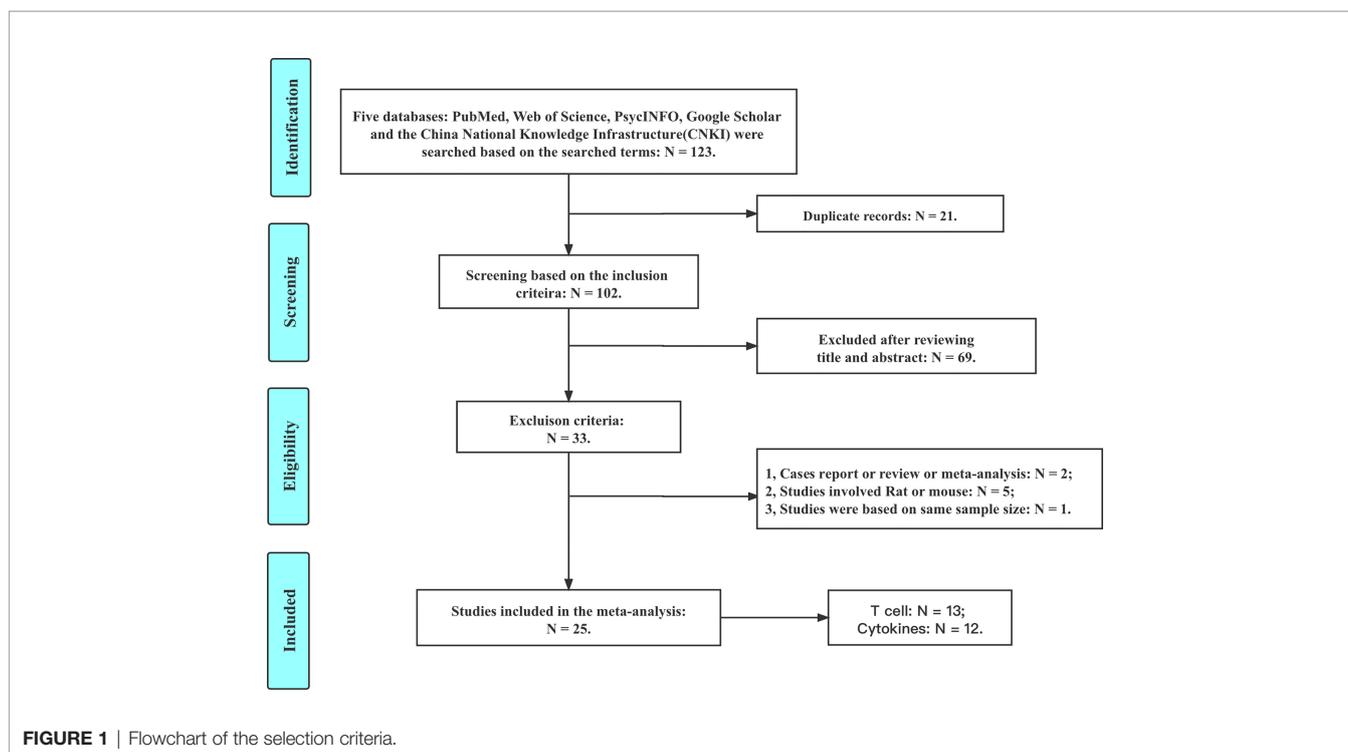
measure the effect size in each included study (for the SMD calculation formula, please see **Supplementary Figure 1**). An SMD value between 0.2 and 0.5 is considered mild-to-moderate, whereas an SMD value between 0.5 and 0.8 indicates that the efficacy is moderate-to-large (26). Moreover, the mean difference (MD) is also used to calculate the effect size of the meta-analysis. If the included studies are based on the same sample and same technique, the MD is used; if not, the SMD is used. We consider a p value < 0.05 to be statistically significant, and all the analyses are performed in R (version 3.5.3) using the “meta” or “metafor” package (27).

RESULTS

The Description of the Included Studies

Based on the inclusion and exclusion criteria, a total of 25 studies are included in this meta-analysis (details are shown in **Figure 1**). There are 13 studies reporting the CD3, CD4, and CD8 levels; 4 studies reporting the IL-2 level; 4 studies reporting the IL-4 level; 7 studies reporting the IL-6 level; 4 studies reporting the IL-8 level; 5 studies reporting the IL-12 level; 4 studies reporting the INF- γ level; and 8 studies reporting the TNF- α level.

We summarize the expression of several proinflammatory cytokines and T cells in TS patients and healthy controls. All included studies measure cytokine levels in serum or plasma from participants with TS. The expression of seven cytokines (TNF- α , IL-2, IL-4, IL-6, IL-8, IL-12 and IFN- γ) and the proportions of T cells (CD3, CD4, CD8) are summarized.



Furthermore, we list the authors, publication years, countries, sample sizes (patients/controls), mean ages (years), types of proinflammatory cytokines and T cells, YGTSS scores (mean \pm standard deviation) and the techniques used in each included study (Table 1).

Quality Assessment and Publication Bias for the Included Studies

Assessments of the CASP scale for each included study are shown in Supplementary Table 1 (all included studies met the criteria for quality assessment). Egger's test values, the degree of the test, and the p value are shown in Table 2. No publication bias is identified for the meta-analysis of CD3, CD4, CD8, IL-2, IL-4, IL-6, IL-8, IL-12 and TNF- α ($p > 0.05$). However, significant publication bias is identified in the meta-analysis of IFN- γ ($p = 0.02$). Therefore, the included studies for IFN- γ are not suitable for the meta-analysis. Details are shown in Table 2.

Meta-Analysis of T Cells

Because the included studies of T cells are based on the same types of samples and the same technique, the MD was used to show the pooled effect size of T cells. The pooled MDs of CD3, CD4, CD8 and CD4/CD8 cells with 95% confidence intervals

(CIs) were calculated. Based on the random-effects model, the pooled MDs are -1.45 (95% CI: -3.44, 0.54) for CD3 cells, -4.44 (95% CI: -6.80, -2.08) for CD4 cells, 1.94 (95% CI: -0.08, 3.97) for CD8 cells, and -0.20 (95% CI: -0.32, -0.08) for CD4/CD8 cells. Details are shown in Figure 2.

Meta-Analysis of Proinflammatory Cytokines

Due to the measured cytokine concentrations derived from different sample sources (plasma and serum) in the included studies, the pooled SMD with 95% CIs is used to assess the effect size of proinflammatory cytokines. When the I^2 of the pooled SMD is more than 50%, the random-effects model is selected. We found that the pooled SMD is 0.82 (95% CI: -2.37, 0.73) for IL-2, -0.01 (95% CI: -1.16, 1.15) for IL-4, 1.36 (95% CI: 0.00, 2.72) for IL-6, 2.22 (95% CI: -0.38, 4.81) for IL-8, 1.10 (95% CI: -0.15, 2.36) for IL-12, and 2.39 (95% CI: 0.93, 3.84) for TNF- α (Figure 3). Since publication bias was detected for IFN- γ , we presented the results for IFN- γ in Supplementary Figure 2 as evidence of lower grade.

Sensitivity Analysis of the Meta-Analysis

Sensitivity analysis is performed to explore the heterogeneity of the pooled SMD. The results indicate that there are no studies with I^2 changes greater than 5% in the meta-analysis of IL-2, IL-

TABLE 1 | The included studies for this meta-analysis.

Study	Year	Country	Patient/ Control	Age (years)	YGTSS score	Sample	Cell types/Cytokines	Technique
Zeynep et al. (28)	2021	Turkey	48/24	11.6/11.6	-	peripheral blood	CD3, CD4, CD8 T cells	flow cytometry
Ma (29)	2021	China	80/80	8.9/9.0	-	serum	TNF- α , IL-2, IL-6, IL-8	ELISA
Liu (30)	2020	China	100/78	8.8/9.6	-	serum	IL-8	ELISA
Hou ^a et al. (31)	2018	China	150/80	7.5/7.6	-	peripheral blood	CD3, CD4, CD8 T cells	flow cytometry
He (32)	2018	China	66/38	8.8/9.1	-	peripheral blood	CD3, CD4, CD8 T cells	flow cytometry
Pranzatelli et al. (33)	2017	USA	5/26	10/-	50 \pm 31	peripheral blood	CD3, CD4, CD8 T cells	flow cytometry
Lu et al. (34)	2017	China	21/30	9.8/10.1	-	peripheral blood	CD3, CD4, CD8 T cells	flow cytometry
Fan et al. (35)	2017	China	74/20	7.9/9.0	-	serum	TNF- α , IL-6	ELISA
Chen et al. (36)	2016	China	40/40	7.9/7.2	-	peripheral blood	CD3, CD4, CD8 T cells	flow cytometry
Cheng et al. (37)	2016	China	52/52	-/-	-	peripheral blood, serum	CD3, CD4, CD8 T cells, TNF- α , IL-6, IL-8	flow cytometry, ELISA
Gao et al. (38)	2016	China	40/40	8.8/8.2	65.31 \pm 9.85	serum	IFN- γ , IL-4	ELISA
Erzhen et al. (39)	2015	China	58/45	9.7/8.9	31.18 \pm 6.70	peripheral blood	CD3, CD4, CD8 T cells	flow cytometry
Zhang et al. (40)	2015	China	31/30	9.0/8.0	-	peripheral blood	CD3, CD4, CD8 T cells	flow cytometry
Zhang et al. (41)	2014	China	41/60	10.0/10.0	-	serum	IFN- γ , IL-12, IL-2, IL-4	ELISA
Tang et al. (42)	2014	China	30/30	10.7/10.8	16.14 \pm 6.94	serum	TNF- α , IL-12	ELISA
Luo et al. (43)	2014	China	40/24	7.7/8.1	-	serum	TNF- α , IL-2	ELISA
Liu et al. (44)	2013	China	57/43	9.7/9.4	-	peripheral blood	CD3, CD4, CD8 T cells	flow cytometry
Li et al. (45)	2013	China	32/30	10.1/10.7	-	peripheral blood, serum	CD3, CD4, CD8 T cells, IL-6, IL-8	flow cytometry, ELISA
Yu-hang et al. (46)	2012	China	40/40	13.0/12.4	-	plasma	IL-6	ELISA
Ji (47)	2011	China	33/30	10.0/9.6	-	peripheral blood	CD3, CD4, CD8 T cells	flow cytometry
Gabbay et al. (48)	2009	USA	32/16	11.2/15.1	22.0 \pm 6.11	plasma	TNF- α , IL-12, IL-6	ELISA
Zhang (49)	2008	China	30/30	10.1/10.5	-	peripheral blood	CD3, CD4, CD8 T cells	flow cytometry
Mao (50)	2008	China	25/15	-	-	serum	TNF- α , IL-12	ELISA
Leckman et al. (51)	2005	USA	46/31	11.8/12.5	-	serum	IFN- γ , IL-12, TNF- α , IL-2, IL-4, IL-6	ELISA
Hou et al. ^b (31)	2018	China	40/40	7.5/7.6	-	serum	IFN-γ IL-4	ELISA

YGTSS, Yale Global Tic Severity Scale; IL, Interleukin; TNF- α , tumor necrosis factor alpha; IFN- γ , Interferon gamma; ELISA, the enzyme-linked immunosorbent assay; Hou XJa and Hou XJb were from the same study but different sample.

Bold vaule means same study with different sample.

TABLE 2 | The publication bias by Egger test.

Meta-analysis	Number of included studies	T value	df	p-value
IL-2	4	1.67	2	0.24
IL-4	4	-1.05	2	0.40
IL-6	7	1.60	5	0.17
IL-8	4	2.75	2	0.11
IL-12	5	3.08	3	0.05 (0.0542)
TNF- α	8	1.65	6	0.15
IFN- γ	4	6.44	2	0.02*
CD3	13	-0.60	11	0.56
CD4	13	-0.23	11	0.82
CD8	13	-0.65	11	0.53
CD4/CD8	11	-0.03	9	0.97

* $P < 0.05$.

6, IL-8, IL-12, TNF- α , CD4, and CD8. However, in the sensitivity analysis of IL-4, one study might have increased the heterogeneity (with I^2 changes greater than 5%) (41). When we exclude this study, the modified pooled SMD for IL-4 is -0.52 (95% CI: -1.32, 0.29). In the sensitivity analysis of CD3, one study might have increased the heterogeneity (40). After the exclusion of this study, the modified pooled MD for CD3 cells is -0.95 (95% CI: -2.77, 0.88).

Subgroup Analysis and Meta-Regression Analysis

Subgroup analysis by 'Mean Age' (Group A below 10 years old, Group B above 10 years old) is performed in the meta-analysis of TNF- α and IL-6 (the number of included studies for these two studies is more than 5). However, no significant difference was identified in the test for the subgroup differences (random effect model) of IL-6 ($p = 0.24$) and TNF- α ($p = 0.57$) (Supplementary Figure 3).

Meta-regression analysis of 'Mean Age' and 'Publication Year' for CD4 and CD8 was performed, and the results of the meta-regression analysis are summarized in Table 3. Only the 'Publication Year' for CD8 was significant (accounting for 31.80% of the heterogeneity, $p = 0.02$).

Other Immunological Indicators Associated With Tourette Syndrome

In addition to T cells and peripheral proinflammatory cytokines, we also searched for other immunological indicators associated with Tourette syndrome. The data for the first author, publication year, sample size, mean and standard deviation of these immunological indicators in the experimental group and the control group are listed in Table 2 as the Supplementary Materials. We found equivocal results in immunoglobulin- and B-cell-related studies on Tourette syndrome. Of note, one study reported increased monocytes/macrophages in Tourette syndrome patients, while the fact that only one publication mentioned the change in monocytes/macrophages made us unable to perform any meaningful meta-analysis (52).

DISCUSSION

In the present study, our results indicate that the levels of proinflammatory cytokines are increased in pediatric patients with Tourette syndrome. Increased CD4 T-cell and decreased CD8 T-cell levels were identified. The effect sizes of the meta-analysis of proinflammatory cytokines, including IL-6 and TNF- α , were moderate to large, while those of T cells, including CD4, were small to moderate. Other immunological indicators, such as B cells, monocytes/macrophages and immunoglobulins, might also be associated with Tourette syndrome, but further evidence is needed. Taken together, our meta-analysis consolidates the features of immune dysfunction in patients with Tourette syndrome.

Accumulated studies have deemed TS a neurodevelopmental disorder induced by dysregulated immune function, especially inflammatory responses. The TNF- α level was shown to be upregulated in 7/9 (78%) included studies, and the IL-6 level was upregulated in 6/9 (67%) studies. In this meta-analysis, TNF- α and IL-6 levels in peripheral blood were significantly increased in TS patients compared with healthy controls. However, no significant difference was identified in the expression of IL-2, IL-4, and IL-8 between TS patients and healthy controls (0 is included in the pooled SMD of these ILs). Notably, another recent meta-analysis of the immune implications in Tourette syndrome, performed by Lamothe et al. (7), only focused on ASO antibodies and anti-DNase B antibodies rather than proinflammatory cytokines. Due to the limited cytokine data, this study did not come to a conclusion about the involvement of specific cytokines in TS neurobiology.

Activation of the immune system triggered by infection is believed to be closely related to the development of TS, which has been shown in many previous studies. In contrast, a recent European multicenter study on tics in children found that GAS exposure was not associated with chronic tic disorder (CTD) (20). Interestingly, while *Mycoplasma pneumoniae* IgG positivity is not associated with a diagnosis of CTD or tic onset, it presents with a positive relationship with the severity of tic symptoms (53). This implies that differential immune status triggered by various pathogens possibly participates in different steps of TS pathogenesis.

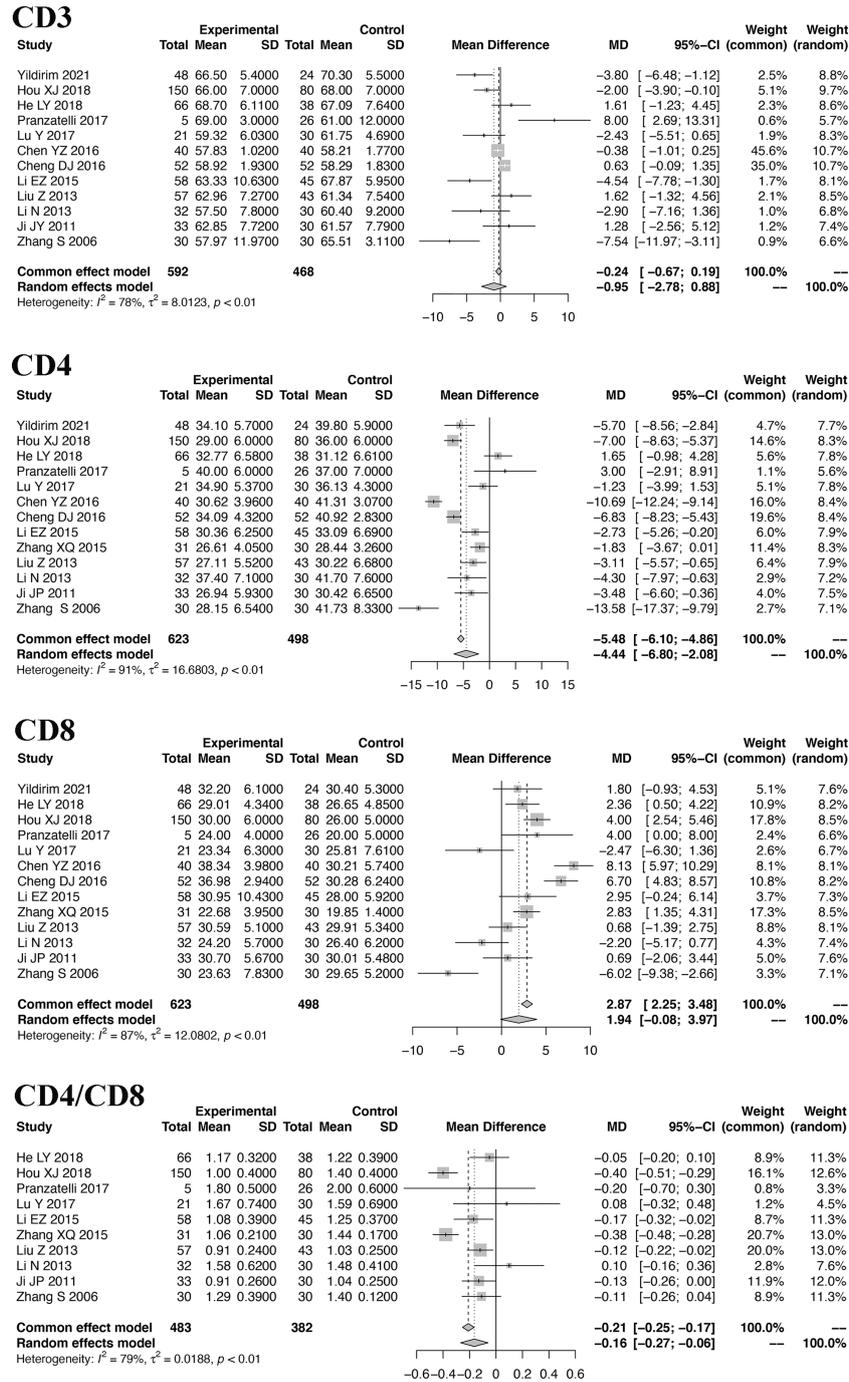


FIGURE 2 | Forest plot of the meta-analysis of T cells.

IL-12 is a critical cytokine for immune activation, including activating natural killer (NK) cells and inducing CD4 T-cell differentiation into Th cells (54). Meanwhile, IL-12 is important for macrophage activation, inflammatory M1-type transformation and the production of macrophage-derived TNF- α and IL-6 (55, 56). Early in 2005, Leckman et al. (51) reported increased

IL-12 levels in patients with TS. However, in our meta-analysis, we did not find an association of IL-12 with TS. To answer whether IL12 is implicated in the onset and progression of TS requires more bench work and more input from different studies.

Based on the results of the present study, we identified reduced total circulating CD4 T cells accompanied by an

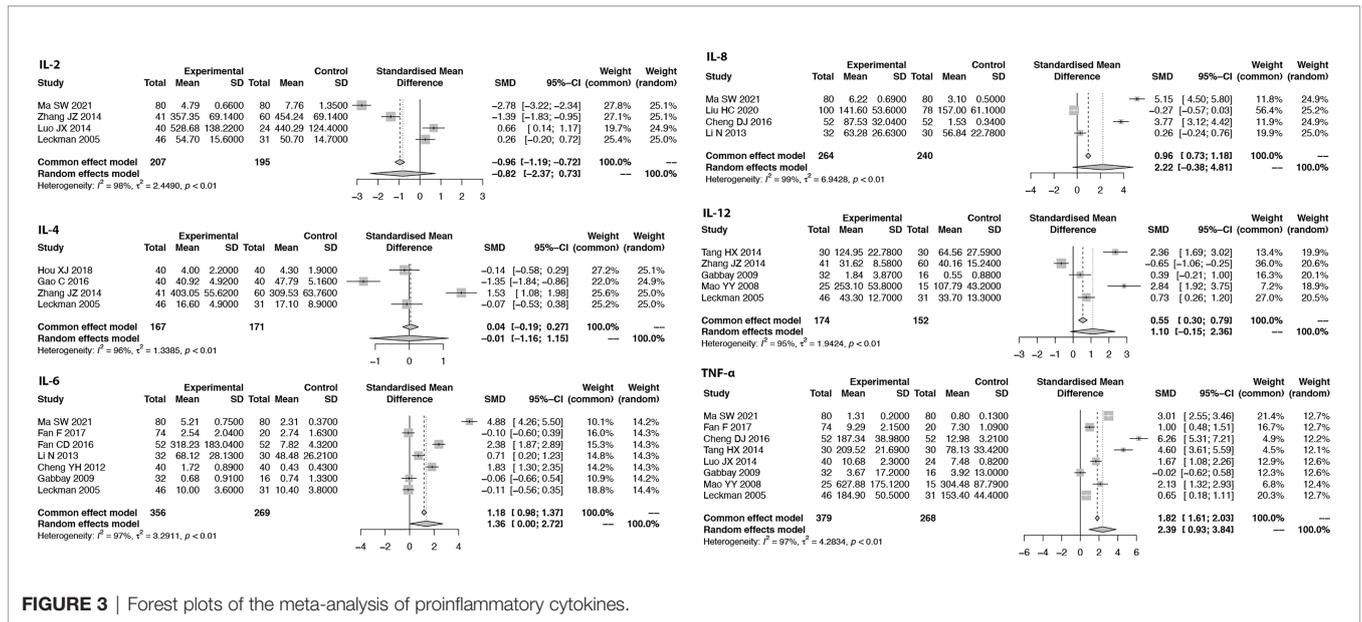


FIGURE 3 | Forest plots of the meta-analysis of proinflammatory cytokines.

increased proportion of CD8 T cells in TS patients. Recently, a study on a TS animal model showed a reduction in rat splenic CD4 cells (57). Notably, CD4 T cells are typically divided into regulatory T (Treg) cells and conventional T helper (Th) cells. The participating role of Treg cells in TS is controversial, as one reported a reduction in the number of Treg cells and another reported an increase in activated Treg cells (58). The reduction in CD4 T helper cells could not provide confident support for the features of Treg cells, as our meta-analysis did not probe to that resolution. Instead of meta-analysis, more solid laboratory experiments need to be done to depict the role of Treg cells in TS patients.

During an infectious state, the peripheral immune system is activated, accompanied by changes in the number of T cells and increased proinflammatory cytokines. A study by Hsu et al. suggests that an activated peripheral immune system might harm the neuronal-immune system (10). Moreover, it should be noted that microglial activation might also play an important role in the neuronal-immune system of patients with TS (59). For example, a transcriptome analysis of the basal ganglia in postmortem brains from nine patients with TS indicated microglial activation in the striatum (60). Indeed, TNF-α and IL-6 have been proven to subserve the regulation of the blood-brain barrier (BBB) (61–63). Some proinflammatory cytokines

may contribute to disrupting the BBB and promoting the transendothelial migration of immune cells (64, 65). With the accumulated proinflammatory cytokines crossing the BBB, microglial activation might occur in the brain (66).

Due to the limited number of studies, meta-analyses on B cells or immunoglobulins are scarce. The current study attempts to obtain information from studies on B cells and immunoglobulins. We failed to see clear effects of B cells and immunoglobulins on the development of TS. Regarding the role of monocytes/macrophages in TS, only one study with a small sample size identified increased cell numbers of monocytes/macrophages (52). More evidence is needed to explore their potential roles in immune dysfunction in TS patients. Moreover, which immune cells (including T cells, B cells or macrophages) produce elevated TNF-α and IL-6 levels in the peripheral immune system might be an important topic for future research.

Small total samples were subjected to our meta-analysis due to the limited number of available publications related to TS that enchain our analysis resolution. Hopefully, as an increasing number of TS-related publications become available, a larger sample size across different age groups could be achieved in the near future. Second, due to the limited number of included studies, a limited number of subgroup analyses or meta-regression analyses were performed to represent the

TABLE 3 | The meta-regression analysis for the Mean Age and Publication Year to CD4 and CD8.

Predictors	Number of included studies	Tau ²	I ²	H ²	R ²	QM	P value
Publication Year to CD4	13	15.50	92.10%	12.65	7.10%	2.19	0.14
Publication Year to CD8	13	8.24	86.23%	7.26	31.80%	5.61	0.02*
Mean Age to CD4	13	18.25	92.65%	13.60	0.00%	0.15	0.70
Mean Age to CD8	13	11.01	89.15%	9.21	8.87%	2.02	0.16

* $P < 0.05$; Tau², estimated amount of residual heterogeneity; I², residual heterogeneity or unaccounted variability; H², unaccounted variability / sampling variability; R², amount of heterogeneity accounted for; QM: the statistic of the test of predictors.

heterogeneity of the meta-analysis. Last, but most importantly, the prominent heterogeneity of the data warned by our quality control step indicates that other factors could interfere with our results. For example, treatment with medicines for Tourette syndrome may change the levels of proinflammatory cytokines and T cells (67). However, due to the unavailability of the related data of the included studies, we did not explore the potential sources of the data heterogeneity, which, if we were able to accomplish, would remarkably consolidate our analysis and improve the grade of evidence.

CONCLUSIONS

In the present meta-analysis, our results reveal increased levels of proinflammatory cytokines and deviated T-cell proportions and provide evidence for immune dysfunction in pediatric patients with TS. The proinflammatory milieu with increased IL-6 and TNF- α levels as well as reduced CD4 T helper cells is characterized. Verification of the pathophysiological roles of T cells as well as these proinflammatory cytokines in pediatric TS patients is valuable. That being said, we could still not exclude the pathogenic role of other cells, such as monocytes/macrophages or B cells, in TS due to the scarce data thus far. Furthermore, the correlation of microglial activation, which is supposed to have a direct linkage with the clinical symptoms of TS, with the immune dysregulation found in the present study is worth exploring.

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AUTHOR CONTRIBUTIONS

For this manuscript, YiL and XW took the initiative, performed the data analysis, and completed the draft. YaL searched the included studies, and HY polished the language. YC and JG provided detailed suggestions for this study. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fimmu.2022.843247/full#supplementary-material>

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