Meta Analysis

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Efficacy and safety of cyclosporine-based regimens for primary immune thrombocytopenia: a systematic review and meta-analysis

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Abstract

Objective: To conduct a meta-analysis assessing the efficacy and safety of cyclosporine-based combinations for primary immune thrombocytopenia (ITP).

Methods: Randomized controlled clinical trials were collected by systematically searching databases (PubMed®, MEDLINE®, EMBASE, The Cochrane Library, China National Knowledge Infrastructure) from inception to June 2022. All studies included patients with ITP who received cyclosporine-based regimens. We performed comprehensive analyses of the overall response rate (ORR), complete response (CR) rate, partial response (PR) rate, relapse rate, platelet count, and adverse drug reaction (ADR) rate.

Results: Seven studies (n = 418) were ultimately included. According to a fixed-effects model, cyclosporine-based combinations improved the ORR and CR rate and reduced the relapse rate. The ADR rate was not increased in the cyclosporine-based combination group. Cyclosporine-based regimens effectively increased the platelet count. Subgroup analysis illustrated that cyclosporine-based combinations were linked to higher ORRs in both children (odds ratio [OR] = 5.74, 95% confidence interval [CI] = 1.79–18.41) and adults (OR = 5.46, 95% CI = 2.48–12.02) and a higher CR rate in adults (OR = 2.97, 95% CI = 1.56–5.63).

Conclusion: Cyclosporine exhibited efficacy in the treatment of ITP without increasing the risk of ADRs.

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Keywords
Primary immune thrombocytopenia, cyclosporine, meta-analysis, adverse drug reaction, platelet count, overall response, complete response, partial response

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Introduction

Primary immune thrombocytopenia (ITP) is an autoimmune hemorrhagic disease occurring in children and adults, and its clinical manifestations include thrombocytopenia, skin and mucosal bleeding, and serious life-threatening visceral bleeding.[1] Its incidence is estimated to be 2 to 5 per 100,000 persons in the general population.[2] The pathogenesis of ITP is extremely complex, and it is mainly attributable to the loss of immune tolerance in the body, increasing platelet destruction or causing an abnormal deficiency of platelets produced by megakaryocytes.[3] When patients with ITP have significant bleeding symptoms and/or a platelet count of less than 20,000 to 30,000/mL, multiple first-line drugs such as corticosteroids, intravenous immunoglobulin (IVIg), and anti-D are administered to reduce anti-platelet autoantibody production and platelet destruction.[4,5] However, after first-line drug therapy, some patients do not experience effective remission and cure, and others experience disease recurrence. Therefore, there is an urgent need for novel options for second-line therapy.[6] Cyclosporine is a widely used potent immunosuppressant that can effectively act on both humoral and cellular immunity.[7] Multiple studies demonstrated that cyclosporine plays an important role in regulating multiple immune cell types and related inflammatory factors, and the drug can inhibit the activities of helper T cells and $CD8^+$ T lymphocytes. It can suppress the proliferation and differentiation of T lymphocytes by inhibiting IL-2 and regulate protein expression in dendritic cells, macrophages, and neutrophils.[8,9] Cyclosporine plays a key therapeutic role in multiple immune-related diseases such as systemic lupus erythematosus, Sjögren's syndrome, and psoriatic arthritis.[10,11] Furthermore, as the main second-line drug for the treatment of ITP, cyclosporine can improve the total effective rate of clinical treatment in patients with ITP and reduce the recurrence rate.[12,13] A recent retrospective study found that cyclosporine effectively treated children with refractory ITP and prevented splenectomy.[14]

Given the pivotal role of cyclosporine as a potent therapy for the treatment of ITP, we conducted a systematic review and meta-analysis of published data to verify the efficacy and safety of cyclosporine in ITP treatment.

Materials and methods

Study methods

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[15] It was registered to PROSPERO (CRD42022342352). This study strictly abided by a pre-set protocol. All clinical protocols were reviewed and approved by the hospital ethics committee. Written informed consent was obtained from the participants.

Data source and search strategy

From inception to June 2022, relevant publications listed in databases (PubMed®,

MEDLINE®, EMBASE, The Cochrane Library, China National Knowledge Infrastructure [CNKI]) were systematically searched using a series of keywords. The critical search strategy for PubMed was as follows: ("immune thrombocytopenia" [MeSH Terms] OR "thrombocytopenia" [Title/Abstract] OR "Idiopathic thrombocytopenic purpura" [Title/Abstract] OR "ITP" [Title/Abstract]) AND ("cyclosporine" [MeSH Terms] OR "cyclosporine A" [MeSH Terms] OR "CsA" [Title/Abstract]) AND ("randomized controlled trials" [MeSH Terms] OR "controlled clinical trial" [Publication Type] OR "clinical trial" [Publication Type] OR "clinical study" [Publication Type]). Similar strategies were adapted for the other databases. There were no language restrictions during the course of searching. A manual review of the reference lists related to principal studies was also conducted to identify all potentially eligible studies.

Study selection

The inclusion criteria were as follows: (i) randomized controlled clinical trials; (ii) patients with ITP; (iii) cyclosporine for ITP treatment regardless of its doses and courses; (iv) pooled analyses of the overall response rate (ORR), complete response (CR) rate, partial response (PR) rate, relapse rate, effective duration, adverse drug reactions (ADRs), and platelet count. The exclusion criteria were as follows: (i) duplicate studies, retrospective studies, reviews, case reports, conference abstracts, and irrelevant topics; (ii) studies conducted in animals and cells; (iii) studies on secondary ITP; and (iv) the ORR, CR rate, or PR rate was not reported.

Data extraction and quality assessment

The following information from the included studies was extracted by two investigators (LX and LJ): authors, publication year, country, ITP stage, sample size, age, sex, intervention measures and course of treatment, and main outcomes. Two investigators (ZW and LJ) independently extracted the relevant data from the study according to the same standard. Any discrepancies were resolved by consulting a third investigator (BJ).

Two investigators (BJ and LJ) independently assessed the methodological quality of the trials that met the inclusion criteria according to the Cochrane Collaboration Risk of Bias tool. The research quality assessment mainly included the following contents: (i) random sequence generation; (ii) allocation concealment; (iii) blinding of participants and personnel; (iv) blinding of outcome assessment; (v) incomplete outcome data; (vi) selective reporting; and (vii) other bias that could impact the bias of studies such as the equality of baseline data between groups in the studies.

Statistical analyses

Efficacy and safety outcomes were analyzed using Review Manager (version 5.3, International Cochrane Collaboration Network, London, UK). All of the event rates were analyzed as dichotomous variables. Continuous variables were evaluated using the standardized mean difference (SMD) and 95% confidence interval (CI). In two-tailed tests, $P < 0.05$ was considered statistically significant. Heterogeneity was assessed using the chi-square test, and the extent of heterogeneity was expressed as the I^2 statistic. In the case of heterogeneity ($P < 0.1$, $I^2 > 50\%$), a random-effects model was applied. Otherwise, a fixed-effects model was applied. If there was significant heterogeneity, subgroup analysis was performed. Funnel plots were used to evaluate publication bias.

Results

Literature search

The entire selection process is displayed in Figure 1. Initially, 295 relevant articles were retrieved from five databases (PubMed®: 64; EMBASE: 40; The Cochrane Library: 30; MEDLINE®: 24; CNKI: 137). In total, 116 duplicate studies were removed. Among the remaining 179 studies, 146 were excluded after the screening the titles and abstracts. After reading the full text of 33 studies,[16–22] seven eligible studies were included in the meta-analysis.

Characteristics of the included studies

All included studies were published between 2013 and 2020. These studies involved a total of 418 patients with ITP, including 211 in the treatment groups and 207 in the control groups. Three studies included 211 children,[16,17,22] and the four other studies included 207 adults.[18–21] The characteristics of the included studies are presented in Table 1.[16–22]

Results of the risk of bias assessment

The results of the related bias assessment of all seven trials using the Cochrane tool are

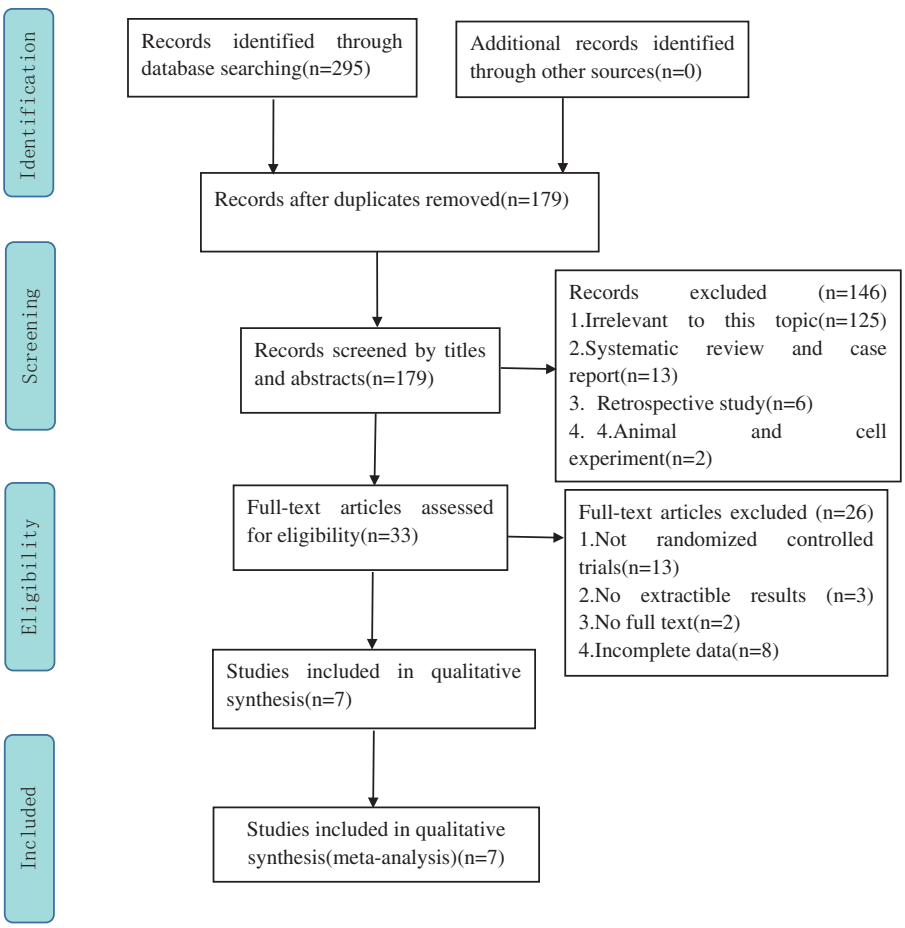

Figure 1. Literature search and study selection flowchart.

Table 1. Characteristics of the seven randomized controlled trials included in a meta-analysis of the efficacy and safety of cyclosporine in patients with ITP.[16–22]

Author/year	Country	Classification	Interventions TG/CG	n	Age, years	Sex (M/F)	Treatment duration	Main outcomes
Wu et al.[16]/2020	China	Chronic ITP	CsA, 3–4 mg/(kg·day), BID + IVIg, 400 g/(kg·day), 5 days	26	5.19 ± 0.64	14/12	1 month	OR, CR, PR, ADR
			IVIG, 400 mg/(kg·day), 5 days	26	6.01 ± 0.71	15/11		
Ma et al.[17]/2020	China	Refractory ITP	CsA, 3.5 mg/(kg day), bid + MPSS, 15 mg/(kg day), qd, 3 days + PAT, 1 mg/(kg day), 10 mg once	49	5.76 ± 1.81	28/21	2 weeks	OR, CR, PR, ADR, PC
			MPSS, 15 mg/(kg day), qd, 3 day + PAT, 1 mg/(kg·day), 10 mg once	49	3.45 ± 1.19	25/24		
Yang et al.[18]/2019	China	Newly diagnosed ITP	CsA, 3 mg/(kg·day), bid + DXM, 40 mg/day, 4 days	25	34 ± 6	11/14	4 months	OR, CR, PR, ED, R, PC
			DXM, 40 mg/day, 4 days	25	33 ± 5	12/13		
Ge et al.[19]/2018	China	Refractory ITP	CsA, 5 mg/(kg·day) + VCR, 2 mg, qw	22	46.22 ± 1.68	10/12	4 months	OR, CR, PR, PC
			VCR, 2 mg, qw	21	34.78 ± 6.21	10/11		
Luo et al.[20]/2017	China	Refractory ITP	CsA, 3–4 mg/(kg·day), bid + RTX, 100 mg, qw	39	34.78 ± 3.47	15/24	3 months	OR, CR, PR, ADR, PC
			RTX, 100 mg, qw	39	35.69 ± 3.65	14/25		
Cui et al.[21]/2013	China	Corticosteroid-resistant ITP	CsA, 1.5–2 mg/(kg·day), bid + rhTPO, 1 μg/kg, 14 days	19	33	9/10	3 months	OR, R
			rhTPO, 1 μg/kg, 14 days	17	35	7/10		
Morteza et al.[22]/2020	Iran	Chronic ITP	CsA, 5 mg/(kg·day), bid	31	9.9 ± 6.5	14/17	6 months	OR, CR, PR, PC
			SRL, 6 mg, qd	30	8.7 ± 7.4	14/16		

TG, treatment group; CG, control group; CsA, cyclosporine A; IVIg, intravenous immunoglobulin; MPSS, methylprednisolone sodium succinate; PAT, prednisone acetate tablets; DXM, dexamethasone; VCR, vincristine; RTX, rituximab; rhTPO, recombinant human thrombopoietin; SRL, sirolimus; M, male; F, female; qd, once a day; bid, twice a day; qw, once a week; OR, overall response; CR, complete response; PR, partial response; R, relapse; ADR, adverse drug reaction; ED, effective duration; PC, platelet count.

presented in detail in Figure 2. Three studies explicitly described the random sequence generated by a random number table or block randomization; thus, their bias was considered low. One study described the random sequence generated based on interventions; thus, its bias was considered high. Three other studies only mentioned the word 'randomization,' and thus, their bias was considered unclear. No studies mentioned whether allocation concealment was performed. Only one study used a single-blinded method. In addition, the evaluation of clinical indicators by three independent researchers in another study was not affected. The ORR, CR rate, PR rate, relapse rate, and platelet count are commonly used in clinical observation, and thus, all seven studies had a blinded outcome assessment. No patients were lost to follow-up or withdrawn from the studies, and thus, the risk of bias for incomplete outcome data was low. The selective reporting bias was also low among all included studies.

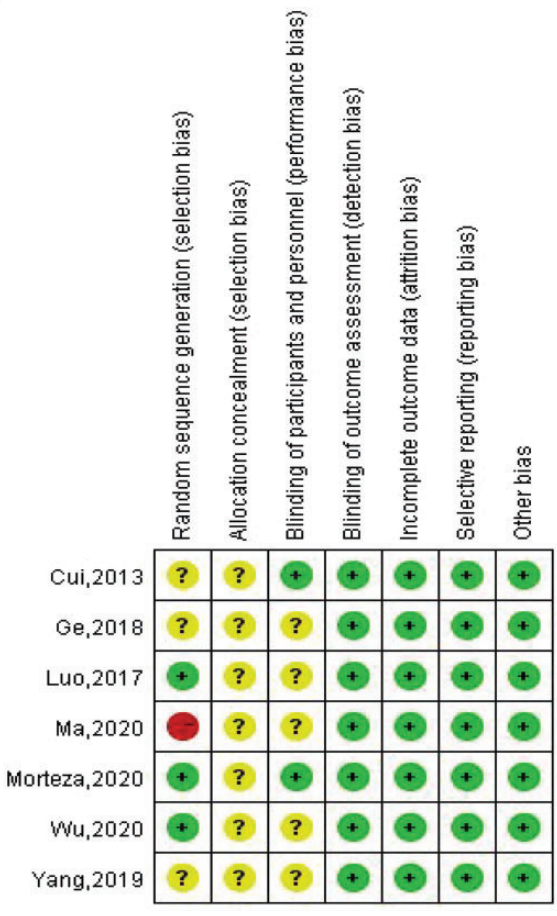

Figure 2. Risk of bias graph and summary of bias assessment of the seven randomized controlled trials included in a meta-analysis of the efficacy and safety of cyclosporine for patients with immune thrombocytopenia.

Analysis of efficacy outcomes

OR rate. All seven studies reported OR rates.[16–22] Pooled results revealed homogeneity among the studies ($P = 0.21$, $I^2 = 28\%$); therefore, a fixed-effects model was used. The OR rate was significantly higher in the cyclosporine-based combination group than in the control group (odds ratio [OR] = 5.55, 95% CI = 2.89–10.68, $P < 0.00001$, Figure 3a). The age of the participants varied among the seven studies, prompting us to conduct a subgroup analysis based on age (children or adults with ITP, Figure 3b). Subgroup analysis revealed no significant heterogeneity for children ($P = 0.16$, $I^2 = 45\%$) or adults with ITP ($P = 0.20$, $I^2 = 36\%$). Therefore, a fixed-effects model was used. The results demonstrated that the OR rate was significantly higher in the cyclosporine-based regimen group than in the control group in both children (OR = 5.74, 95% CI = 1.79–18.41, $P = 0.003$) and adults (OR = 5.46, 95% CI = 2.48–12.02, $P < 0.0001$).

CR rate. Six studies reported the CR rate.[16–20,22] Pooled results revealed homogeneity among the studies ($P = 0.64$, $I^2 = 0\%$). Therefore, a fixed-effects model was used. The CR rate was significantly higher in the cyclosporine-based combination group than that in the control group (OR = 2.18, 95% CI = 1.42–3.34, $P = 0.0003$, Figure 4a). Subgroup analysis based on age revealed heterogeneity for both children ($P = 0.51$, $I^2 = 0\%$) and adults with ITP ($P = 0.80$, $I^2 = 0\%$, Figure 4b). Therefore, a fixed-effects model was applied in the analysis. In children with ITP, the CR rate was higher in the cyclosporine-based combination group than in the control group, albeit without significance (OR = 1.70, 95% CI = 0.95–3.02). In adults with ITP, the CR rate was significantly higher in the cyclosporine-based

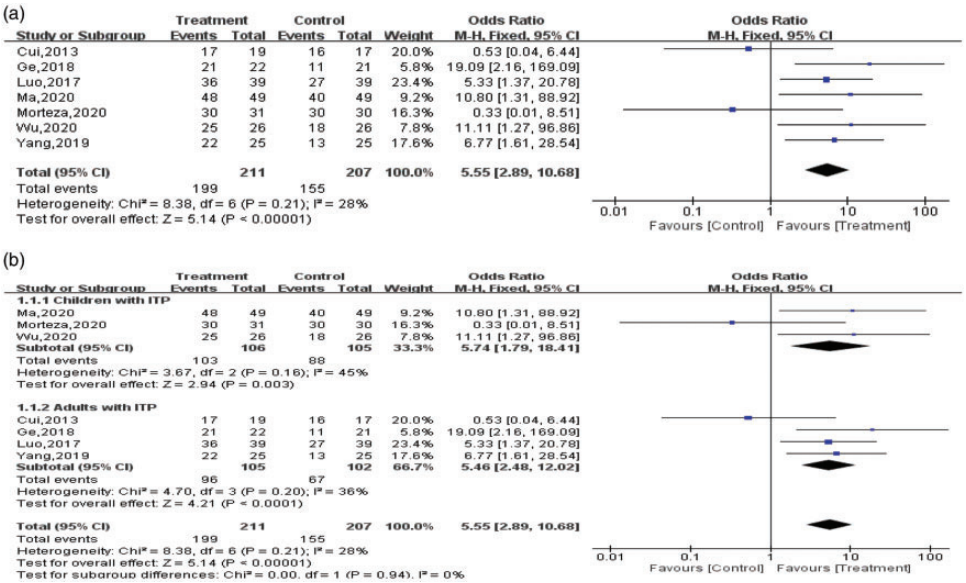

Figure 3. Forest plot presenting the ORR for cyclosporine-based combination therapy in patients with immune thrombocytopenia using a fixed-effects model.[16–22] (a) ORR of all seven studies and (b) Subgroup analysis based on age. ORR, overall response rate.

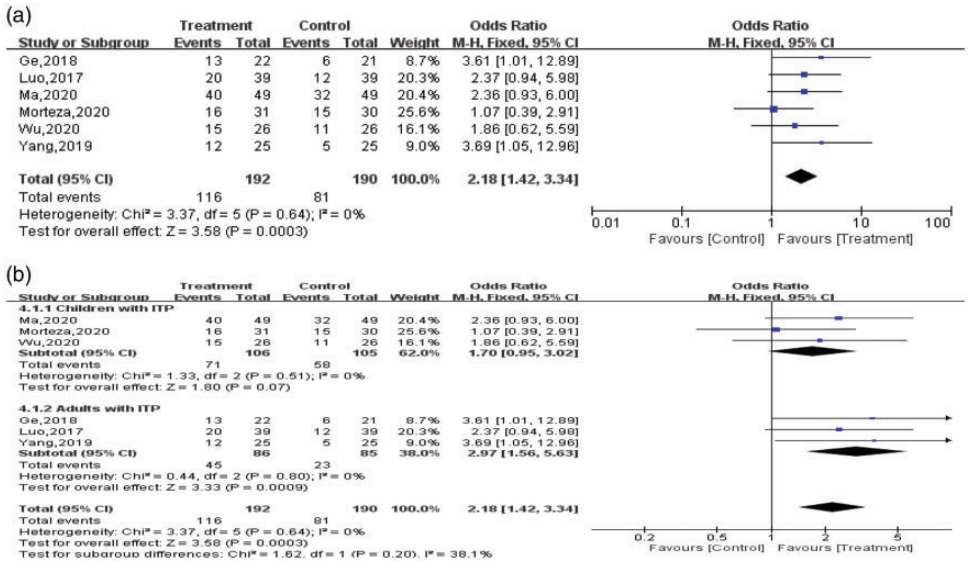

Figure 4. Forest plot presenting the CR rate for cyclosporine-based combination therapy in patients with immune thrombocytopenia using a fixed-effects model.[16–20,22] (a) CR rate of six studies and (b) Subgroup analysis based on age. CR, complete response.

combination group (OR = 2.97, 95% CI = 1.56–5.63, $P = 0.0009$).

PR rate. Six studies reported the PR rate.[16–20,22] Pooled results revealed homogeneity among the studies ($P = 0.92$, $I^2 = 0\%$), and thus, a fixed-effects model was used. The PR rate was not different between the cyclosporine-based combination and control groups (OR = 1.20, 95% CI = 0.77–1.86, Figure 5a). Subgroup analysis based on age revealed heterogeneity for both children ($P = 0.65$, $I^2 = 0\%$) and adults with ITP ($P = 0.83$, $I^2 = 0\%$, Figure 5b). Therefore, a fixed-effects model was used. However, the PR rate did not differ between the cyclosporine-based combination group and control group in both children (OR = 1.08, 95% CI = 0.58–2.00) and adults with ITP (OR = 1.34, 95% CI = 0.71–2.50).

Relapse rate. Two studies reported the relapse rate.[18,21] Pooled results revealed homogeneity between the studies ($P = 0.28$, $I^2 = 14\%$); therefore, a fixed-effects model was used. The relapse rate was significantly lower in the cyclosporine-based combination group than in the control group (OR = 0.03, 95% CI = 0.01–0.12, $P < 0.00001$, Figure 6).

Platelet count after treatment. Four studies reported the platelet count after treatment.[17–20] Pooled results revealed significant heterogeneity among the studies ($P < 0.00001$, $I^2 = 94\%$); therefore, a random-effects model was used. The pooled evidence demonstrated that cyclosporine-based combination therapy significantly increased the platelet count (SMD = 3.92, 95% CI = 2.23–5.61, $P < 0.00001$, Figure 7).

Analysis of safety outcomes. Three studies reported the ADR rate.[15,16,19] The pooled results were homogeneous ($P = 0.21$, $I^2 = 37\%$); therefore, a fixed-effects model was used. The ADR rate did not differ

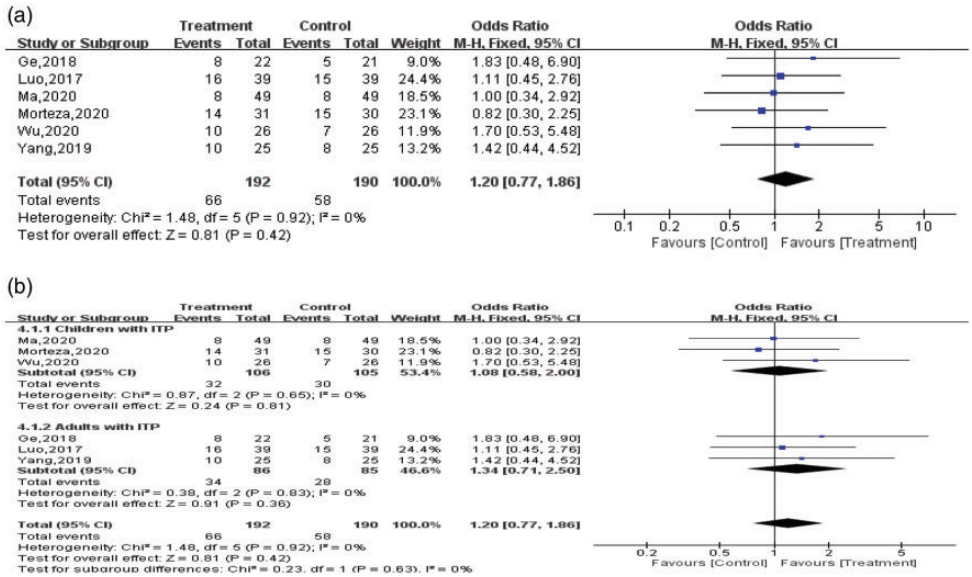

Figure 5. Forest plot presenting the PR rate for cyclosporine-based combination therapy in patients with immune thrombocytopenia using a fixed-effects model.[16–20,22] (a) PR rate of six studies and (b) Subgroup analysis based on age. PR, partial response.

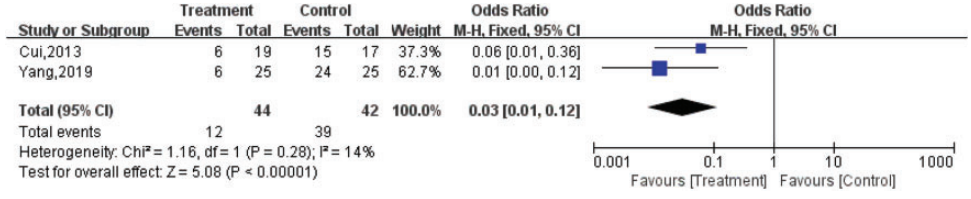

Figure 6. Forest plot presenting the relapse rate for cyclosporine-based combination therapy in patients with immune thrombocytopenia using a fixed-effects model.[18,21]

between the two groups (OR = 0.53, 95% CI = 0.22–1.25, $P = 0.15$, Figure 8).

Analysis of publication bias. Funnel plots were used to measure publication bias. The funnel plots of the CR, PR, relapse, and ADR rates displayed no significant asymmetry, suggesting that there was no obvious publication bias in the included literature. Therefore, the results of the systematic evaluation are credible. However, the funnel plots of the OR rate and platelet count exhibited slight asymmetry (Figure 9).

Discussion

This meta-analysis provides the first review of the efficacy and safety of cyclosporine in the treatment of ITP. The results of this analysis illustrated that cyclosporine-based combination therapy increased the ORR and CR rate and reduced the relapse rate. Furthermore, cyclosporine-based combination therapy significantly increased the platelet count, and no obvious ADRs were detected. The results of subgroup analysis demonstrated that the cyclosporine-based

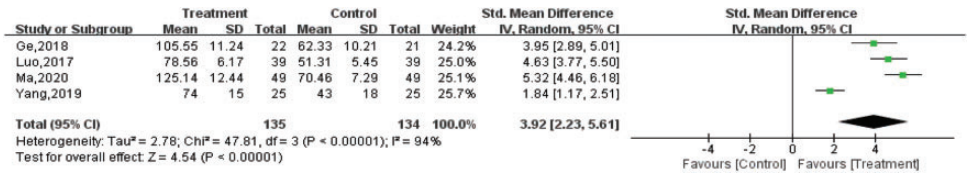

Figure 7. Forest plot presenting the platelet count after treatment with cyclosporine-based combination therapy in patients with immune thrombocytopenia using a random-effects model.[17–20]

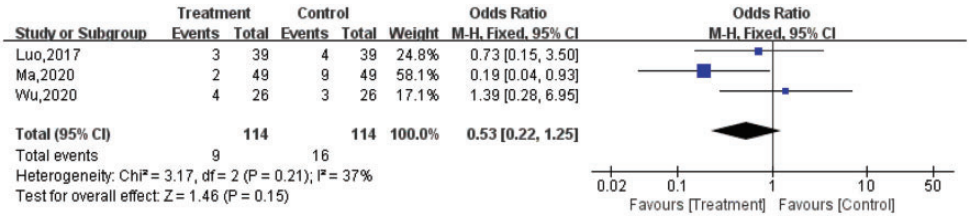

Figure 8. Forest plot showing adverse drug reaction of cyclosporine-based combination therapy for patients with immune thrombocytopenia using a fixed-effect model.[15,16,19]

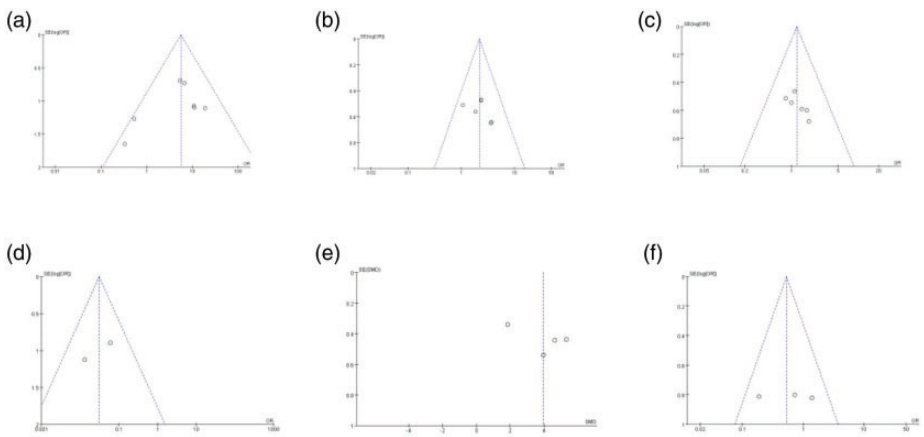

Figure 9. The funnel plot investigating publication bias, (a) Publication bias of the ORR. (b) Publication bias of the CR rate. (c) Publication bias of the PR rate. (d) Publication bias of the response rate. (e) Publication bias of the platelet count and (f) Publication bias of the ADR rate.[16–22]
ORR, overall response rate; CR, complete response; PR, partial response.

combination therapy increased the ORR in both children and adults and increased the CR rate only in adults. The main pathogenic feature of ITP is the abnormal loss of autoimmune tolerance. This mainly includes the abnormal activation of the monocyte/macrophage system and cytotoxic T lymphocytes in the body, and the number and function of immune cells are abnormal, leading excessive platelet phagocytosis.[3] In addition, the number or function of helper and regulatory T lymphocytes can be abnormal, and the balance of the immune system is dramatically disturbed.

These abnormalities lead to increased levels of inflammatory mediators, a decrease in the secretion of anti-inflammatory factors, and the destruction of platelets.[23] Relevant research found that the proportion of Th1 and Th17 cells is significantly increased in patients with ITP, the proportion of Th2 and regulatory T lymphocytes is decreased, and the secretion of inflammatory cytokines such as IFN-γ and IL-17 is increased, thereby altering the immune balance.[24] When the quantity and function of regulatory B lymphocytes are obviously decreased and the inhibitory function of monocyte activation is impaired, the secretion of anti-inflammatory factors such as IL-10 and TGF-β is decreased, which is the principal pathological mechanism of the phagocytosis of platelets and occurrence of ITP.[25,26] Consequently, regulating the abnormal immune response, inhibiting overactivated immune cells and related cytokines, and rebuilding immune tolerance are the key goals for improving and treating ITP. Dexamethasone and IVIg are widely employed as the first-line treatments for ITP in the clinic. However, for a considerable number of patients, the effect of routine hormone therapy is not satisfactory, and high-dose glucocorticoid therapy has many adverse effects in some patients.[4,5] In clinical practice, the second-line treatments for ITP mainly include rituximab, thrombopoietin receptor agonist, fostamatinib, and immunosuppressive agents. The diagnosis of refractory ITP mainly relies on the exclusion of other conditions and the experience of clinicians, thereby complicating treatment and highlighting the need for multiple treatment options.[27,28] As an effective immunosuppressant, cyclosporine can treat a variety of autoimmune diseases, such as experimental autoimmune uveitis, systemic juvenile idiopathic arthritis, nephrotic syndrome, and dry eye syndrome.[29–32] Cyclosporine can regulate abnormal immune cells in patients with ITP, suppress abnormally activated immune responses, and play an important role in the protection of platelets coated with anti-platelet autoantibodies.[12] Related research found that after repeated cyclosporine A administration, two patients with chronic severe refractory ITP experienced long-term complete remission, and their adverse reactions were relatively mild.[33] The results of the present analysis demonstrated that cyclosporine-based combination therapy can effectively improve the condition of patients with a certain degree of safety. This meta-analysis had the following limitations: (i) the strength of the analysis might have been limited because of limitations regarding the number of studies and patients; (ii) many studies were not included in this analysis because of incomplete data and information, thereby precluding a comprehensive analysis of cyclosporine in the treatment of ITP; (iii) because the included studies were mainly conducted in China, the applicability of the data to other countries and populations is unclear; and (iv) there was some heterogeneity because of inconsistencies in the related data for platelet counts after treatment in the included studies. The results of this meta-analysis suggest that cyclosporine is an effective drug for the treatment of ITP, as it improved the ORR in children and adults with ITP. In addition, cyclosporine-based combination therapy has no obvious side effects, suggesting its greater safety. Additional larger trials are required to provide clearer evidence of the efficacy and safety of this drug.

Author contributions

Xiaojing Li and Yongming Zhou were responsible for the study design. Xiaojing Li and Jiekai Li independently searched and screened the literature and extracted the primary data. Wenwei Zhu and Jiekai Li independently extracted the data. Jizhang Bao analyzed the study data. Xiaojing Li and Wenwei Zhu wrote the manuscript. Jizhang Bao was responsible for editing the manuscript. Yongming Zhou revised the

manuscript. All authors read and approved the final version of the manuscript.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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Supplemental material

Supplemental material for this article is available online.

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