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Cardiac markers of multisystem inflammatory syndrome in children (MIS-C) in COVID-19 patients: A meta-analysis

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Objective: A meta-analysis of laboratory cardiac markers for multisystem inflammatory syndrome in children (MIS-C) was performed in patients with coronavirus disease 2019 (COVID-19).

Methods: Eight databases were searched until April 10, 2021, for studies on cardiac markers, including B-type natriuretic peptide (BNP), N-terminal pro-BNP (NT-proBNP), troponin, aspartate aminotransferase (AST), in MIS-C patients.

Results: Of the 2583 participants enrolled in 24 studies, 1613 patients were diagnosed with MIS-C. MIS-C patients exhibited higher BNP levels than patients with non-severe COVID-19 [SMD (95% CI): 1.13 (0.48, 1.77), p < 0.05]. No significant differences in BNP levels were observed between patients with MIS-C and severe COVID-19 [SMD (95% CI): 0.29 (−0.07, 0.65), p = 0.117]. Comparisons of MIS-C patients to all COVID-19 patients revealed no significant differences in levels of troponin [SMD (95% CI): 0.13 (−0.07, 0.32), p = 0.212] or AST [SMD (95% CI): 0.10 (−0.11, 0.31), p = 0.336]. Compared to patients with non-severe MIS-C, those with severe MIS-C exhibited higher levels of BNP [SMD (95% CI): 0.26 (0.04, 0.48), p < 0.05], but no differences in troponin [SMD (95% CI): 0.05 (−0.06, 0.16) p = 0.387] or AST [SMD (95% CI): 0.19 (−0.34, 0.71), p = 0.483] were observed. Moreover, there was no significant difference in BNP [SMD (95% CI): −0.21 (−1.07, 0.64), p = 0.624] or troponin [SMD (95% CI): −0.07 (−0.45, 0.31), p = 0.710] between MIS-C with and without coronary artery abnormality. Sensitivity analyses were performed to assess stability. No publication bias was detected based on Begg’s test.

Conclusions: The key cardiac marker that showed differences between patients with MIS-C/non-severe COVID-19 and between patients with severe/non-severe MIS-C was BNP. Other markers, such as troponin and AST, did not exhibit notable differences in indicating cardiac injury between patients with MIS-C and COVID-19.

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1. Introduction

Coronavirus disease 2019 (COVID-19), which is caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread globally to become a significant burden worldwide [1]. The presentation of COVID-19 in children ranges from mild to severe, and a variety of complications develop during disease progression. Increasing numbers of pediatric patients with severe systemic hyperinflammation, shock or Kawasaki-like syndrome associated with COVID-19 have been widely reported worldwide [2,3]. This condition was identified as multisystem inflammatory syndrome in children (MIS-C), also termed pediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PMIS/PIMS-TS) [4]. The term MIS-C is used throughout this meta-analysis.

The SARS-CoV-2 virus binds to angiotensin-converting enzyme 2 (ACE2) receptors, which are highly expressed in the lungs, myocytes and vascular endothelial cells [5]. Cardiac involvement is frequent in MIS-C and presents as a wide range of conditions, such as systemic hyperinflammatory conditions, including acute myocardial dysfunction or arrhythmias, or severe conditions, such as cardiogenic shock or...
hypotension [6]. Patients with MIS-C show similar characteristics to Kawasaki disease with an associated risk of complications, such as coronary artery abnormality (CAA), including coronary artery dilation or aneurysm [2,3]. Critical MIS-C cases need interventions, such as cardiac support or extracorporeal membrane oxygenation (ECMO) therapy, and diligent long-term follow-up due to the risk of cardiac progression [6].

Cardiac markers [7], including brain natriuretic peptide (BNP), N-terminal pro-brain natriuretic peptide (NT-pro BNP), troponin, and aspartate aminotransferase (AST), are frequently used clinical parameters to predict the progression of deterioration in earlier phases. Natriuretic peptides are primarily synthesized in the heart and upregulated by myocardial stress. BNP and its precursor hormone NT-pro BNP are suitable laboratory cardiac markers for the diagnosis and risk stratification of heart failure [7]. NT-pro BNP is also a potential biomarker for predicting coronary artery lesions in patients with Kawasaki disease [8]. Troponin is a muscle-associated protein that is released into the blood circulation during cell injury, and it is used as a cardiac marker for screening and detecting cardiac injury [9]. Because of its cardiac specificity, the laboratory cardiac marker troponin may be the criterion for the diagnosis of myocardial injury [10]. AST, also named glutamate oxaloacetate transaminase (GOT), is released from necrotic cardiac myocytes and may be detected in serum [7]. Several studies reported elevated BNP or NT pro-BNP and troponin levels in patients with severe COVID-19 who were admitted to intensive care units, required ventilation or died [11,12]. Laboratory parameters of inflammatory or cardiac markers are frequently used to optimize management guidelines in clinical practice. An increasing number of studies reported the characteristics of cardiac markers in MIS-C patients, but no relative meta-analysis on these studies was performed. The present study performed a meta-analysis to provide evidence-based data on the characteristics of cardiac laboratory markers in MIS-C patients to assist clinicians in the management of MIS-C patients. The early identification of the characteristics of cardiac involvement in MIS-C patients is vital in designing prompt treatment modalities and preventing cardiovascular complications.

2. Methods

The study was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, and it is registered in the International Prospective Register of Systematic Reviews database (PROSPERO) (CRD42020220509).

2.1. Literature search and selection

Two investigators (YZ and LY) systematically searched the PubMed, Embase, Web of Science, Ovid, Cochrane Library, PROSPERO, Wanfang Med Online (Chinese) and China National Knowledge Infrastructure (CNKI) databases for relevant articles from database inception to April 10, 2021. The search terms, relevant synonyms and medical subject heading (MESH) terms used were “coronavirus disease 2019”, “COVID-19”, “severe acute respiratory syndrome coronavirus 2”, “SARS-CoV-2”, “multisystem inflammatory syndrome”, “MIS-C”, “pediatric inflammatory multisystem syndrome”, “pediatric multisystem inflammatory syndrome”, “PIMS-TS”, “PMIS”, “Kawasaki-like disease”, and “hyperinflammatory syndrome”. A manual search of the article references was also performed. The following inclusion criteria for the studies in the meta-analysis were used: 1) cohort studies or case-control studies; 2) the patients had MIS-C, PIMS-TS or PMIS; and 3) the primary cardiac biomarker outcomes included at least BNP/NT-pro BNP or troponin, and the secondary outcome included AST. We excluded studies with no relevant outcomes or no original data and reviews, case series, editorials or opinions. Two investigators (YZ and LY) independently screened the titles, abstracts and full texts of eligible studies and subsequently assessed the studies for inclusion. All discrepancies were resolved via discussion with a third investigator (YH).

2.2. Quality assessment

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) for observational studies [13]. According to the criteria, each item was scored as 0 or 1, with 4 points in selection, 2 points in comparability and 3 points in outcome/exposure. The overall score ranged from 0 to 9, and the studies were classified as low (1–3), moderate (4–6) or high (7–9) quality based on the total point score. Any dispute was resolved via discussion among the reviewers.

2.3. Data collection

Two investigators (YZ and LY) extracted the data using Microsoft Excel. The data included study details (author, publication year, country, study design, participant age, study period, number of patients, and number of cases/controls) and cardiac marker outcomes (BNP/NT-pro BNP, troponin, and AST). Among the study groups, patients with severe COVID-19 were defined as COVID-19 patients with acute respiratory distress syndrome (ARDS) who required mechanical ventilation or invasive respiratory support or patients with an increase in positive pressure support above baseline and who did not meet the diagnostic criteria for MIS-C. Severe MIS-C patients were defined as patients who met the diagnostic criteria for MIS-C and required admission to the ICU, invasive respiratory support or mechanical ventilation and patients who suffered complications, such as shock, needed inotropic support or fluid resuscitation, or had a fatal outcome.

2.4. Statistical analysis

Heterogeneity was estimated using the chi-squared test and the I² statistic. An I² value less than 50% indicated no presence of statistical heterogeneity, and a fixed effects model (FEM) was used in these cases. When the I² value was greater than 50%, statistical heterogeneity was present, and a random effects model (REM) was used. I² values of 50% and 75% indicated moderate and high heterogeneity, respectively. Sensitivity analysis was performed to explore the source of heterogeneity. After excluding potential clinical heterogeneity, REMs were generated using the DerSimonian and Laird methods to evaluate the effect sizes. Due to different units for serum levels of cardiac markers, continuous variables are presented as standard mean differences (SMDs) and corresponding 95% confidence intervals (95% CIs) using forest plots. Begg’s test and funnel plots were used to evaluate publication bias. A P value <0.05 was considered statistically significant. The analyses were performed using STATA v12 (Stata Corp, College Station, TX, USA).

3. Results

3.1. Study selection, characteristics and quality assessment

A total of 3944 studies were identified from the database search. Of these, 2055 duplicate studies were removed; 1663 studies were excluded after title and abstract screening, and 202 were excluded following full text screening based on the set inclusion criteria. Twenty-four studies [14-37] were ultimately included in the meta-analysis (Fig. 1). A total of 2583 participants, comprising 1613 MIS-C patients and 970 COVID-19 patients, were included in the meta-analysis. Fifteen studies [14,15,20-24,28-33,35,37] compared MIS-C and COVID-19, and nine of these studies [14,15,22-24,30,31,33,37] compared MIS-C with severe COVID-19. Eight studies [16-18,25-27,34,35] compared severe MIS-C with non-severe MIS-C, and three studies [17,19,26] compared MIS-C with CAA and MIS-C without CAA. The quality scores of the included studies ranged from 6 to 9, with three studies of moderate quality and 21 studies of high quality. The detailed characteristics are presented in Table 1.
3.2. Meta-analysis (Table 2)

3.2.1. MIS-C vs. COVID-19 (including severe COVID-19) (Fig. 2)

No statistically significant heterogeneity was found for the cardiac markers BNP ($p = 0.196, I^2 = 27.9\%$), troponin ($p = 0.883, I^2 = 0\%$), or AST ($p = 0.075, I^2 = 47.7\%$) in comparisons of MIS-C and COVID-19 patients (with subgroups of severe and non-severe COVID-19). A FEM was used to combine the effect size.

The results indicated that BNP levels were higher in MIS-C patients than in patients with non-severe COVID-19 [SMD (95% CI): 1.13 (0.48, 1.77), $p < 0.05$]. There was no significant difference in BNP levels between patients with MIS-C and severe COVID-19 [SMD (95% CI): 0.29 (−0.07, 0.65), $p = 0.117$] or troponin [SMD (95% CI): 0.13 (−0.07, 0.32), $p = 0.212$] and AST levels [SMD (95% CI): 0.10 (−0.11, 0.31), $p = 0.336$] between MIS-C and COVID-19 patients.

Seven studies compared the cardiac marker troponin and AST between severe and non-severe MIS-C patients. No significant heterogeneity was observed in these studies for troponin ($p = 0.591, I^2 = 0.00\%$) or AST ($p = 0.505, I^2 = 0.00\%$), and the FEM was used to combine the effect size. The results showed no significant difference in troponin [SMD (95% CI): 0.05 (−0.06, 0.16), $p = 0.387$] or AST [SMD (95% CI): 0.19 (−0.34, 0.71), $p = 0.483$] levels between severe and non-severe MIS-C patients.

3.2.2. Severe MIS-C vs. non-severe MIS-C (Fig. 3)

The heterogeneity of the six studies that compared the cardiac marker BNP between severe and non-severe MIS-C was high ($p < 0.01, I^2 = 77.2\%$), and the results of the two models (REM and FEM) were inconsistent, which indicates that the combined results were considered unreliable. Sensitivity analysis was performed by excluding each study, one at a time, to identify the possible source of heterogeneity. This analysis revealed that the study of Pouletty [25] was a major source of heterogeneity. After exclusion of this study, the result of REM [16-18,34,35] with moderate heterogeneity ($p < 0.05, I^2 = 58.6\%$) indicated that the BNP levels of severe MIS-C patients were higher [SMD (95% CI): 0.26 (0.04, 0.48), $p < 0.05$] than those of non-severe MIS-C patients.

3.2.3. MIS-C with CAA vs. MIS-C without CAA (Fig. 4)

Comparison of MIS-C patients with and without CAA revealed no significant heterogeneity for BNP [17,19] ($p = 0.620, I^2 = 0\%$) or troponin [17,19,26] ($p = 0.709, I^2 = 0\%$). The FEM results showed no significant difference in BNP [SMD (95% CI): −0.21 (−1.07, 0.64), $p = 0.624$] or troponin [SMD (95% CI): −0.07 (−0.45, 0.31), $p = 0.71$] levels.

3.2.4. Sensitivity analysis and publication bias

Except for the comparison of BNP between severe and non-severe MIS-C patients, the results of sensitivity analyses were not affected by the exclusion of any study, which indicated that the meta-analysis had high reliability and stability. The results of Begg’s test indicated no evidence of publication bias in the analysis.

4. Discussion

The rapid worldwide spread of COVID-19 affects all age groups, including pediatric patients [1]. Despite the lower incidence of COVID-19 in children, MIS-C is now a common condition in pediatric COVID-19 patients [6]. New reports [2,3,6] showed overlapping characteristics...
of MIS-C with other conditions, such as Kawasaki disease, myocarditis and toxic shock syndrome. Patients with MIS-C present with different characteristics of cardiac involvement, such as valvulitis, coronary artery dilation or aneurysms, myocardial dysfunction and fulminant myocarditis. [38] MIS-C rapidly progresses to hyperinflammation syndrome, severe myocarditis or shock and requires support and monitoring of the cardiac or respiratory system in the pediatric intensive care unit (PICU) [3,39]. Because myocardial involvement is the hallmark of a hyperinflammatory state, cardiac markers are widely monitored in the management of MIS-C [40]. MIS-C is a newly emerging contagious disease, and it is critical to identify the characteristics of MIS-C patients to help create early recognition and optimal management strategies. Therefore, we focused on cardiac markers of MIS-C and performed this meta-analysis to summarize the existing evidence and further the management of MIS-C. This analysis included 24 studies comprised of 2583 COVID-19 patients, including 1613 MIS-C patients. The results indicated

**Table 1**

| Author                  | Country | Study design | Age range | Study period          | Cases/controls | Number | Risk of bias |
|-------------------------|---------|--------------|-----------|-----------------------|----------------|--------|--------------|
| Diorio C 2020           | USA     | Prospective  | \         | April 3–May 15, 2020  | MIS-C          | 6      | 8            |
|                         |         |              |           |                       | Severe COVID-19* | 9      |              |
|                         |         |              |           |                       | Non-severe COVID-19* | 5      |              |
| Anderson EM 2020        | USA     | \           |           | April–May 2020        | MIS-C          | 10     | 7            |
|                         |         |              |           |                       | Severe COVID-19* | 9      |              |
| Pereira MFB 2020        | Brazil  | Cross-sectional | 0-18y  | April 16–June 21, 2020 | MIS-C          | 6      | 7            |
|                         |         |              |           |                       | COVID-19       | 60     |              |
| Pierce CA 2020          | USA     | \           |           | March 13–May 17, 2020  | MIS-C          | 20     | 7            |
|                         |         |              |           |                       | Severe pediatric COVID-19* | 4      |              |
|                         |         |              |           |                       | Non-severe pediatric COVID-19* | 41     |              |
|                         |         |              |           |                       | Severe adult COVID-19* | 27     |              |
|                         |         |              |           |                       | Non-severe adult COVID-19* | 33     |              |
| Prata-Barbosa A 2020    | Brazil  | Prospective  | 1 m-19y   | March 1–May 31, 2020   | MIS-C          | 10     | 8            |
|                         |         |              |           |                       | COVID-19       | 69     |              |
|                         |         |              |           |                       | MIS-C          | 15     | 6            |
|                         |         |              |           |                       | Severe COVID-19 | 14     |              |
|                         |         |              |           |                       | MIS-C          | 16     |              |
|                         |         |              |           |                       | Severe COVID-19 | 13     |              |
|                         |         |              |           |                       | MIS-C          | 13     |              |
|                         |         |              |           |                       | COVID-19       | 41     |              |
|                         |         |              |           |                       | MIS-C          | 52     | 8            |
|                         |         |              |           |                       | COVID-19       | 404    |              |
|                         |         |              |           |                       | MIS-C          | 5      |              |
|                         |         |              |           |                       | COVID-19       | 8      |              |
|                         |         |              |           |                       | MIS-C          | 20     |              |
|                         |         |              |           |                       | MIS-C          | 17     |              |
|                         |         |              |           |                       | MIS-C          | 7      |              |
|                         |         |              |           |                       | MIS-C          | 15     |              |
|                         |         |              |           |                       | MIS-C          | 8      |              |
|                         |         |              |           |                       | MIS-C with CAA | 27     |              |
|                         |         |              |           |                       | MIS-C without CAA | 50     |              |
|                         |         |              |           |                       | MIS-C          | 36     |              |
|                         |         |              |           |                       | MIS-C          | 42     |              |
|                         |         |              |           |                       | MIS-C          | 29     |              |
|                         |         |              |           |                       | MIS-C          | 29     |              |
|                         |         |              |           |                       | MIS-C with CAA | 8      |              |
|                         |         |              |           |                       | MIS-C without CAA | 50     |              |
|                         |         |              |           |                       | MIS-C          | 4      |              |
|                         |         |              |           |                       | MIS-C          | 8      |              |
|                         |         |              |           |                       | MIS-C          | 21     |              |
|                         |         |              |           |                       | MIS-C          | 8      |              |
|                         |         |              |           |                       | MIS-C          | 8      |              |
|                         |         |              |           |                       | MIS-C          | 11     |              |
|                         |         |              |           |                       | MIS-C          | 18     |              |
|                         |         |              |           |                       | MIS-C          | 9      |              |
|                         |         |              |           |                       | MIS-C          | 11     |              |
|                         |         |              |           |                       | MIS-C          | 19     |              |
|                         |         |              |           |                       | MIS-C          | 12     |              |
|                         |         |              |           |                       | MIS-C          | 30     |              |
|                         |         |              |           |                       | MIS-C          | 7      |              |
|                         |         |              |           |                       | MIS-C          | 64     |              |
|                         |         |              |           |                       | MIS-C          | 432    |              |
|                         |         |              |           |                       | MIS-C          | 22     |              |
|                         |         |              |           |                       | MIS-C          | 11     |              |
|                         |         |              |           |                       | MIS-C          | 14     |              |
|                         |         |              |           |                       | COVID-19       | 16     |              |
|                         |         |              |           |                       | MIS-C          | 4      |              |
|                         |         |              |           |                       | COVID-19       | 8      |              |

Notes: MIS-C, multisystem inflammatory syndrome in children; COVID-19, coronavirus disease 2019; CAA, coronary artery abnormality.

* Severe COVID-19: respiratory process requiring invasive respiratory support or mechanical ventilation or an increase in positive pressure support above baseline without meeting the criteria for MIS-C; non-severe COVID-19 (minimal COVID-19): requiring hospitalization but did not otherwise meet the criteria for MIS-C or exhibit severe symptoms.

* Severe MIS-C: MIS-C with shock, requiring ventilation or admission to the ICU, or with a fatal outcome.
that the BNP levels of MIS-C patients were higher than those with non-severe COVID-19, and severe MIS-C patients exhibited higher BNP levels than non-severe MIS-C patients. No significant differences in BNP levels were observed between MIS-C and severe COVID-19 patients or MIS-C patients with and without CAA. No significant differences in troponin levels were observed between MIS-C and COVID-19 patients with severe or non-severe MIS-C, and MIS-C patients with and without CAA. Similarly, no significant difference was observed in AST levels between MIS-C patients with COVID-19 and patients with severe or non-severe MIS-C.

COVID-19 may present with involvement of major organs, including the cardiovascular system [6]. Myocardial cells infected with SARS-CoV-2 may directly cause myocardial injury and lead to myocarditis, impairment of cardiac function or malignant arrhythmias, and eventual cardiac failure [41,42]. Up to 28% of COVID-19 patients have myocardial injury [43]. Some fatal cases of COVID-19 were also associated with cardiac injury caused by fulminant myocarditis [44]. Autopsies have shown inflammatory infiltrate in myocardial tissue with a high viral load [45-47], and a high proportion of MIS-C patients exhibit elevated levels of cardiac markers, including troponin, and BNP/pro-BNP [2,48]. Our meta-analysis showed that MIS-C patients showed higher BNP levels than patients with non-severe COVID-19, but no significant difference was found in BNP levels between patients with MIS-C and severe COVID-19. We demonstrated that MIS-C patients may share an equal elevation in BNP levels with patients with severe COVID-19. This finding may assist clinicians in designing optimal management guidelines based on the diagnosis of MIS-C and COVID-19 in children.

It is imperative to note a higher tendency to develop a severe condition in the clinical management of MIS-C. The meta-analysis showed that BNP levels were higher in patients with severe MIS-C than patients with non-severe MIS-C, but troponin and AST levels were not significantly different between patients with severe and non-severe MIS-C. The observed difference in BNP levels between patients with severe and non-severe MIS-C may indicate a difference in prognosis. Researchers also suggested the routine measurement of cardiac markers. Dynamic measurements may be useful for clinicians to monitor and predict the disease course and help triage patients to a different level of care.

MIS-C has some overlapping features with Kawasaki disease and CAA, including coronary artery dilation or aneurysms, and these features have been reported in 6–24% of patients [6]. Some studies reported large or giant coronary artery aneurysms [3,17]. Close and prompt follow-up is indicated for patients with CAA development. Therefore, questions remained in clinical practice about which index to rely on for early detection and the triage of MIS-C patients into high- and low-risk groups for CAA [9]. However, the results of our meta-analysis did not show differences in BNP or troponin levels between patients with MIS-C and COVID-19 in children.
Patients with severe MIS-C exhibited higher levels of BNP than patients with non-severe MIS-C, but no differences were observed in troponin or AST levels. AST: aspartate aminotransferase; BNP: B-type natriuretic peptide; MIS-C, multisystem inflammatory syndrome in children.

Fig. 3. Comparisons of severe and non-severe MIS-C: (A) BNP; (B) troponin; (C) AST. Patients with severe MIS-C exhibited higher levels of BNP than patients with non-severe MIS-C, but no differences were observed in troponin or AST levels. AST: aspartate aminotransferase; BNP: B-type natriuretic peptide; MIS-C, multisystem inflammatory syndrome in children.
between MIS-C patients with and without CAA. This result suggests that serum cardiac markers are not suitable for evaluating the risk of CAA progression in MIS-C patients, which indicates a need to search for other relevant clinical indicators.

With the onset of MIS-C symptoms, clinicians should be aware of the complications associated with cardiac symptoms. Therefore, despite the lack of differences in cardiac markers between MIS-C and severe COVID-19 patients and between MIS-C patients with and without CAA, attention should be paid to identifying the presence of severe MIS-C. Evaluation of cardiac function and important organs and intense monitoring are recommended for MIS-C patients.

Our meta-analysis has some limitations. First, all of the included studies were observational studies with small sample sizes. The statistical power may not have been sufficient due to the small sample sizes. Second, cardiac markers, including BNP and troponin levels, were secondary, and not primary, outcomes in most of the studies. Third, the sensitivity analysis revealed moderate heterogeneity for BNP between patients with severe MIS-C and non-severe MIS-C, which may have affected the accuracy of our results. Fourth, there is a gap in the literature on creatinine kinase (CK) and creatinine kinase-myocardial band (CK-MB) as specific cardiac damage markers, the inclusion of which would be beneficial.

In summary, the evidence from our study indicates higher BNP levels in MIS-C patients vs. patients with non-severe COVID-19 and patients with severe MIS-C vs. non-severe MIS-C. However, BNP, troponin and AST did not show significant differences in the comparisons of MIS-C vs. COVID-19 patients, patients with severe MIS-C vs. non-severe MIS-C, and MIS-C patients with CAA vs. MIS-C patients without CAA. Cardiac involvement in MIS-C plays a significant role in disease progression and must be identified and monitored carefully. Cardiac markers, including BNP, troponin, and AST, should play a role in the monitoring, management and prognosis prediction of MIS-C, but abnormal levels may not correlate with direct coronary artery lesions. Cardiac markers may be monitored longitudinally at different intervals in admitted MIS-C patients to predict potential deterioration during the disease course. Due to the limited quantity and quality of the studies included in this meta-analysis, more prospective studies, including high-quality randomized controlled trials, are needed to verify the results.

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Data availability statement

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

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