**Introduction**

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been spreading as a global pandemic worldwide.1 In pediatric population, multisystem inflammatory syndrome in children (MIS-C) is noted to be a novel syndrome that is temporally associated with previous exposure to SARS-CoV-2. A series of cases of MIS-C have been reported from different countries, and an increasing number of studies about MIS-C have been published around the world.2-4 MIS-C patients may present with a combination of ventricular dysfunction, shock and/or Kawasaki-like disease.5 Furthermore, MIS-C involves injury to multiple organs, including but not limited to the heart. Notably, MIS-C has been reported to largely overlap with Kawasaki disease (KD), especially with regard to the clinical manifestations. Whether MIS-C is a distinct clinical entity, a result of SARS-CoV-2 infection, or a coincident occurrence with the incidence of KD is under debate and remains unclear.6 However, some differences in these two disease conditions have been identified, and it is possible that they are derived from different pathophysiologies, which have not yet been clarified. The pathophysiology of KD is not very clear but is likely triggered by the immunological cascade that occurs with asymptomatic infection in genetically susceptible individuals.7

Similarities and differences in laboratory parameters between MIS-C and KD/KDSS have been reported in various studies. Although laboratory parameters could not cover all the distinctions between MIS-C and KD/KDSS, we hope that elaboration will benefit mechanistic research, such as proteomics and metabonomics. Therefore, we performed a meta-analysis to discuss and elucidate the similarities and differences among MIS-C and known associated conditions, including KD and KDSS, focusing on laboratory parameters.

**Methods**

**Literature search**

This meta-analysis was undertaken based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (CRD42021255036). We conducted a literature search in the MEDLINE, EMBASE, Web of Science, PROSPERO and Cochrane Library databases from inception to May 31, 2021. The following terms were used for the search: *COVID-19, SARS-CoV-2*, *multisystem inflammatory syndrome, MIS-C, pediatric inflammatory multisystem syndrome, pediatric multisystem inflammatory syndrome, PIMS‐TS, PMIS and Kawasaki disease*. We also reviewed the reference lists of included studies to identify additional articles.

**Selection criteria**

To be eligible for the meta-analysis, the included studies had to be observational studies that investigated the difference between MIS-C and KD/KDSS. Eligible studies reported comparisons of patients with MIS-C and those with KD/KDSS and also provided information on laboratory parameters, including hematology [white blood cell count (WBC) or leukocyte count, absolute lymphocyte count (ALC), absolute neutrophil count (ANC), hemoglobin (Hb) and platelet count (PLT)], inflammatory markers [C-reactive protein (CRP), procalcitonin (PCT), D-dimer, ferritin and erythrocyte sedimentation rate (ESR)], cardiac markers [N-terminal pro-brain natriuretic peptide (NT-proBNP), troponin, aspartate aminotransferase (AST) and creatine phosphokinase (CPK)] and biochemistry values [albumin, alanine aminotransferase (ALT), creatinine and sodium (Na)]. Reviews, editorials, comments, correspondence letters and qualitative studies were excluded.

**Data extraction and quality assessment**

Two investigators (Yan Zhao and Chunling Zhou) independently performed the data extraction and quality assessment. Discrepancies were resolved by discussion. We extracted the following information: first author, publication year, country, study period, age of participants, sample size, and relevant laboratory data. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of observational studies based on the three areas of selection, comparability and outcome/exposure. The studies with a NOS score >6 were categorized as high quality, and the studies with a NOS score of 4-6 were categorized as medium quality. Articles of poor quality (NOS score of 0-3) were excluded.8

**Statistical analysis**

Quantitative data were extracted from individual included studies. For the quantitative data, weighted mean differences (WMDs) were the first choice in the pooled effect sizes, but for different units of laboratory values or large deviations from the mean, standard mean differences (SMDs) were calculated. The Q test and I2 statistic were used to evaluate statistical heterogeneity. I2 values of 25%, 50% or 75% individually represented low, medium or high heterogeneity. If the I2 value was <50%, a fixed-effect model (FEM) was used; otherwise, a random-effect model (REM) was chosen. If the I2 value was >75%, statistical heterogeneity was obvious and could be eliminated by adjustment for the clinical confounding factors, subgroup analysis and sensitivity analysis. Potential publication bias was assessed by Egger’s tests and funnel plots. Stata 12.0 (Statacorp, College Station, Texas)9 was used for meta-analysis and drawing graphs.

**Results**

**Study characteristics**

We identified 2436 relevant articles. A total of 941 duplicated articles were removed, and 1123 articles were excluded by title and abstract screening. Next, 372 articles with full texts were reviewed, and 354 articles were excluded at this stage as they did not meet the selection criteria. Eighteen studies with full texts were assessed for eligibility, and of these, 12 studies10-21 with 3073 participants (969 MIS-C patients, 2053 KD patients and 51 KDSS patients) were eligible for the meta-analysis. The flow diagram of the study selection process is described in E-figure 1. Among the eligible studies, 11 studies compared MIS-C and KD, and 2 studies compared MIS-C and KDSS. For the quality assessment, 3 studies were of moderate quality, and 9 studies were of high quality (E-table in the supplement). Table 1 summarizes the detailed characteristics of the included studies and quality assessment.

**Meta-analysis of hematology** (Table 2, Figure 1)**10-16,18-20**

Seven studies were included in the analysis of the levels of WBCs or leukocytes between MIS-C patients and KD/KDSS patients. Meta-analysis showed that the WBC levels (×109/L) of MIS-C patients were lower than those of KD/KDSS patients [WMD (*95% CI*): -3.93 (-6.04, -1.82), *p*<0.001; heterogeneity: *p*<0.05, I2=50.6%] with moderate heterogeneity in the REM. We conducted a subgroup analysis based on control groups of KD or KDSS patients. The outcomes of subgroup analysis indicated that the WBC count (×109/L) was lower in MIS-C patients than in KD patients [WMD (*95% CI*): -4.47 (-6.98, -1.96), *p*<0.001; heterogeneity: *p*=0.067, I2=51.5%] with REM, but there were no significant differences in the WBC counts (×109/L) between MIS-C and KDSS patients [WMD (*95% CI*): -2.81 (-6.90, 1.28), *p*=0.178; heterogeneity: *p*=0.132, I2=50.6%] with REM.

Ten studies reported the ALC. The pooled results with FEM showed that the ALC of MIS-C patients was significantly lower than that of KD patients [SMD (*95% CI*): -0.84 (-0.99, -0.69), *p*<0.001; heterogeneity: *p*=0.125, I2=33.1%].

Six studies reported the ANC, and there was high heterogeneity (I2 >75%). In the subgroup analysis, there was no significant difference in the ANC [SMD (*95% CI*): -0.20 (-0.64, 0.24), *p*=0.377; heterogeneity: *p*<0.05, I2=65.4%] between MIS-C and KD patients, and the ANC of MIS-C patients was higher than that of KDSS patients [SMD (*95% CI*): 0.80 (0.40, 1.21), *p*<0.001]. Because only one study reported the ANC in the subgroup of MIS-C and KDSS patients, heterogeneity was not calculated.

Six studies reported Hb levels, and there was high heterogeneity (I2 >75%). In the subgroup analysis, there was no significant difference in Hb [SMD (*95% CI*): -0.02 (-0.29, 0.25), *p*=0.899; heterogeneity: *p*=0.224, I2=31.5%] between MIS-C and KD patients, and MIS-C patients had lower Hb levels than KDSS patients [SMD (*95% CI*): -0.75 (-1.10, -0.39), *p*<0.05; heterogeneity: *p*=0.152, I2=46.9%].

Ten studies reported PLT count, and high heterogeneity was present (I2 >75%). We conducted a subgroup analysis based on the control groups of KD or KDSS patients. In the subgroup analysis, the MIS-C patients showed a lower PLT count than KD patients [SMD (*95% CI*): -1.35 (-1.54, -1.15), *p*<0.001; heterogeneity: *p*=0.136, I2=36.7%] and KDSS patients [SMD (*95% CI*): -0.69 (-1.01, -0.38), *p*<0.001; heterogeneity: *p*=0.651, I2=0.0%].

**Meta-analysis of inflammatory markers** (Table 2, Figure 2)**10-21**

The meta-analysis showed that MIS-C patients had higher CRP levels (mg/L) [WMD (*95% CI*): 79.86 (58.24, 101.48), *p*<0.001; heterogeneity: *p*<0.05, I2=51.3%], higher D-dimer levels [SMD (*95% CI*): 0.63 (0.39, 0.86), *p*<0.001; heterogeneity: *p*=0.842, I2=0.0%] and higher ferritin levels (ng/mL) [WMD (*95% CI*): 539.16 (426.77, 651.55), *p*<0.001; heterogeneity: *p*=0.514, I2=0.0%] than KD patients. The outcome in the ESR subgroup indicated that the MIS-C patients had lower ESR levels (mm/hr) [WMD (*95% CI*): -43.42 (-55.82, -31.01), *p*<0.001; heterogeneity: *p*=0.705, I2=0.0%] than KDSS patients. However, there were no significant differences in PCT levels (ng/ml) [WMD (*95% CI*): 1.35 (-0.17, 2.87), *p*=0.082; heterogeneity: *p*=0.209, I2=36.7%] or ESR levels (mm/hr) [WMD (*95% CI*): 7.58 (-7.93, 23.08), *p*=0.34; heterogeneity: *p*=0.245, I2=28.8%] between MIS-C and KD patients.

**Meta-analysis of cardiac markers** (Table 2, Figure 3)**13,14,16-20**

Regarding cardiac markers, the meta-analysis showed that a higher CPK level (U/L) was noted in MIS-C patients than in KD patients [WMD (*95% CI*): 31.26 (6.20, 56.31), *p*<0.05; heterogeneity: *p*=0.785, I2=0.0%]. In addition, there were no statistically significant differences in NT-proBNP level [SMD (*95% CI*): 0.05 (-0.15, 0.25), *p*=0.631; heterogeneity: *p*=0.55, I2=0.0%], troponin level [SMD (*95% CI*): 0.17 (-0.08, 0.43), *p*=0.183; heterogeneity: *p*=0.873, I2=0.0%] or AST level (U/L) [WMD (*95% CI*): 8.41 (-4.00, 20.83), *p*=0.184; heterogeneity: *p*=0.664, I2=0.0%].

**Meta-analysis of biochemistry/basic metabolic profile (BMP)** (Table 2, Figure 4)10,11,13-17,19-21

For biochemistry, the meta-analysis indicated that MIS-C patients had lower albumin levels [SMD (*95% CI*): -1.25 (-1.54, -0.96), *p*<0.001; heterogeneity: *p*=0.364, I2=7.5%], lower ALT levels (U/L) [WMD (*95% CI*): -14.93 (-22.78, -7.08), *p*<0.001; heterogeneity: *p*=0.115, I2=35.5%], lower sodium (Na) levels (mmol/L) [WMD (*95% CI*): -3.83 (-4.79, -2.86), *p*<0.001; heterogeneity: *p*=0.048, I2=50.6%] and higher creatinine levels [SMD (*95% CI*): 1.87 (1.44, 2.29), *p*<0.001; heterogeneity: *p*=0.358, I2=2.7%] than KD patients. There was moderate heterogeneity in the comparison of sodium (Na) levels, and the REM was used for the pooled results. In addition, the albumin level between MIS-C and KDSS patients was not significantly different [SMD (*95% CI*): 0.30 (-0.18, 0.78), *p*=0.216; heterogeneity: *p*=0.317, I2=12.8%].

**Sensitivity analysis and publication bias**

The sensitivity analysis supported the stability and reliability of the outcomes. With Egger’s test, none of the comparison groups showed statistically significant publication bias.

**Discussion**

Since late April 2020, an alert about the pediatric population presenting with an emerging condition called MIS-C has been issued around the world.22 Initial reports during the pandemic mainly indicated that children were ‘immune to’ COVID-19 or were only mildly symptomatic or asymptomatic if affected by COVID-19. However, as the pandemic progressed, studies on this new hyperinflammatory syndrome, MIS-C, have started to emerge worldwide.23 Some common features overlapped between MIS-C patients and KD patients. Indeed, previous studies6,24,25 have shown that MIS-C shares common features with KD. Common symptoms may include fever, rash, conjunctivitis, mucocutaneous inflammation signs, elevated inflammation and coronary artery abnormality.26 However, there were some differences that MIS-C was more common in older children and in Western nations, exhibited increased gastrointestinal and nervous system involvement, and showed increased incidence of myocarditis or shock. KD predominately affects younger children, especially those under 5 years of age.7 Based on the question of how laboratory parameters or specific biomarkers compare between MIS-C and KD patients, we conducted a systematic review and meta-analysis to show the characteristics of laboratory parameters between the two different diseases.

In terms of hematology, our results suggested that compared with KD patients, MIS-C patients had lower levels of WBC, ALT and PLT and similar ANC and levels of Hb. Among them, the ALT level was significantly lower in MIS-C patients than in KD patients, supporting that lymphopenia is also a confirmatory characteristic of COVID-19. A lower ALC may indicate an association with COVID-19, which is caused by SARS-CoV-2, as similar clinical features are shared by patients with COVID-19.27 Although thrombocytosis is common in KD,28 the PLT count in MIS-C was lower than that of KD in our analysis. This difference may be due to the variation in potential immunopathogenesis. The pathogenesis of KD is known to be mediated by immune complexes that can activate inflammatory cells, resulting in the recruitment of platelets, leading to thrombocytosis.29 In contrast, for MIS-C with viral-associated hyperinflammatory syndromes, during the process of eradicating the virus, some mediators that mainly stimulate CD8+ cells to kill virus-infected cells inadvertently suppress bone marrow function, leading to thrombocytopenia. Therefore, the hypothesis30 that the PLT count may be able to help us differentiate between MIS-C and KD was proposed and may be partially supported by our study findings.

In terms of inflammatory markers, MIS-C presents with a severe inflammatory state evidenced by elevated CRP, D-dimer and ferritin levels, but PCT and ESR failed to show a significant difference between MIS-C and KD patients. The acute-phase reactant ESR showed a lower level in MIS-C patients than in KDSS patients. The laboratory results of inflammatory markers showed severe systemic inflammation or strong inflammatory reactions, promoting a hyperinflammatory response in children with MIS-C. Moreover, both MIS-C and KD patients exhibited elevated inflammatory markers; however, more obvious elevation of inflammatory markers was observed in MIS-C patients than in KD patients, especially with regard to CRP, D-dimer and ferritin. D-dimer and ferritin showed higher levels in MIS-C patients, similar to macrophage activation syndrome.31 However, few studies on classic KD have reported a similar status. These findings on the existing differences between MIS-C and KD might help us distinguish between these two diseases.32 D-dimer, a surrogate of disseminated intravascular coagulation, can reflect the presence of coagulation disorders or thrombosis, which have been reported in adult severe COVID-19 patients. The associated reason was hypothesized to be endothelial damage with hyperinflammation. Moreover, elevated D-dimer levels have been reported to be related to increased mortality.33 Because of the high levels of D-dimer, anticoagulation therapy has been considered for the treatment and management of MIS-C patients.

In terms of cardiac markers, MIS-C patients had higher CPK levels than KD patients. However, there was no significant difference in the levels of NT-proBNP, troponin and AST. Among different cardiac damage biomarkers, CPK or CKMB is limited to being a specific cardiac damage marker given its cardiac specificity. Cardiac troponin was truly cardiac-specific.34 Indeed, CPK elevation was observed in MIS-C patients compared with KD patients, but there was no difference in troponin level. Therefore, whether MIS-C patients have more severe cardiac damage or myocardial injury than KD patients should be considered with caution, as the current evidence is not sufficient. In addition, the cardiac biomarker NT-proBNP is tested in the essential evaluation and routine diagnosis of heart failure.34 NT-proBNP failed to show a significant difference between MIS-C and KD patients. The lack of correlation of cardiac markers between MIS-C and KD may suggest that pathological changes in the circulatory system may not be a direct consequence of the severity of inflammation.

In terms of biochemistry, MIS-C patients had lower levels of albumin, sodium and ALT and higher levels of creatinine than KD patients. The albumin level of MIS-C patients was not significantly different from that of KDSS patients. In many clinical situations, the status of hypoalbuminemia has been thought to be related to severe illness and mortality.35,36 As a result of inflammation, the increasing permeability of capillaries, increasing expression of vascular endothelial growth factor, and the increasing escape, increasing distribution volume, shortened half-life, and decreasing total mass of albumin are considered to be the associated pathophysiologies of hypoalbuminemia. Hypoalbuminemia is thought to be a consequence of inflammation and reflects the inflammatory state. Therefore, low albumin levels are a valuable indicator of the severity of inflammation.37 The association between inflammation and albumin levels makes it a suitable instrument for the assessment of the disease process. This finding might assist in the optimal diagnosis and management program for MIS-C based on KDSS. Furthermore, our meta-analysis showed that the sodium level of MIS-C patients was lower than that of KD patients. This outcome was consistent with that of other studies on adult COVID-19 patients.38,39 This result indicated that sodium balance disorders, especially hyponatremia, were a common condition in COVID-19 patients and were thought to be associated with critical illness and increased mortality. Early identification of sodium balance disorders is useful for the management of MIS-C. In addition, the creatinine level of MIS-C patients was reported to be higher than that of KD patients. Similar results of kidney involvement have also been presented in other case reports.40 Biochemistry features suggest systemic inflammation involving multiple organs, such as the liver and kidney. Therefore, we should be keenly aware of the possible involved organs and learn more about the wide spectrum of this disease.

MIS-C is an evolving syndrome of SARS-CoV-2 infection in children, and there is much to explore and learn. Indeed, our meta-analysis compared the characteristics of laboratory parameters between MIS-C and KD patients and provided possible explanations for the findings. The outcomes contained vast information. Due to analytical issues, laboratory parameters might not be the gold standard for the diagnostic criteria. However, numerous laboratory parameters were reviewed to provide some clinical evidence for follow-up mechanistic studies, such as proteomics and metabonomics.

Some limitations should be considered. First, it was performed based on observational studies, and the reliability of the results was limited. Second, the sample sizes in some studies were small. Third, the number of included studies about KDSS was too small. Fourth, substantial heterogeneity was noted in the results, although the heterogeneity was partially improved by subgroup analysis. Fifth, certain studies performed intensive evaluations and presented immense information, whereas there was a dearth of information regarding the patients in others.

In conclusion, there have been significant inconsistencies in reporting the laboratory parameters in the comparisons of MIS-C and KD patients. Our meta analysis found that compared to KD patients, MIS-C patients had different characteristics of hematology (decreased WBC count, decreased ALC and decreased PLT count), inflammatory markers (increased CRP, increased D-dimer and increased ferritin), cardiac markers (similar levels of NT-proBNP and troponin) and biochemistry (decreased albumin, decreased sodium, decreased ALT and increased creatinine). In addition, compared to KDSS patients, MIS-C patients had a decreased PLT count, decreased ESR, decreased Hb level, increased ANC and a similar WBC count and albumin level. Notably, MIS-C has some similarities with KD but also has specific unique characteristics. The overlapping characteristics between MIS-C and KD might occur because the two diseases are different results of similar possible pathophysiologies. Monitoring laboratory parameters might help the management of MIS-C patients, especially in obtaining a differential diagnosis from KD or KDSS. Furthermore, elucidating the potential mechanisms of MIS-C will be conducive to providing further insights for management or prevention. Follow-up studies on the mechanism are needed in the future.

**Legends:**

E-figure 1: Flow diagram of the study selection process.

Figure 1: Forest plots of laboratory hematology parameters (ALC, absolute lymphocyte count; ANC, absolute neutrophil count; KD, Kawasaki disease; KDSS, Kawasaki disease shock syndrome; MIS-C, multisystem inflammatory syndrome in children; PLT, platelet count; WBC, white blood cell count.)

Figure 2: Forest plots of laboratory parameters of inflammatory markers (CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; KD, Kawasaki disease; KDSS, Kawasaki disease shock syndrome; MIS-C, multisystem inflammatory syndrome in children; PCT, procalcitonin.)

Figure 3: Forest plots of laboratory parameters of cardiac markers (AST, aspartate aminotransferase; CPK, creatine phosphokinase; NT-proBNP, N-terminal pro-brain natriuretic peptide.)

Figure 4: Forest plots of laboratory biochemistry parameters (ALT, alanine aminotransferase; KD, Kawasaki disease; KDSS, Kawasaki disease shock syndrome; MIS-C, multisystem inflammatory syndrome in children; Na, sodium.)

Table 1: Detailed characteristics of the included studies

Table 2: Results of meta-analysis

E-table in the Supplement