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RESEARCH ARTICLE

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The inflammatory markers of multisystem inflammatory syndrome in children (MIS-C) and adolescents associated with COVID-19: A meta-analysis

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Abstract

To conduct a systematic review and meta-analysis to characterize inflammatory markers in comparisons of multisystem inflammatory syndrome in children (MIS-C) versus severe/non-severe COVID-19, severe MIS-C versus non-severe MIS-C, and among age groups of MIS-C. Nine databases were searched for studies on inflammatory markers of MIS-C. After quality checks, data were pooled using a fixed or random effects model. Inflammatory markers included white blood cell count (WBC) or leukocytes, absolute lymphocyte count (ALC), absolute neutrophil count (ANC), platelet count (PLT), C-reactive protein (CRP), procalcitonin (PCT), ferritin, D-dimer, lactate dehydrogenase (LDH), fibrinogen, and erythrocyte sedimentation rate (ESR) for comparisons by severity and age. Twenty-one studies with 1735 participants yielded 787 MIS-C patients. Compared to non-severe COVID-19 patients, MIS-C patients had lower ALC and higher ANC, CRP, and D-dimer levels. Compared to severe COVID-19 patients, MIS-C patients had lower LDH and PLT counts and higher ESR levels. Severe MIS-C patients had higher levels of WBC, ANC, CRP, D-dimer, and ferritin than non-severe MIS-C patients. For MIS-C, younger children (0–5 years) had lower CRP and ferritin levels than middle-aged/older children/adolescents. Measurement of inflammatory markers might assist clinicians in accurate evaluation and diagnosis of MIS-C and the associated disorders.

KEYWORDS

COVID-19, inflammatory markers, meta-analysis, MIS-C/PMIS/PIMS-TS, pediatrics, SARS-CoV-2

Abbreviations: 95% CI, 95% confidence interval; ACE2, angiotensin-converting enzyme 2; ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CDC, Centers for Disease Control and Prevention; COVID-19, the 2019 novel coronavirus disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FEM, fixed effects model; KD, Kawasaki disease; LDH, lactate dehydrogenase; MIS-C, multisystem inflammatory syndrome in children; NOS, Newcastle–Ottawa Scale; PCT, procalcitonin; PIMS-TS, Pediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV-2; PLT, platelet count; PMIS, pediatric multisystem inflammatory syndrome; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO, International Prospective Register of Systematic Reviews database; RCPCH, Royal College of Pediatrics and Child Health; REM, random effects model; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SMD, standard mean differences; WBC, white blood cell count; WHO, World Health Organization; WMD, weighted mean deviations.

1 | INTRODUCTION

The 2019 novel coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread rapidly all over the world. During the earlier phase of the pandemic, children were thought to be "immune" or largely spared from the comorbidities and mortality associated with COVID-19.[1] However, recent studies have reported severe or even critical complications to have developed among children with COVID-19.[2,3] In particular, an unusual syndrome of fever and hyperinflammatory process has emerged in pediatric populations with COVID-19.[4] The syndrome has been described as Pediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV-2 (PIMS-TS) or pediatric multisystem inflammatory syndrome (PMIS) by the Royal College of Pediatrics and Child Health (RCPCH)[5] and as Multisystem Inflammatory Syndrome in Children (MIS-C) by the World Health Organization (WHO)[6] and Centers for Disease Control and Prevention (CDC).[7] The preliminary case definitions were proposed, with MIS-C specifically characterized as a hyperinflammatory syndrome with multiorgan involvement and some clinical features that also overlap with Kawasaki disease (KD).[8] The term MIS-C is used throughout this meta-analysis.

Several studies have reported laboratory features of MIS-C that are related to the known hyperinflammatory syndrome, however, these were limited by smaller sample sizes or descriptive studies to derive conclusions with strong external validity.[9–12] Moreover, as per our knowledge, there are no meta-analyses in the literature that have compared the inflammatory markers of MIS-C among several known conditions to be associated with it, including COVID-19. In this study, we performed a meta-analysis to elucidate the inflammatory markers between MIS-C and known associated conditions including COVID-19, along with an internal comparison of MIS-C based on its severity and age.

2 | METHODS

We conducted the research according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and registered our review on the International Prospective Register of Systematic Reviews database (PROSPERO) on September 28, 2020; PROSPERO ID (CRD42020211402).

2.1 | Search strategy

Two authors (Yan Zhao and Lijuan Yin) carried out a search of the databases PubMed, Ovid, MEDLINE, Embase, Web of Science, Cochrane Library, PROSPERO, China National Knowledge Infrastructure (CNKI), and Wanfang database. We searched for any articles published in English from database build-up to November 23, 2020. Medical Subject Heading (MESH) and keywords with synonyms used included *coronavirus disease 2019*, *coronavirus 2019*, *COVID-19*, *COVID19*, *2019 novel coronavirus*, *2019nCoV*, *2019-nCoV*, *nCoV-2019*, *severe acute respiratory syndrome coronavirus 2*, *SARS-CoV-2*, *SARS2*, and *multisystem inflammatory syndrome*, *MIS-C*, *pediatric inflammatory multisystem syndrome*, *pediatric multisystem inflammatory syndrome*, *PIMS-TS*, *PMIS*, *Kawasaki-like disease*, *Kawasaki Disease*, *hyperinflammatory syndrome*. A manual search of references from selected studies was also conducted to keep the search inclusive.

2.2 | Inclusion and exclusion criteria

The inclusion criteria were (1) patients diagnosed MIS-C by CDC or WHO, or PMIS/PIMS-TS by RCPCH; (2) studies showing comparisons between one of the following: MIS-C versus severe/non-severe COVID-19, severe MIS-C versus non-severe MIS-C, and age groups of MIS-C; (3) reported outcomes in the form of inflammatory markers specific to white blood cell count (WBC) or leukocytes, absolute lymphocyte count (ALC), absolute neutrophil count (ANC), platelet count (PLT), C-reactive protein (CRP), procalcitonin (PCT), ferritin, D-dimer, lactate dehydrogenase (LDH), fibrinogen, erythrocyte sedimentation rate (ESR), etc. The exclusion criteria were (1) review articles, guidelines, consensus of opinions, case reports, case series, basis research, or other unrelated topics outside the scope of this review; (2) descriptive studies, studies without experimental/control group, not analytical study or experimental study.

2.3 | Data extraction

We reported baseline characteristics and outcomes as available from the selected studies, which included author information, country, the age range of study participants, time period of the study, number of included patients, and diagnostic information were extracted. The different kinds of inflammatory markers were extracted as our target data.

2.4 | Quality assessment

We used the Newcastle–Ottawa Scale (NOS)[13] to perform a quality assessment on all observational studies (case–control and cohort). Based on the scoring system of the NOS scale, we checked for selection (4 points), comparability (2 points), and outcome/exposure (3 points) for each study. A score of 1–3, 4–6, and 7–9 points indicated low, moderate, and high quality, respectively. Two investigators (Yan Zhao and Lijuan Yin) individually performed data extraction and quality assessment for each study. Discrepancies were resolved by a consensus that included a third investigator (Ying Huang).

2.5 | Statistical analysis

We calculated weighted mean deviations (WMD), standard mean differences (SMD), and corresponding 95% confidence intervals (95% CIs) from data within the included studies. Furthermore, we performed *Q* test

to assess overall heterogeneity, and I^2 test for quantitative assessment to assess the degree of heterogeneity. For studies with $p < .1$ or $I^2 > 50\%$, indicative of non-negligible heterogeneity, a REM was generated to combine the numerical values. In contrast, for studies with no significant heterogeneity, a FEM was adopted. I^2 values of 25%, 50%, and 75%, respectively, represented low, moderate, and high heterogeneity, respectively. For studies with $I^2 > 50\%$, sensitivity analysis and subgroup analysis were performed to probe the source of heterogeneity. For studies with $I^2 > 75\%$, indicative of large heterogeneity, we did not use the combined result as they were rendered inconclusive. If the results of the two models (REM and FEM) were generally consistent, the combined result was considered reliable. In contrast, if the results were inconsistent, the combined results were considered unreliable. For analyses of over 10 studies, Begg's test and Egger's test were used to assess publication bias. STATA (StataCorp)[14] was used to perform all the statistical analyses.

3 | RESULTS

3.1 | Study characteristics

The initial literature search yielded 2972 articles from all the databases. A final total of 21 studies[15–35] were included after screening based on the inclusion criteria (Figure 1). All of the studies had a total of 1735 participants which included 787 MIS-C patients. Except for three studies,[22,29,31] the rest of the studies had fewer than 100 enrolled participants. Twelve studies[15–22,30,31,33,34] compared MIS-C and COVID-19 along with subgroup analysis of MIS-C and severe/non-severe COVID-19; seven studies[23–27,32,35] compared severe and non-severe MIS-C, while two studies[28,29] compared MIS-C across different age groups (0–4/0–5 years representing the young age of infants or preschoolers, 5–12/6–12 years representing the middle age of school-age and 13–20 years representing adolescents/young adults of puberty or postpuberty). All study features and characteristics are presented in Table 1. In the quality assessment of study design for the selected studies, three studies[16,18,33] were deemed of moderate quality, with scores of 6, and the remaining 18 studies were deemed of high quality, with scores above 7 (eTable in the Supplement).

3.2 | Meta-analysis of inflammatory markers (Table 2)

3.2.1 | MIS-C versus severe/non-severe COVID-19 (Figures 2 and 3)[15–22,30,31,33,34]

We found no statistically significant difference in WBC or leukocytes ($\times 10^9$/L) (WMD (95% CI): 0.54 (−0.29, 1.38), $p = .203$), PCT (SMD (95% CI): 0.04 (−0.38, 0.46), $p = .855$) and ferritin (SMD (95% CI): 0.01 (−0.29, 0.31), $p = .939$) levels. However, PLT ($\times 10^9$/L) levels

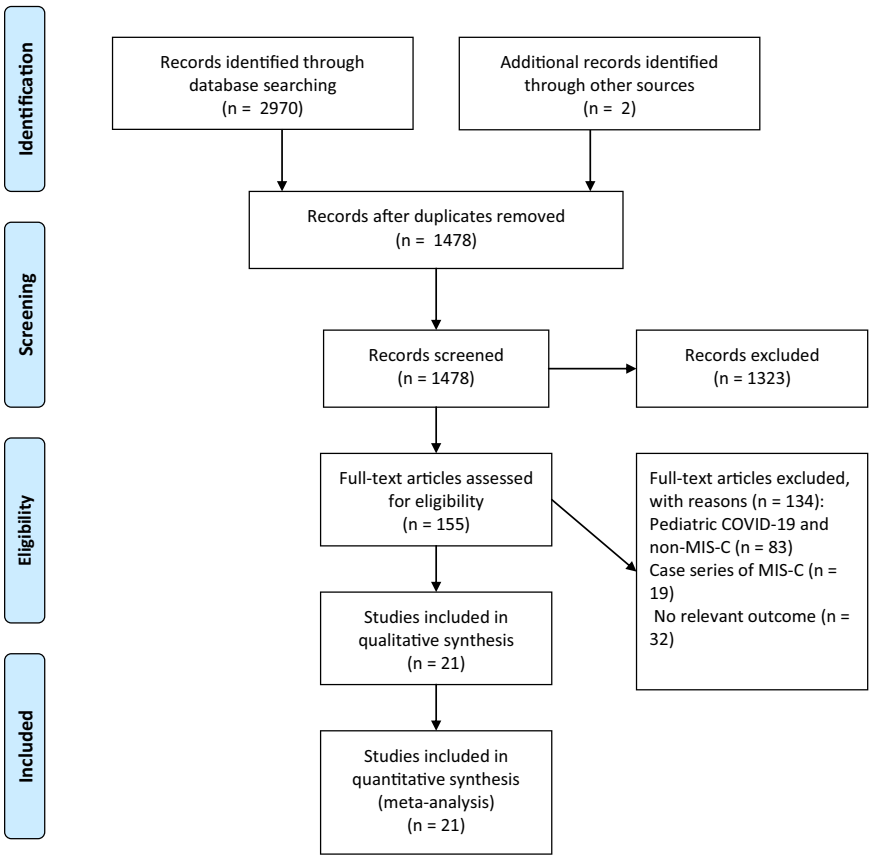

FIGURE 1 Flow diagram

TABLE 1 Detailed characteristics of included studies

Author	Country	Study design	Age range	Study period	Cases/controls	Number	Diagnosis method of MIS-C/PMIS/PIMS-TS
Rostad 2020[15]	United States	Prospective	0–21 years	March 17–May 26, 2020	MIS-C	10	CDC
					COVID-19	10	
Consiglio 2020[16]	Rome/Italy/Sweden	\	0–19 years	March 17–May 15, 2020	MIS-C	13	WHO
					COVID-19	41	
Pereira 2020[17]	Brazil	Cross-sectional	0–18 years	April 16–June 21, 2020	MIS-C	6	CDC
					COVID-19	60	
Weisberg 2020[18]	United States	\	4–17 years	March–June, 2020	MIS-C	15	CDC
					Severe COVID-19	14	
Pierce 2020[19]	United States	\	0–24 years	March 13–May 17, 2020	MIS-C	20	CDC
					Severe COVID-19[a]	4	
					Non-severe COVID-19[a]	41	
Diorio 2020[20]	United States	Prospective	\	April 3–May 15, 2020	MIS-C	6	CDC
					Severe COVID-19[a]	9	
					Non-severe COVID-19[a]	5	
Anderson 2020[21]	United States	\	\	April–May, 2020	MIS-C	10	CDC
					Severe COVID-19[a]	9	
					Non-severe COVID-19[a]	10	
Swann 2020[22]	United Kingdom	Prospective	0–19 years	Jan 17–July 17, 2020	MIS-C	52	WHO
					COVID-19	404	
Prata-Barbosa 2020[30]	Brazil	Prospective	1 month–19 years	March 1–May 31, 2020	MIS-C	10	CDC
					Severe COVID-19	69	
Fernandes 2020[31]	United States	Ambispective	≤22 years	March 1–May 22, 2020	MIS-C	69	CDC
					Respiratory COVID-19	143	
					Other COVID-19	69	
Weisberg 2021[33]	United States	\	3–18 years	March–June, 2020	MIS-C	16	CDC
					Severe COVID-19	13	
					Non-severe COVID-19	31	
Vella 2020[34]	United States	\	0–18 years	April–June, 2020	MIS-C	14	CDC
					COVID-19	16	
Whittaker 2020[23]	United Kingdom	Retrospective	3 months–17 years	March 23 and May 22, 2020	Severe MIS-C[b]	29	CDC/WHO/RCPCH
					Non-severe MIS-C[b]	29	
Pouletty 2020[24]	France	Retrospective	\	April 2020–	Severe MIS-C[b]	7	Kawa-COVID-19[c]
					Non-severe MIS-C[b]	9	
Davies 2020[25]	United Kingdom	Retrospective	0–18 years	April 1–May 10, 2020	Severe MIS-C[b]	36	RCPCH
					Non-severe MIS-C[b]	42	

(Continues)

TABLE 1 (Continued)

Author	Country	Study design	Age range	Study period	Cases/controls	Number	Diagnosis method of MIS-C/PMIS/PIMS-TS
Torres 2020[26]	Chile	Ambispective	0–14 years	May 1–June 24, 2020	Severe MIS-C at admission[b]	16	CDC
					Non-severe MIS-C at admission[b]	11	
					Severe MIS-C in hospitalization[b]	16	
					Non-severe MIS-C in hospitalization[b]	11	
Lee 2020[27]	United States	Retrospective	1 month–17 years	March 17–June 6, 2020	Severe MIS-C[b]	17	CDC/WHO
					Non-severe MIS-C[b]	9	
Corwin 2020[32]	United States	Retrospective	0–21 years	March 1–May 15, 2020	Severe MIS-C[b]	5	CDC
					Non-severe/moderate MIS-C[b]	8	
					Non-severe/mild MIS-C[b]	20	
Jain 2020[35]	India	\	\	May 1–July 15, 2020	Severe MIS-C[b]	15	WHO
					Non-severe MIS-C[b]	8	
Dufort 2020[28]	United States	Retrospective	0–20 years	March 1–May 10, 2020	0–5 years	31	CDC
					6–12 years	42	
					13–20 years	26	
Feldstein 2020[29]	United States	Ambispective	3.3–12.5 years	March 15–May 20, 2020	0–4 years	66	CDC
					5–12 years	75	
					13–20 years	45	

Abbreviations: CDC, Centers for Disease Control and Prevention; COVID-19, the 2019 novel coronavirus disease; MIS-C, multisystem inflammatory syndrome in children; PMIS, pediatric multisystem inflammatory syndrome; PIMS-TS, Pediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV-2; RCPCH, Royal College of Pediatrics and Child Health; WHO, World Health Organization.

[a]Severe COVID-19: respiratory process requiring invasive respiratory support or mechanical ventilation or an increase in positive pressure support above their baseline and did not meet criteria for MIS-C; Non-severe COVID-19: COVID-19 that did not otherwise meet criteria for MIS-C or severe symptoms.

[b]Severe PMIS/PIMS-TS/MIS-C: PMIS/PIMS-TS/MIS-C with shock which was defined as needing inotrope support or fluid resuscitation >20 ml/kg, or PMIS/PIMS-TS/MIS-C that required invasively ventilated or admission to ICU, or PMIS/PIMS-TS/MIS-C with severe disease course, which was defined by a necessity for intensive care (at least one organ failure) and/or fatal outcome.

[c]Kawa-COVID-19: presenting features of KD-like systemic inflammatory disease, associated with a proven or highly suspected SARS-CoV-2 infection.

were overall lower in MIS-C patients than COVID-19 patients (WMD (95% CI): −95.16 (−112.15, −78.17), $p < .001$), as observed in the fixed-effects model.

For other inflammatory markers, due to the presence of significant heterogeneity of outcomes, subgroup analyses were performed for MIS-C versus COVID-19, based on the severity of COVID-19. COVID-19 patients not meeting the criteria for MIS-C were categorized into severe COVID-19 (patients requiring intensive care unit [ICU], or requiring invasive respiratory support, or requiring mechanical ventilation, or fatal outcome) and non-severe COVID-19 (patients with minimal symptoms or asymptomatic, without severe symptoms). Compared to non-severe COVID-19 patients, MIS-C patients had lower ALC ($\times 10^6$/L) levels (WMD (95% CI): −1110.43 (−1477.75, −743.11), $p < .001$), while MIS-C patients had higher levels for ANC ($\times 10^6$/L) (WMD (95% CI): 2392.68 (1636.71, 3148.64), $p < .001$), CRP (SMD (95% CI): 1.09 (0.70, 1.48), $p < .001$) and D-dimer (SMD (95% CI): 1.61 (1.19, 2.04), $p < .001$). Compared to severe COVID-19 patients, MIS-C patients had lower levels for LDH (SMD (95% CI): −0.91 (−1.39, −0.43), $p < .001$) and higher levels of ESR (mm/h) (WMD (95% CI): 34.52 (14.23, 54.80), $p < .005$), while the same levels of ALC ($\times 10^6$/L), ANC ($\times 10^6$/L), CRP, and D-dimer (WMD (95% CI): −7.54 (−302.05, 286.96), WMD (95% CI): −144.77 (−2879.45, 2589.92), SMD (95% CI): 0.12 (−0.20, 0.44), SMD (95% CI): −0.26 (−0.61, 0.10), $p > .05$).

TABLE 2 Results of meta-analysis

Case/control	EM	WMD/SMD (95% CI)	*p*	Heterogeneity *p*	Heterogeneity I_2 (%)	
MIS-C versus severe/non-severe COVID-19						
WBC ($\times 10^9$/L)	FEM	0.54 (−0.29, 1.38)	.203	.126	34.1	WMD
PLT ($\times 10^9$/L)	FEM	−95.16 (−112.15, −78.17)	<.001	.276	17.1	WMD
PCT	FEM	0.04 (−0.38, 0.46)	.855	1.000	0.0	SMD
Ferritin	FEM	0.01 (−0.29, 0.31)	.939	.184	30.6	SMD
ALC ($\times 10^6$/L)		NA				WMD
Non-severe COVID-19	REM	−1110.43 (−1477.75, −743.11)	<.001	.001	68.0	
Severe COVID-19	REM	−7.54 (−302.05, 286.96)	.960	.956	0.0	
ANC ($\times 10^6$/L)	REM	1976.79 (1116.09, 2837.49)	<.001	.176	26.5	WMD
Non-severe COVID-19	REM	2392.68 (1636.71, 3148.64)	<.001	.512	0.0	
Severe COVID-19	REM	−144.77 (−2879.45, 2589.92)	.917	.171	43.4	
CRP	REM	0.68 (0.36, 1.00)	<.001	<.001	67.7	SMD
Non-severe COVID-19	REM	1.09 (0.70, 1.48)	<.001	.003	67.9	
Severe COVID-19	REM	0.12 (−0.20, 0.44)	.455	.986	0.0	
D-dimer		NA				SMD
Non-severe COVID-19	REM	1.61 (1.19, 2.04)	<.001	.382	2.0	
Severe COVID-19	REM	−0.26 (−0.61, 0.10)	.156	.273	20.5	
LDH		NA				SMD
Non-severe COVID-19	REM	0.11 (−0.28, 0.50)	.570	.382	0.0	
Severe COVID-19	REM	−0.91 (−1.39, −0.43)	<.001	.202	32.9	
ESR (mm/h)		NA				WMD
Non-severe COVID-19	FEM	−3.57 (−32.82, 25.67)	.881	.678	0.0	
Severe COVID-19	FEM	34.52 (14.23, 54.80)	<.005	.806	0.0	
Severe MIS-C versus non-severe MIS-C						
WBC ($\times 10^9$/L)	FEM	2.84 (0.79, 4.90)	<.010	.358	9.3	WMD
ALC	FEM	−0.60 (−0.91, −0.30)	<.001	.114	41.5	SMD
ANC ($\times 10^9$/L)	FEM	3.28 (2.01, 4.55)	<.001	.118	48.9	WMD
PLT ($\times 10^9$/L)	FEM	−20.43 (−41.53, 0.68)	.058	.120	40.6	WMD
CRP (mg/L)	FEM	68.64 (46.19, 91.09)	<.001	.196	27.9	WMD
Fibrinogen (mg/dl)	REM	−0.01 (−1.59, 1.58)	.991	.074	68.8	WMD
D-dimer (μg/ml)	FEM	2.50 (1.78, 3.21)	<.001	.347	10.8	WMD
Ferritin (ng/ml)	FEM	362.50 (130.25, 594.76)	<.005	.525	0.0	WMD
Age groups of MIS-C[a]						
Younger versus medium age						
Ferritin (ng/ml)	FEM	−285.78 (−457.04, −114.53)	<.010	.652	0.0	WMD
Younger versus older age						
CRP (mg/L)	FEM	−88.75 (−122.67, −54.84)	<.001	.567	0.0	WMD
D-dimer (μg/ml)	FEM	1.49 (0.37, 2.61)	<.010	.267	18.9	WMD
ESR (mm/h)	FEM	−7.79 (−16.38, 0.80)	.076	.261	20.8	WMD

(Continues)

TABLE 2 (Continued)

Case/control	EM	WMD/SMD (95% CI)	p	Heterogeneity p	Heterogeneity I_2 (%)	
Medium versus older age						
CRP (mg/L)	FEM	−24.95 (−58.96, 9.06)	.150	.214	35.2	WMD
Ferritin (ng/ml)	REM	−91.69 (−413.85, 230.46)	.577	.148	52.2	WMD

Note: NA: not available, because there's large heterogeneity (I2 > 75%), or the combined result was considered to be unreliable if the results of two models (REM and FEM) were inconsistent.

Abbreviations: ALC, absolute lymphocyte count; ANC, absolute neutrophil count; COVID-19, the 2019 novel coronavirus disease; CRP, C-reactive protein; EM, effects model; ESR, erythrocyte sedimentation rate; FEM, fixed effects model; LDH, lactate dehydrogenase; MIS-C, multisystem inflammatory syndrome in children; PLT, platelet count; PCT, procalcitonin; REM, random effects model; SMD, standard mean differences; WBC, white blood cell count; WMD, weighted mean deviations; 95% CI, 95% confidence interval.

[a]0–4/0–5 years representing the young age of infants or preschoolers, 5–12/6–12 years representing the middle age of school-age, and 13–20 years representing adolescents/young adults (puberty or postpuberty).

A moderate degree of heterogeneity was reported in three comparisons: ALC in MIS-C versus non-severe COVID-19 ($p = .001$, $I^2 = 68.0\%$), CRP in MIS-C versus COVID-19 ($p < .05$, $I^2 = 67.7\%$) and CRP in MIS-C versus non-severe COVID-19 ($p < .05$, $I^2 = 67.9\%$). The rest of the comparisons showed no significant difference in statistical heterogeneity.

3.2.2 | Severe MIS-C versus non-severe MIS-C (Figure 4)[23–27,32,35]

Severe MIS-C was recognized as the cases with shock needing inotrope support or fluid resuscitation >20 ml/kg, or requiring invasively ventilation support, or with admission to ICU, or fatal outcome. Severe MIS-C patients had higher levels of WBC ($\times 10^9$/L), ANC ($\times 10^9$/L), CRP (mg/L), D-dimer (μg/ml), and ferritin (ng/ml) (WMD (95% CI): 2.84 (0.79, 4.90), 3.28 (2.01, 4.55), 68.64 (46.19, 91.09), 2.50 (1.78, 3.21), and 362.50 (130.25, 594.76), $p < .01$) and lower levels of ALC (SMD (95% CI): −0.60 (−0.91, −0.30), $p < .001$) compared to non-severe MIS-C patients. For levels of PLT ($\times 10^9$/L) and fibrinogen (mg/dl) (WMD (95% CI): −20.43 (−41.53, 0.68) and −0.01 (−1.59, 1.58), $p > .05$), there were no significant differences between both groups. The comparison of fibrinogen ($p = .074$, $I^2 = 68.8\%$) levels showed a moderate degree of heterogeneity. The rest of the comparisons showed no significant differences in statistical heterogeneity.

3.2.3 | MIS-C in different age groups of children (young children [0–5 years] versus middle-age children [6–12 years] versus adolescents/young adults [13–20 years])[28,29]

MIS-C patients in young children had lower levels of ferritin (ng/ml) (WMD (95% CI): −285.78 (−457.04, −114.53), $p < .01$) than those in middle-age children.

MIS-C patients in young children had lower CRP (mg/L) (WMD (95% CI): −88.75 (−122.67, −54.84), $p < .001$) and mildly higher D-dimer (μg/ml) (WMD (95% CI): 1.49 (0.37, 2.61), $p < .01$) levels than those in adolescents/young adults, but had same levels of ESR (mm/h) (WMD (95% CI): −7.79 (−16.38, 0.80), $p = .076$).

MIS-C patients in middle age and adolescents/young adults had the same levels of CRP (mg/L) (WMD (95% CI): −24.95 (−58.96, 9.06), $p = .150$) and ferritin (ng/ml) (WMD (95% CI): −91.69 (−413.85, 230.46), $p = .577$). The comparison with ferritin levels ($p = .148$, $I^2 = 52.2\%$) showed a moderate degree of heterogeneity.

3.2.4 | Sensitivity analysis and publication bias

The results from sensitivity analysis were fairly similar and verified the stability of our analytical models. In addition, results from both the models (random effects model [REM] and fixed effects model [FEM]) were consistent, which indicated reliability in interpreting the combined results. As the number of included studies in each comparison group was less than 10, we did not assess for publication bias.

4 | DISCUSSION

The recent COVID-19 pandemic poses a huge challenge to global public health. With the associated comorbidities being rapidly discovered, MIS-C has rapidly emerged as a threat to pediatric populations diagnosed with COVID-19.[1] New studies have confirmed the presence of hyperinflammatory syndrome in patients with MIS-C.[2–4] In this study, we conducted a meta-analysis to identify the inflammatory markers of MIS-C for evidence-based monitoring of disease progression. We found that inflammatory markers, including WBC, ALC, ANC, PLT, CRP, PCT, ferritin, D-dimer, LDH, fibrinogen, and ESR, were different while comparing MIS-C versus severe/non-severe COVID-19, severe MIS-C versus non-severe MIS-C, and age groups of MIS-C.

MIS-C, a consequence of an exacerbated immune system response or a maladaptive response,[36] is characterized by hyperinflammation and cytokine storm, including the massive release of

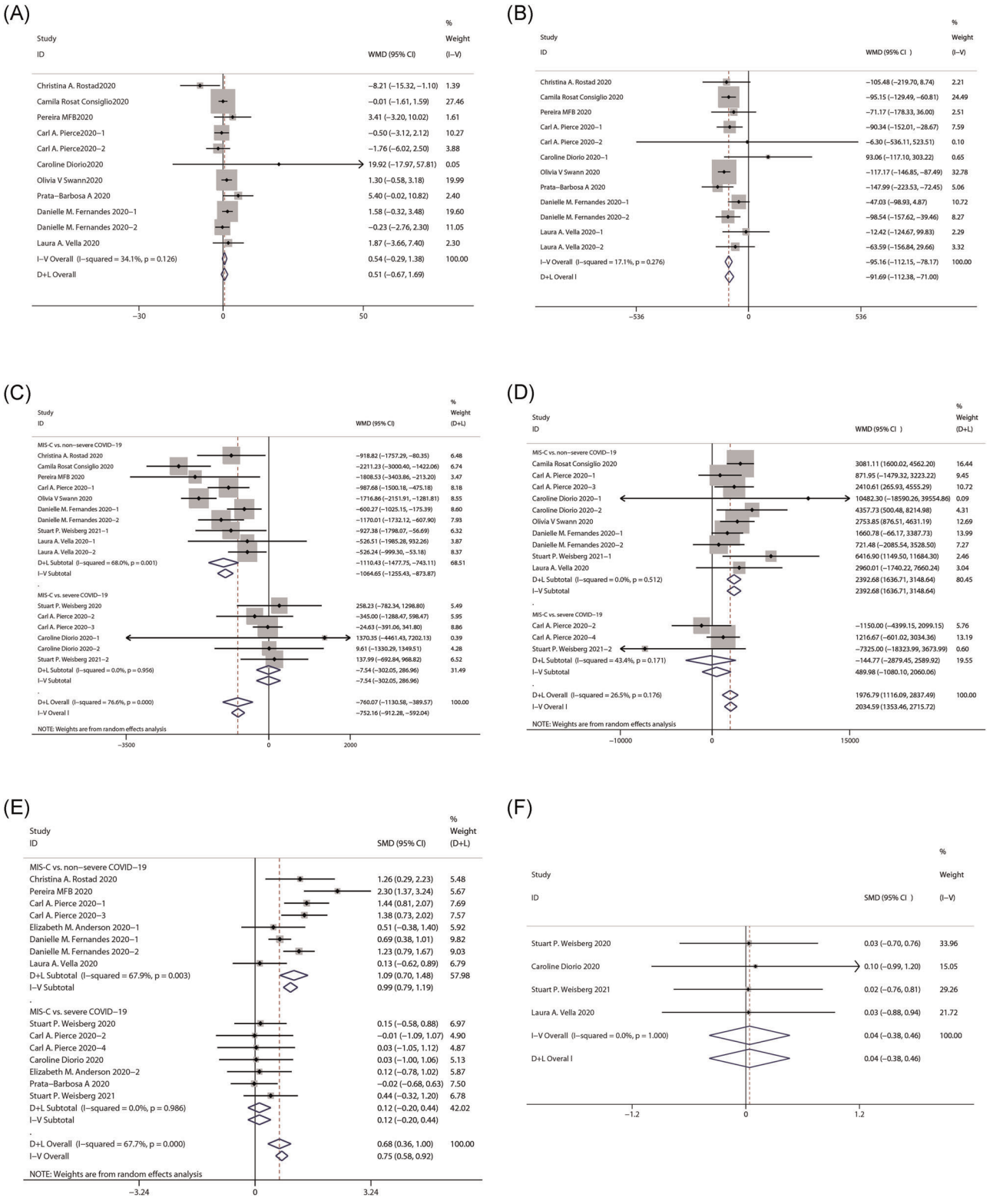

FIGURE 2 Forest plots of MIS-C versus severe/non-severe COVID-19: (A) WBC; (B) PLT; (C) ALC; (D) ANC; (E) CRP; (F) PCT. ALC, absolute lymphocyte count; ANC, absolute neutrophil count; COVID-19, the 2019 novel coronavirus disease; CRP, C-reactive protein; MIS-C, multisystem inflammatory syndrome in children; PCT, procalcitonin; PLT, platelet count; SMD, standard mean differences; WBC, white blood cell count; WMD, weighted mean deviations

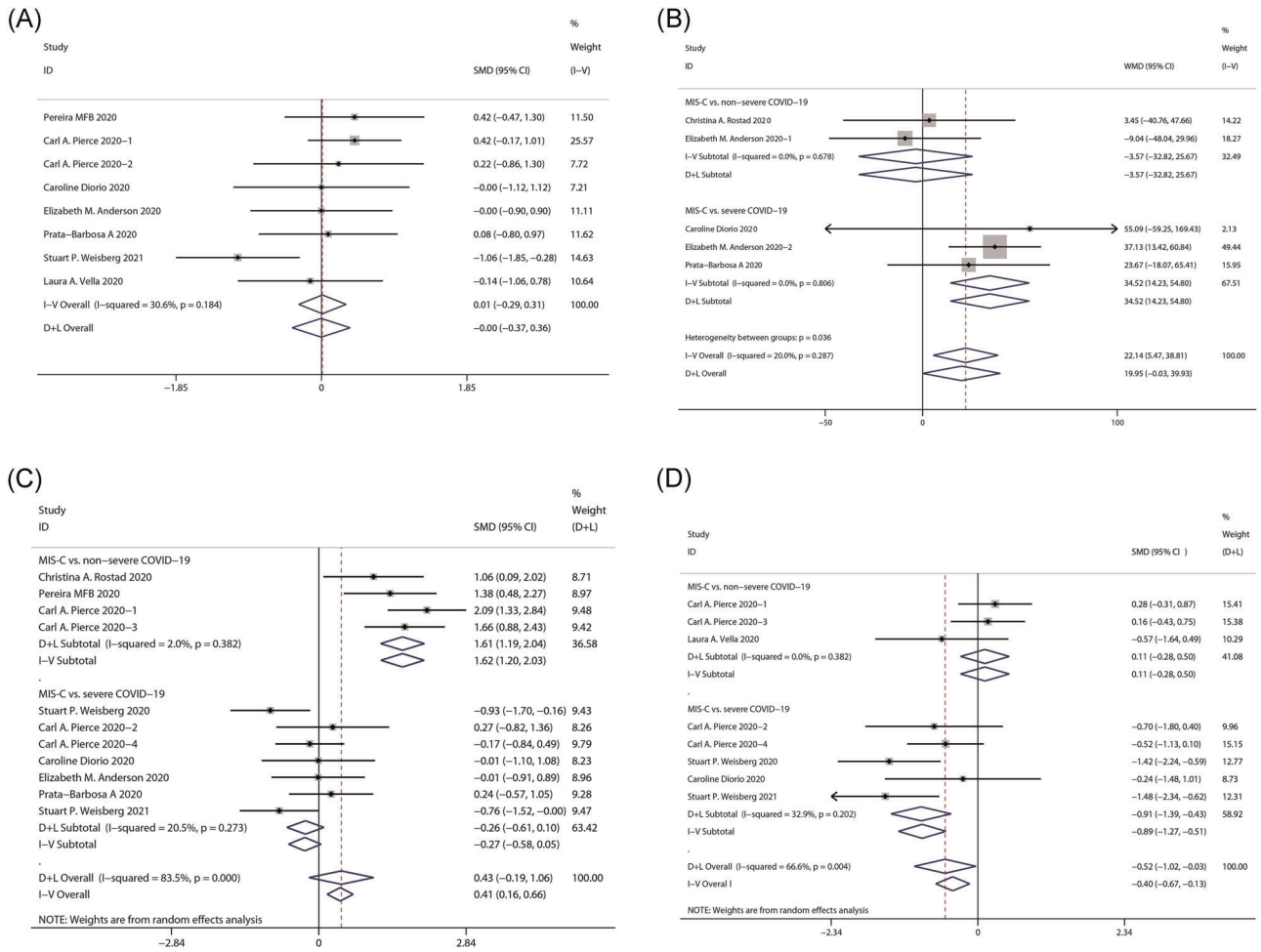

FIGURE 3 Forest plots of MIS-C versus severe/non-severe COVID-19: (A) ferritin; (B) ESR; (C) D-dimer; (D) LDH. COVID-19, the 2019 novel coronavirus disease; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; MIS-C, multisystem inflammatory syndrome in children; SMD, standard mean differences; WMD, weighted mean deviations

inflammatory mediators and exaggerated activation of the immune system, which could be partly demonstrated by the laboratory inflammatory markers.[37] Our results showed no significant differences in WBC, PCT, and ferritin between the MIS-C patients and COVID-19 who did not meet the MIS-C criteria. Further analyses indicated decreased ALC, elevated ANC, elevated CRP, and elevated D-dimer between MIS-C and non-severe COVID-19, but not between MIS-C and severe COVID-19. This important finding may help in designing optimal diagnostic and treatment modalities for MIS-C based on the severity of COVID-19. Moreover, pediatric SARS-CoV-2 patients have the risk of critical progress with severe COVID-19 or MIS-C.[20] Both MIS-C and severe COVID-19 exhibited prominent systemic inflammation, including a similar degree of ANC, CRP, D-dimer, and ALC level. In the comparison of MIS-C and severe COVID-19, except for the lower level of LDH and a higher level of ESR, other inflammatory markers of ALC, ANC, CRP, and D-dimer failed to show significant differences. Hence, due to the failure for discriminating between MIS-C and severe COVID-19, the application values of peripheral blood routine tests are limited, even though it can easily be completed in most hospitals or clinics. More valuable measures, such as immunologic and cytokine profiling, from tertiary care centers or central laboratories are needed to guide the immunomodulatory therapy in the management of pediatric critical patients with SARS-CoV-2.[20] Although the pathophysiology of COVID-19 or MIS-C has not been understood in detail, some studies[38,39] have explained conditions of exacerbated immunological response, cytokine storm, hyperinflammation, reactive epithelial change, vascular damage, coagulopathy, which might contribute to our outcomes of the different changes of inflammatory markers. However, the majority of the explanation for the underlying immune pathogenesis of MIS-C remains unknown and warrants further research.

Patients with severe MIS-C patients showed elevated WBC, CRP, D-dimer, and ferritin levels, compared to patients with non-severe MIS-C. We found that cytokine storm was more common in severe cases of MIS-C. In the management of MIS-C patients, the dynamic monitoring of inflammatory markers, including WBC, CRP, D-dimer, and ferritin, could be helpful to pediatricians to effectively evaluate the progress of MIS-C in the early phases before the disease transforms to a severe state where critical care would be

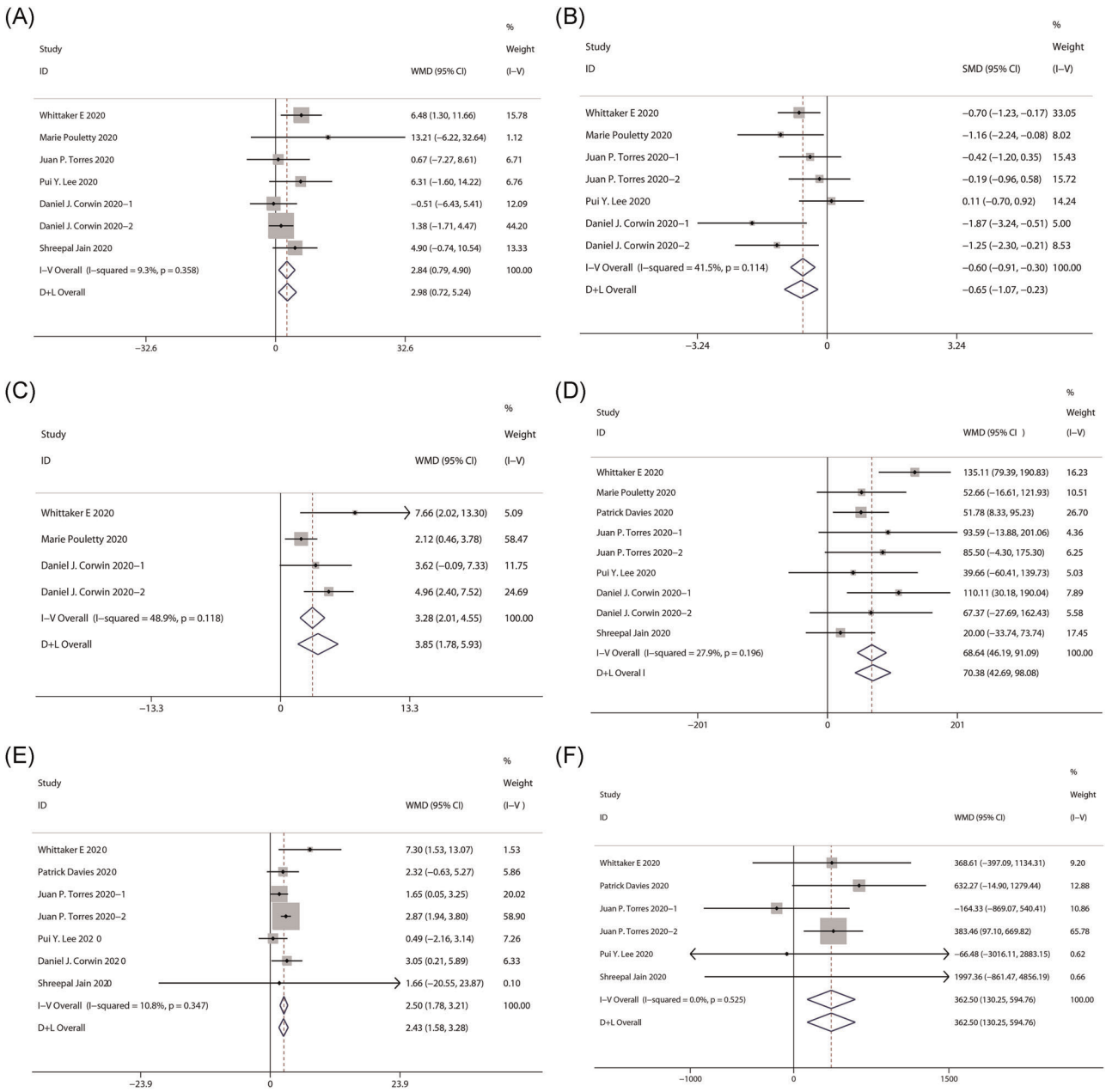

FIGURE 4 Forest plots of severe MIS-C versus non-severe MIS-C: (A) WBC; (B) ALC; (C) ANC; (D) CRP; (E) D-dimer; (F) ferritin. ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CRP, C-reactive protein; MIS-C, multisystem inflammatory syndrome in children; SMD, standard mean differences; WBC, white blood cell count; WMD, weighted mean deviations

needed. In addition, the optimal laboratory markers, as stated in our study, can help establish a predictive model to early distinguish the potentially severe cases from non-severe cases. Once the inflammatory storm is discovered, early and prompt intervention is necessary to improve the prognosis. Recently increasing evidence has suggested inflammatory biomarkers such as the neutrophil to lymphocytes ratio and platelet-to-lymphocyte ratio have the potentiality and ability to be reliable predictors of disease course and severity in COVID-19,[40] as well as a variety of other acute medical conditions,[41,42] such as cerebral hemorrhage and major cardiac events in clinical practice. However, this information could not be synthesized in our literature review and thus further research is recommended on this area.

When comparing age groups of MIS-C, young children (including infants and preschoolers) had lower CRP than adolescents/young adults (during puberty or postpuberty), and lower ferritin levels than middle-age children (school-age), indicating less inflammatory response in young children. These differences of MIS-C could potentially be interpreted with the differences in the exposure likelihood of SARS-CoV-2 infection, or with the differences in nasal expression of angiotensin-converting enzyme 2 (ACE2), which is the receptor of SARS-CoV-2 infection, in different age groups.[43]

Our study should be considered in light of several limitations. First, some of the outcomes may have residual heterogeneity, although sensitivity analyses and subgroup analyses were conducted. Hence the results should be interpreted with caution. Second, the selected studies were mainly non-randomized controlled studies. Third, the majority of the studies were limited by smaller sample sizes. Some studies enrolled relatively fewer subjects, and smaller sizes may reduce statistical power and influence the heterogeneity. Fourth, the number of included studies in each comparison was less than 10, which did not allow us to detect publication bias. Finally, we were unable to investigate the underlying mechanisms of inflammatory markers in MIS-C, as we did not have relevant information to do the same.

In conclusion, our meta-analysis demonstrated that the inflammatory markers, especially WBC, ALC, ANC, PLT, CRP, ferritin, D-dimer, LDH, fibrinogen, and ESR levels, were correlated with MIS-C. Furthermore, studies with a larger sample size, longer follow-up duration and of randomized nature are strongly recommended based on the implications of this study. Measurement or dynamic monitoring of the inflammatory markers studied in this study might assist pediatricians to effectively evaluate and manage children and adolescents with MIS-C, especially with priority during the COVID-19 pandemic.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Yan Zhao conceptualized the original idea, conducted a literature search, screened studies, extracted data, assessed the quality of studies, performed the statistical analysis, conducted the interpretation of data, and drafted the original manuscript. Lijuan Yin co-developed the study design, conducted a literature search, screened studies, extracted data, drafted the original manuscript, and made the decision to submit the paper for publication. Jenil Patel critically reviewed and revised all sections of the manuscript and contributed to finalizing the manuscript. Lei Tang assessed the quality of studies and performed the statistical analysis. Ying Huang supervised the project, resolved disagreements and contributed to drafting the manuscript. All authors reviewed the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in figshare at https://figshare.com/s/f67383194d4617d88916, reference numbers [15–35].

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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