Research Square

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The Inflammatory Markers of Multisystem Inflammatory Syndrome in children (MIS-C) and Adolescents During the COVID-19 Pandemic: A Meta-Analysis

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Abstract

As per the indicated need in literature, we conducted a systematic review and meta-analysis to characterize inflammatory markers of MIS-C patients with COVID-19, Kawasaki disease (KD), and coronary artery abnormalities. We searched nine databases for studies on inflammatory markers of MIS-C. After quality check, 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 studies with 2,990 participants yielded 684 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. Compared to KD patients, MIS-C patients had lower ALC and PLT, and higher CRP and ferritin levels. Severe MIS-C patients had higher levels of WBC, CRP, D-dimer and ferritin. For MIS-C, younger children had lower CRP and ferritin levels than medium-aged/older children. Measurement of inflammatory markers might assist clinicians in accurate evaluation and diagnosis of MIS-C and the associated disorders.

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 hyper-inflammatory 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) by Royal College of Pediatrics and Child Health (RCPCH)[5] and as Multisystem Inflammatory Syndrome in Children (MIS-C) by 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 hyper-inflammatory syndrome with multi-organ involvement and some clinical features that also overlap with Kawasaki disease (KD).[8]

Several studies have reported laboratory features of MIS-C that are related to known hyper-inflammatory 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 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, KD, coronary artery abnormalities along with an internal comparison of MIS-C based on its severity.

Results

Study characteristics

The initial literature search yielded 1397 articles from all the databases. A final total of 20 studies[13–32] were included after screening based on the inclusion criteria (Fig. 1). All of the studies had a total of 2,990 participants

which included 684 MIS-C patients. Except for five studies[20–22, 29,31], rest of the studies had fewer than 100 enrolled participants. Eight studies[13–20] compared MIS-C and COVID-19 along with subgroup analysis of MIS-C and severe/non-severe COVID-19; five studies[13,14,21,22,24] compared MIS-C and KD, five studies[21–23, 25,26] compared severe and non-severe MIS-C, three studies[21,23,27] compared MIS-C with and without coronary artery abnormality, four studies[22,30–32] compared KD during and before SARS-CoV-2 epidemic, while two studies[28,29] compared MIS-C across different age periods (0–4/0–5 years representing the younger age of infants or preschoolers, 5–12/6–12 years representing the medium age of school-age and 13–20 years representing older age of puberty or post-puberty). All study features and characteristics are presented in Table 1. In the quality assessment of study design for the selected studies, three studies[14,16,31] were deemed of moderate quality, with the scores of 6, and the remaining 17 studies were deemed of high quality, with scores above 7. (eTable in the Supplement)

Meta-analysis of inflammatory markers (Table 2, eFigure 2–7)

MIS-C vs. severe/non-severe COVID-19 [13–20]

We found no statistically significant difference in white blood cell count (WBC) or leukocytes ($\times 10^9$/L) [weighted mean deviations (WMD) (*95%CI*): 0.14 (-0.91, 1.18), $p = 0.799$], procalcitonin (PCT) [standard mean differences (SMD) (*95%CI*): 0.05(-0.55, 0.66), $p = 0.864$] and ferritin [SMD (*95%CI*): 0.27(-0.10, 0.65), $p = 0.157$] levels. However, platelet count (PLT) ($\times 10^9$/L) levels were overall lower in MIS-C patients than COVID-19 patients [WMD (*95%CI*): -102.48 (-122.74, -82.22), $p < 0.001$], 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 vs. COVID-19, based on severity of COVID-19. Pediatric patients of COVID-19 not meeting the criteria for MIS-C were categorized into: severe COVID-19 (children with ARDS, or requiring invasive respiratory support, or an increase in positive pressure ventilation above the baseline) and non-severe COVID-19 (children with minimal symptoms or asymptomatic, without requiring invasive respiratory support). Compared to non-severe COVID-19 patients, MIS-C patients had lower absolute lymphocyte count (ALC) ($\times 10^6$/L)levels [WMD (*95%CI*): -1481.71 (-1978.78, -984.63), $p < 0.001$], while MIS-C patients had higher levels for absolute neutrophil count (ANC) ($\times 10^6$/L) [WMD (*95%CI*): 2678.74 (1673.14, 3684.35), $p < 0.001$], C-reactive protein (CRP) [SMD (*95%CI*): 1.38 (0.89, 1.86), $p < 0.001$] and D-dimer [SMD (*95%CI*): 1.56 (0.95, 2.18), $p < 0.001$]. Compared to severe COVID-19 patients, MIS-C patients had lower levels for lactate dehydrogenase (LDH) [SMD (*95%CI*): -0.91 (-1.60, -0.22), $p < 0.05$] and higher levels of erythrocyte sedimentation rate (ESR) (mm/hr) [WMD (*95%CI*): 37.87 (14.66, 61.09), $p < 0.01$], while same levels of ALC($\times 10^6$/L), ANC($\times 10^6$/L), CRP and D-dimer [WMD (*95%CI*): -39.29 (-655.52, 576.95), WMD (*95%CI*): -5708.41 (-17274.50, 5857.68), SMD (*95%CI*): 0.08 (-0.33, 0.50), SMD (*95%CI*): -0.25 (-0.82, 0.31), $p > 0.05$].

A moderate degree of heterogeneity was reported in four comparisons: ALC in MIS-C vs. COVID-19($p < 0.05$, $I^2 = 71.4\%$), ALC in MIS-C vs. non-severe COVID-19($p = 0.043$, $I^2 = 59.4\%$), ANC in MIS-C vs. severe COVID-19($p = 0.063$, $I^2 = 71.0\%$) and CRP in MIS-C vs. COVID-19($p < 0.05$, $I^2 = 69.5\%$). Rest of the comparisons showed no significant difference in statistical heterogeneity.

MIS-C vs. KD[13,14,21,22,24]

Compared to patients with KD, MIS-C patients had lower levels for ALC(× 10^9/L) [WMD (*95%CI*): -2.07 (-2.34, -1.79), $p < 0.001$] and PLT(× 10^9/L) [WMD (*95%CI*): -219.46 (-237.41, -201.51), $p < 0.001$], while higher levels were noted for CRP [SMD (*95%CI*): 0.57 (0.25, 0.90), $p < 0.01$] and ferritin(ng/mL) [WMD (*95%CI*): 647.00 (464.91, 829.09), $p < 0.001$] and the same level was noted for ESR(mm/hr) [WMD (*95%CI*): -21.33 (-61.91, 19.26), $p = 0.303$]. Only one comparison of CRP level showed a moderate degree of heterogeneity ($p = 0.069$, $I^2 = 51.2\%$). Rest of the comparisons showed no significant differences in statistical heterogeneity.

Severe MIS-C vs. non-severe MIS-C[21–23, 25,26]

Severe MIS-C patients had higher levels of WBC (× 10^9/L), CRP (mg/L), D-dimer (μg/mL) and ferritin (ng/mL) [WMD (*95%CI*): 5.41 (1.67, 9.14), 76.30 (49.29, 103.31), 2.46 (1.72, 3.20), 351.64 (118.62, 584.67), $p < 0.01$] compared to non-severe MIS-C patients. For levels of ALC (× 10^9/L), ANC (× 10^9/L), PLT (× 10^9/L), and fibrinogen (mg/dL) [WMD (*95%CI*): -0.32 (-0.65, 0.00), 4.21 (-1.05, 9.47), -17.38 (-38.76, 4.00), -0.01 (-1.59, 1.58), $p > 0.05$], there were no significant differences between both the groups. Two comparisons, ANC ($p = 0.065$, $I^2 = 70.7\%$) and fibrinogen ($p = 0.074$, $I^2 = 68.8\%$) levels showed moderate degree of heterogeneity. Rest of the comparisons showed no significant differences in statistical heterogeneity.

MIS-C with coronary artery abnormality vs. MIS-C without coronary artery abnormality[21,23,27]

There were no statistically significant differences in ALC (× 10^9/L) [WMD (*95%CI*): 0.15 (-0.19, 0.49), $p = 0.400$], PLT(× 10^9/L)[WMD (*95%CI*): -12.45 (-39.70, 14.81), $p = 0.371$], CRP(mg/L)[WMD (*95%CI*): -14.98 (-89.28, 59.31), $p = 0.145$], D-dimer (μg/mL) [WMD (*95%CI*): -0.99 (-2.75, 0.76), $p = 0.268$] and ferritin (ng/mL) [WMD (*95%CI*): 121.11 (-991.64, 1233.87), $p = 0.956$] levels among MIS-C patients with and without coronary artery abnormality. Two comparisons, CRP ($p = 0.147$, $I^2 = 52.3\%$) and ferritin ($p = 0.128$, $I^2 = 56.9\%$) levels, showed a moderate degree of heterogeneity. Rest of the comparisons showed no significant differences in statistical heterogeneity.

KD during SARS-CoV-2 epidemic vs. before SARS-CoV-2 epidemic[22,30–32]

Patients with KD during SARS-CoV-2 epidemic had lower levels of ALC (× 10^9/L) [WMD (*95%CI*): -2.59 (-2.82, -2.37), $p < 0.001$] and higher levels of CRP (mg/dL) [WMD (*95%CI*): 4.59 (2.33, 6.86), $p < 0.001$], compared to patients with KD before SARS-CoV-2 epidemic. There were no significant differences in statistical heterogeneity.

MIS-C in different age groups [younger age (0–5 years) vs. medium age (6–12 years) vs. older age(13–20 years)][28,29]

MIS-C patients in younger age group had lower levels of ferritin (ng/mL) [WMD (*95%CI*): -285.78 (-457.04, -114.53), $p < 0.01$] than those in medium age group.

MIS-C patients in younger age group had lower CRP(mg/L) [WMD(*95%CI*): -88.75 (-122.67, -54.84), $p < 0.001$] and mildly higher D-dimer (μg/mL)[WMD(*95%CI*): 1.49 (0.37, 2.61), $p < 0.01$] levels than those in older age, but had same levels of ESR (mm/hr) [WMD (*95%CI*): -7.79 (-16.38, 0.80), $p = 0.076$].

MIS-C patients in medium and older age groups had same levels of CRP (mg/L) [WMD (*95%CI*): -24.95 (-58.96, 9.06), $p = 0.150$] and ferritin (ng/mL) [WMD (*95%CI*): -91.69 (-413.85, 230.46), $p = 0.577$]. The comparison with

ferritin levels ($p = 0.148$, $I^2 = 52.2\%$) showed a moderate degree of heterogeneity.

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. Since the number of included studies in each comparison group was less than 10, we did not assess for publication bias.

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 hyper-inflammatory 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 vs. COVID-19, MIS-C vs. KD and different categories of MIS-C.

MIS-C, a consequence of an exacerbated immune system response or a maladaptive response, [33] is characterized by hyper-inflammation and cytokine storm, including massive release of inflammatory mediators and exaggerated activation of the immune system, which could be partly demonstrated by the laboratory inflammatory markers.[34] 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 lymphopenia, neutrophilia, 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.

Initial reports in the pandemic mainly indicated children to be ‘immune from’ or were only mildly or asymptomatic if affected by COVID-19. However, with the progression into the pandemic, studies on new hyper-inflammatory syndrome of MIS-C started to widely emerge.[1] These reports and series[35–39] came across from different parts of the world including USA, UK, Italy, France, etc. Previous studies[8,40,41] have shown MIS-C to share common features with KD. Common symptoms may include fever, rash, conjunctivitis, muco-cutaneous inflammation signs (oral, hands or feet), elevated markers of inflammation and coronary artery abnormality.[42] Our results confirmed that the elevated CRP and ferritin were greater in MIS-C, compared to KD. The phase reactant of ESR did not show a significant increase between MIS-C and KD. In addition, lymphocyte counts were significantly lower in MIS-C than KD, implying that lymphopenia is also a confirmatory characteristic of COVID-19. Although thrombocytosis was common in KD,[43] the PLT levels of MIS-C were lower than KD in our analysis. This difference may be due to the variation in potential immunopathogenesis. The pathogenesis of KD has been known to be mediated by immune complex which can activate the inflammatory cells and result in recruitment of platelets, leading to the thrombocytosis.[44] In contrast, for MIS-C with viral-associated hyperinflammatory syndromes, in the process of eradication of the virus, some mediators which mainly stimulate CD8 + cells to kill viral infected cells would suppress bone marrow function inadvertently, leading to the thrombocytopenia. So, the hypothesis[45] was

proposed that PLT may be able to help us differentiate between MIS-C and KD, which may be partially supported by our study findings.

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 managements 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 early phases before the disease transforms to severe state where critical care would be 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.

Due to the partially overlapped features with KD, the coronary artery abnormality could also occur in some MIS-C cases. Coronary artery abnormality, especially aneurysms, is a severe complication and can lead to thrombosis formation and ultimately myocardial infarction, if ruptured.[43] Therefore, it is important to detect the risk factors in earlier stages of MIS-C. However, based on our results, the role of inflammatory markers was not effective for early detection. The comparison of MIS-C patients with and without coronary artery abnormality did not show any differences in inflammatory markers, including ALC, PLT, CRP, D-dimer and ferritin. The lack of correlation between inflammatory markers and coronary artery abnormality may suggest that pathological changes in circulatory system may not be a direct consequence of severity of inflammation.

The markers of KD patients during SARS-CoV-2 epidemic appeared to differ from those before SARS-CoV-2 epidemic, with lower ALC levels and higher CRP levels. Lower ALC levels may indicate association with the current COVID-19 pandemic caused by SARS-CoV-2, as similar clinical features are shared by patients with COVID-19.[46] The higher CRP levels may be associated with the stronger inflammatory reaction of COVID-19. A recent study from Japan[47] suggested that coronavirus family might represent as one of the triggers of KD, eliciting a powerful immune response.

While comparing age groups of MIS-C, younger children (including infants and preschoolers) had lower CRP than older children (during puberty or post-puberty), and lower ferritin levels than medium-aged children (school-age), indicating less inflammatory response in younger 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.[48]

Our study should be considered in light of several limitations. First, some of the outcomes may have residual heterogeneity, although sensitivity analyses and subgroup analysis were conducted. Hence the results should be interpreted with caution. Second, the selected studies were mainly non-randomized controlled studies. Third, 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. The association of PCT and MIS-C warrants further research to confirm the findings. Furthermore, studies with larger sample size, longer follow-up duration and of randomized nature are strongly recommended based on the implications from 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 a priority during the COVID-19 pandemic.

Methods

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

Search strategy

Two authors (YZ and LY) 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 Oct 5, 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, PIMS-TS, Kawasaki-like disease, Kawasaki Disease, hyperinflammatory syndrome*. A manual search of references from selected studies was also conducted to keep the search inclusive.

Inclusion and exclusion criteria

The inclusion criteria were: 1) Patients diagnosed MIS-C by CDC or WHO, or PIMS-TS by RCPCH, or KD during SARS-CoV-2 epidemic; 2) Studies showing comparisons between one of the following: MIS-C vs. COVID-19, severe MIS-C vs. non-severe MIS-C, MIS-C with coronary artery abnormality vs. MIS-C without coronary artery abnormality, etc; 3) reported outcomes in form of inflammatory markers specific to WBC or leukocytes, ALC, ANC, PLT, CRP, PCT, ferritin, D-dimer, LDH, fibrinogen, ESR, etc. The exclusion criteria were1) review articles, guidelines, consensus of opinions, case reports, case series, basis researches, or other unrelated topics outside the scope of this review; 2) descriptive studies, studies without experimental/control group, not analytical study or experimental study.

Data extraction

We reported baseline characteristics and outcomes as available from the selected studies which included author information, country, 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.

Quality assessment

We used the Newcastle-Ottawa Scale (NOS)[49] to perform quality assessment on all observational studies (case-control and cohort). Based on the scoring system of 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 (YZ and LY) individually performed data extraction and quality assessment for each study. Discrepancies were resolved by consensus that included a third investigator (YH).

Statistical analysis

We calculated WMD, SMD and corresponding 95% confidence intervals (*95%CI*) 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* value less than 0.1 or I^2 greater than 50%, indicative of non-negligible heterogeneity, a REM was generated to combine the numerical values. On the contrary, 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 greater than 50%, sensitivity analysis and subgroup analysis were performed to probe the source of heterogeneity. For studies with I^2 greater than 75%, indicative of large heterogeneity, we did not use 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. On the contrary, if the results were inconsistent, the combined results were considered unreliable. For analyses of over ten studies, Begg's test and Egger's test were used to assess publication bias. STATA (Statacorp, College Station)[50] was used to perform all the statistical analyses.

Declarations

Author contributions:

YZ conceptualized the original idea, conducted literature search, screened studies, extracted data, assessed quality of studies, performed statistical analysis, conducted the interpretation of data and drafted the original manuscript. LY co-developed the study design, conducted literature search, screened studies, extracted data, drafted the original manuscript and made the decision to submit the paper for publication. JP critically reviewed and revised all sections of the manuscript and contributed in finalizing the manuscript. LT assessed quality of studies and performed statistical analysis. YH supervised the project, resolved disagreements and contributed in drafting the manuscript. All authors reviewed the manuscript.

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Conflict of Interest Declaration:

There was no financial or personal relationship with other people or organizations that could inappropriately influence this work.

Reprint:

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Tables

Table 1: Detailed characteristics of included studies

author	country	Study type	Age range	Study period	cases/controls	Number	Diagnosis method of MIS-C/PIMS-TS
Christina A. Rostad 2020[13]	USA	prospective	0-21y	March 17-May 26, 2020	MIS-C COVID-19 KD	10 10 5	CDC
Camila Rosat Consiglio 2020[14]	Rome, Italy, Sweden	\	0-19	March 17-May 15, 2020 Sep 2017-June 2019	MIS-C COVID-19 KD	13 41 28	WHO
Pereira MF B 2020[15]	Brazil	cross-sectional	0-18y	April 16-June 21, 2020	MIS-C COVID-19	6 60	CDC
Stuart P. Weisberg 2020[16]	USA	\	4-17y	March-June, 2020	MIS-C Severe COVID-19	15 14	CDC
Carl A. Pierce 2020[17]	USA	\	0-24y	13 March -17 May, 2020	MIS-C Severe COVID-19 Non-severe COVID-19	20 4 41	CDC
Caroline Diorio 2020[18]	USA	prospective	\	April 3-May 15, 2020	MIS-C severe COVID-19 non-severe COVID-19	6 9 5	CDC
Elizabeth M. Anderson 2020[19]	USA	\	\	April-May, 2020	MIS-C severe COVID-19 non-severe COVID-19	10 9 10	CDC
Olivia V Swann 2020[20]	UK	prospective	0-19y	17 Jan-17 July, 2020	MIS-C COVID-19	52 404	WHO
Whittaker E 2020[21]	UK	retrospective	3m-17y	March 23-May 22, 2020	PIMS-TS KD KDSS	58 1132 45	CDC/WHO/RCPCH

Marie Pouletty 2020[22]	France	retrospective	\	April, 2020-	PIMS-TS severe PIMS-TS non-severe KD	7 9 220	Kawa-COVID-19
Patrick Davies 2020[23]	UK	retrospective	0-18y	April 1-May 10, 2020	PIMS-TS with coronary artery abnormality PIMS-TS without coronary artery abnormality severe PIMS-TS non-severe PIMS-TS	28 50 36 42	RCPCH
Rosa Pino 2020[24]	Spain	prospective	\	March 23-May 14, 2020	KD with SARS-COV-2 KD without SARS-COV-2	6 6	Kawa-COVID-19
Juan P. Torres 2020[25]	Chile	ambispective	0-14y	May 1-June 24, 2020	ICU at admission Ward unit at admission ICU in hospitalization Ward unit in hospitalization	16 11 16 11	CDC
Pui Y. Lee 2020[26]	USA	retrospective	1m-17y	March 17-June 6, 2020	Severe MIS-C Non-severe MIS-C	17 9	CDC/WHO
Simone Jhaveri 2020[27]	USA	retrospective	3-20y	April 24-May 16,2020	MIS-C with coronary artery abnormality MIS-C without coronary artery abnormality	4 8	CDC
Elizabeth M. Dufort 2020[28]	USA	retrospective	0-20y	March 1-May 10, 2020	0-5 years 6-12 years 13-20 years	31 42 26	CDC

L.R. Feldstein 2020[29]	USA	ambispective	3.3-12.5y	March 15-May 20, 2020	0-4 years 5-12 years 13-20 years	66 75 45	CDC
Lucio Verdoni 2020[30]	Italy	retrospective	\	Feb 18-April 20, 2020	after SARS-CoV-2 epidemic before SARS-CoV-2 epidemic	10 19	Kawasaki-like disease
Naim Ouldali 2020[31]	France Italy	retrospective	1m-15.5y	Dec, 2005-May, 2020	KD with SARS-CoV-2 epidemic in France KD with SARS-CoV-2 epidemic in Italy KD without SARS-CoV-2 epidemic	10 10 214	KD related to SARS-CoV-2
Kazuki Iio 2020[32]	Japan	retrospective	\	Dec 1, 2019-May 31, 2020	after SARS-CoV-2 epidemic before SARS-CoV-2 epidemic	14 30	KD or Kawasaki-like disease

Table 2: Results of meta-analysis

Case/control	EM	WMD/SMD(95%*CI*)	*p*	heterogeneity		
				p	I^2 (%)	
MIS-C versus COVID-19						
WBC (×10^9/L)	FEM	0.14 (-0.91, 1.18)	0.799	0.134	38.6	WMD
PLT(×10^9/L)	FEM	-102.48 (-122.74, -82.22)	<0.001	0.538	0.0	WMD
PCT	FEM	0.05(-0.55, 0.66)	0.864	0.916	0.0	SMD
Ferritin	FEM	0.27(-0.10, 0.65)	0.157	0.919	0.0	SMD
lymphocyte count(×10^6/L)	REM	-997.94 (-1556.19, -439.68)	<0.001	<0.050	71.4	WMD
Non-severe COVID-19	REM	-1481.71 (-1978.78, -984.63)	<0.001	0.043	59.4	
Severe COVID-19	REM	-39.29 (-655.52, 576.95)	0.910	0.814	0.0	
neutrophil count(×10^6/L)		NA				WMD
Non-severe COVID-19	REM	2678.74 (1673.14, 3684.35)	<0.001	0.468	0.0	
Severe COVID-19	REM	-5708.41 (-17274.50, 5857.68)	0.333	0.063	71.0	
CRP	REM	0.76 (0.27, 1.25)	<0.050	<0.050	69.5	SMD
Non-severe COVID-19	REM	1.38 (0.89, 1.86)	<0.001	0.113	46.4	
Severe COVID-19	REM	0.08 (-0.33, 0.50)	0.691	0.999	0.0	
D-dimer		NA				SMD
Non-severe COVID-19	REM	1.56 (0.95, 2.18)	<0.001	0.218	34.3	
Severe COVID-19	REM	-0.25 (-0.82, 0.31)	0.379	0.228	30.7	
LDH		NA				SMD
Non-severe COVID-19		NA				
Severe COVID-19	REM	-0.91 (-1.60, -0.22)	<0.050	0.260	25.8	
ESR (mm/hr)		NA				WMD
Non-severe COVID-19	FEM	-3.57 (-32.82, 25.67)	0.881	0.678	0.0	
Severe COVID-19	FEM	37.87 (14.66, 61.09)	<0.010	0.763	0.0	
MIS-C versus Kawasaki Disease						
lymphocyte count(×10^9/L)	FEM	-2.07 (-2.34, -1.79)	<0.001	0.849	0.0	WMD
PLT(×10^9/L)	FEM	-219.46 (-237.41, -201.51)	<0.001	0.605	0.0	WMD
CRP	REM	0.57 (0.25, 0.90)	<0.010	0.069	51.2	SMD
Ferritin (ng/mL)	FEM	647.00 (464.91, 829.09)	<0.001	0.274	22.9	WMD
ESR (mm/hr)	FEM	-21.33 (-61.91, 19.26)	0.303	0.466	0.0	WMD

Severe MIS-C versus non-severe MIS-C						
WBC (×10^9/L)	FEM	5.41 (1.67, 9.14)	<0.010	0.532	0.0	WMD
lymphocyte count(×10^9/L)	FEM	-0.32 (-0.65, 0.00)	0.052	0.350	8.6	WMD
neutrophil count(×10^9/L)	REM	4.21 (-1.05, 9.47)	0.117	0.065	70.7	WMD
PLT(×10^9/L)	FEM	-17.38 (-38.76, 4.00)	0.111	0.221	28.5	WMD
CRP(mg/L)	FEM	76.30 (49.29, 103.31)	<0.001	0.252	24.3	WMD
Fibrinogen (mg/dL)	REM	-0.01 (-1.59, 1.58)	0.991	0.074	68.8	WMD
D-dimer (μg/mL)	FEM	2.46 (1.72, 3.20)	<0.001	0.161	39.1	WMD
Ferritin (ng/mL)	FEM	351.64 (118.62, 584.67)	<0.010	0.573	0.0	WMD
MIS-C with coronary artery abnormality versus MIS-C without coronary artery abnormality						
lymphocyte count(×10^9/L)	FEM	0.15 (-0.19, 0.49)	0.400	0.477	0.0	WMD
PLT(×10^9/L)	FEM	-12.45 (-39.70, 14.81)	0.371	0.237	28.4	WMD
CRP(mg/L)	REM	-14.98 (-89.28, 59.31)	0.145	0.147	52.3	WMD
D-dimer (μg/mL)	FEM	-0.99 (-2.75, 0.76)	0.268	0.522	0.0	WMD
Ferritin (ng/mL)	REM	121.11 (-991.64, 1233.87)	0.956	0.128	56.9	WMD
KD during the SARS-CoV-2 epidemic versus before the SARS-CoV-2 epidemic						
lymphocyte count(×10^9/L)	FEM	-2.59 (-2.82, -2.37)	<0.001	0.174	39.6	WMD
CRP(mg/dL)	FEM	4.59 (2.33, 6.86)	<0.001	0.185	35.5	WMD
Age period						
younger vs. medium age						
Ferritin (ng/mL)	FEM	-285.78 (-457.04, -114.53)	<0.010	0.652	0.0	WMD
younger vs. older age						
CRP(mg/L)	FEM	-88.75 (-122.67, -54.84)	<0.001	0.567	0.0	WMD
D-dimer (μg/mL)	FEM	1.49 (0.37, 2.61)	<0.010	0.267	18.9	WMD
ESR (mm/hr)	FEM	-7.79 (-16.38, 0.80)	0.076	0.261	20.8	WMD
medium vs. older age						
CRP(mg/L)	FEM	-24.95 (-58.96, 9.06)	0.150	0.214	35.2	WMD
Ferritin (ng/mL)	REM	-91.69 (-413.85, 230.46)	0.577	0.148	52.2	WMD

Figures

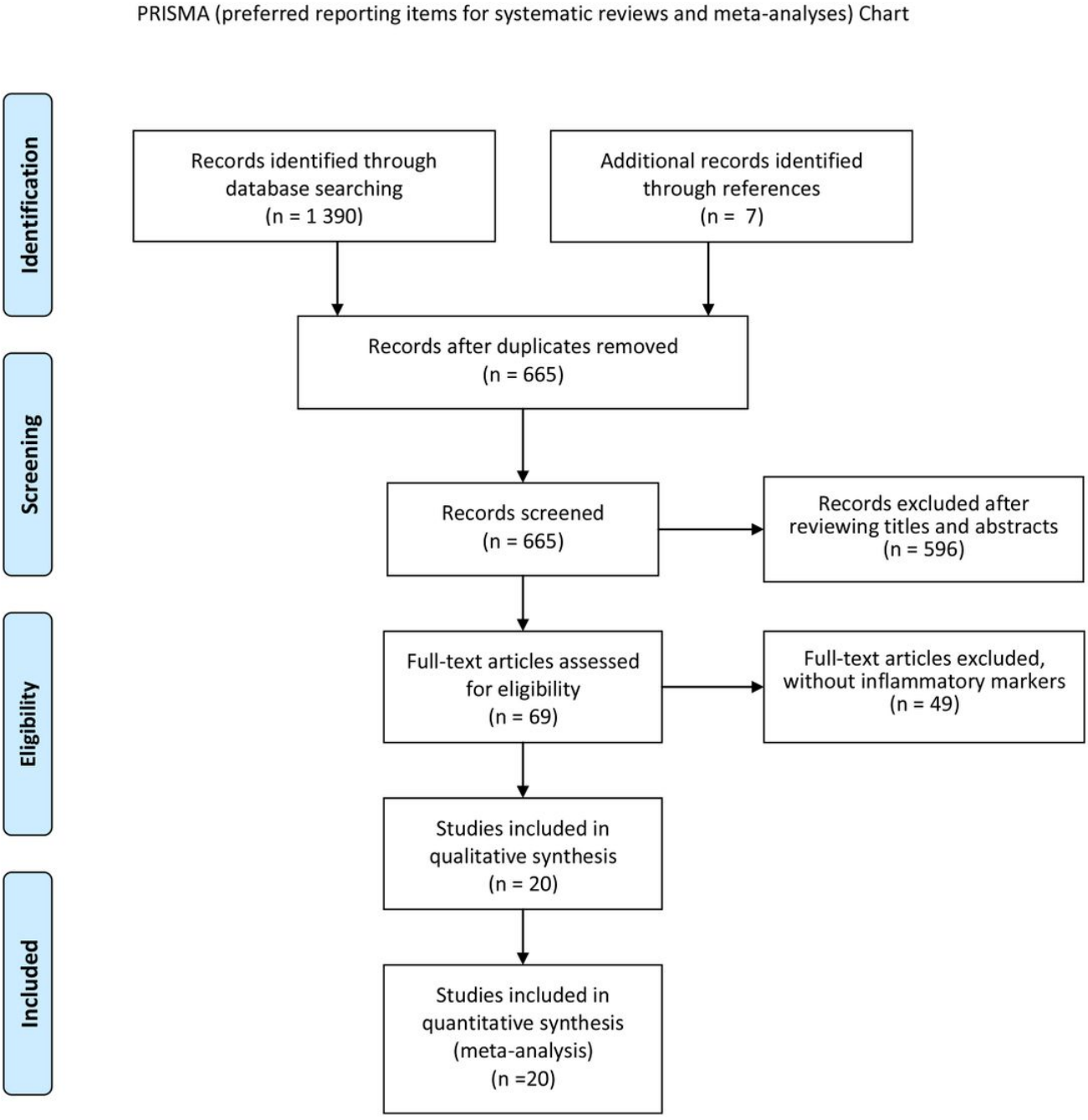

Figure 1

Literature search and filtering of studies.

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