Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

American Journal of Emergency Medicine 49 (2021) 62–70

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

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

Yan Zhao [a], Jenil Patel [b], Ying Huang [c], Lijuan Yin [c,*], Lei Tang [a,**]

[a] Department of Pediatrics, People's Hospital of Chongqing Banan District, Chongqing 401320, China
[b] Department of Epidemiology, Human Genetics and Environmental Sciences, The University of Texas Health Science Center at Houston (UTHealth) School of Public Health, Dallas, TX, USA
[c] Department of Respiratory Medicine, Children's Hospital of Chongqing Medical University, National Clinical Research Center for Child Health and Disorders, Ministry of Education Key Laboratory of Child Development and Disorders, China International Science and Technology Cooperation Base of Child Development and Critical Disorders, Chongqing Key Laboratory of Pediatrics, Chongqing 400014, China

ARTICLE INFO

Article history:
Received 16 February 2021
Received in revised form 7 May 2021
Accepted 14 May 2021

Keywords:
COVID-19
PMIS/PIMS-TS/MIS-C
BNP
Troponin
Children
Meta-analysis

ABSTRACT

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.

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

Abbreviations: ACE2, angiotensin-converting enzyme 2; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; COVID-19, coronavirus disease 2019; CAA, coronary artery abnormality; FEM, fixed effects model; ICU, intensive care units; MIS-C, multisystem inflammatory syndrome in children; NT-proBNP, N-terminal pro-BNP; REM, random effects model; SMD, standard mean differences; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; 95%CI, 95% confidence intervals.

* Correspondence to: L Yin, Department of Respiratory Medicine, Children's Hospital of Chongqing Medical University, Chongqing 400014, China.
** Correspondence to: L Tang, Department of Pediatrics, People's Hospital of Chongqing Banan District, Chongqing 401320, China.
E-mail addresses: zhaoyanwow@126.com (Y. Zhao), yudishengyin4356@sina.com (L. Yin), tangleicqums@163.com (L. Tang).

https://doi.org/10.1016/j.ajem.2021.05.044
0735-6757/

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 I^2 statistic. An I^2 value less than 50% indicated no presence of statistical heterogeneity, and a fixed effects model (FEM) was used in these cases. When the I^2 value was greater than 50%, statistical heterogeneity was present, and a random effects model (REM) was used. I^2 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.

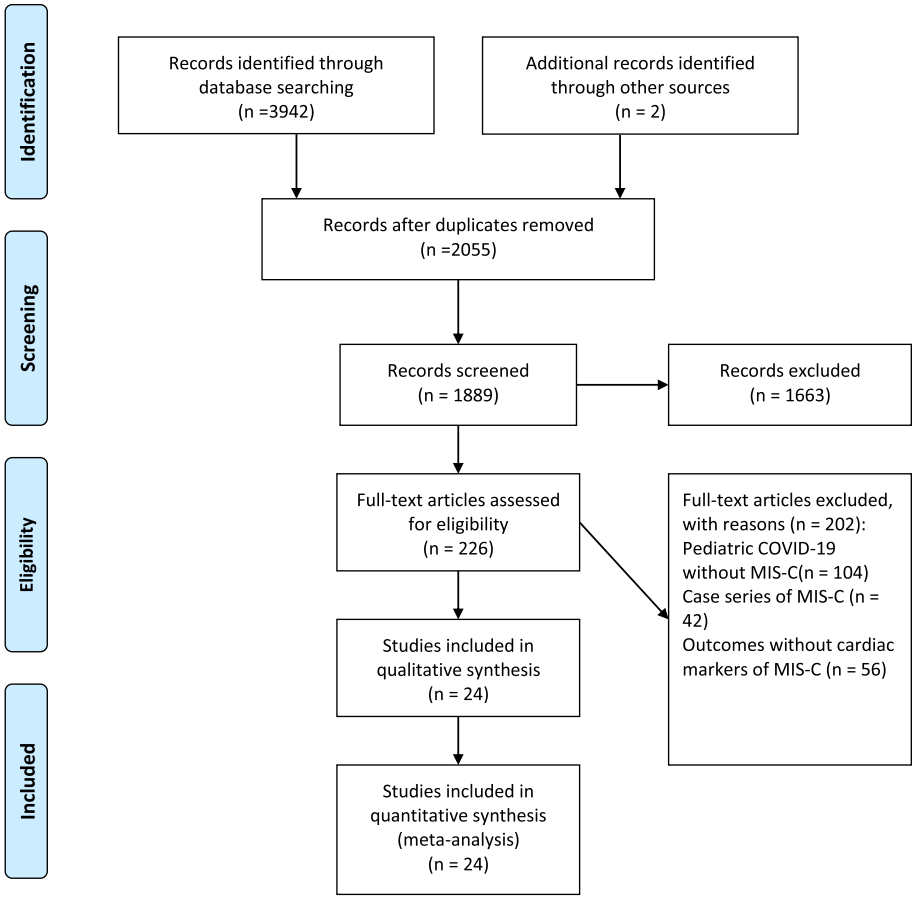

Fig. 1. Flow diagram.

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.

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.

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.

3.2.3. 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

Table 1
Detailed characteristics of the included studies

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[a]	9	
					Non-severe COVID-19[a]	5	
Anderson EM 2020	USA	\	\	April–May 2020	MIS-C	10	7
					Severe COVID-19[a]	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[a]	4	
					Non-severe pediatric COVID-19[a]	41	
					Severe adult COVID-19[a]	27	
					Non-severe adult COVID-19[a]	33	
Prata-Barbosa A 2020	Brazil	Prospective	1 m-19y	March 1–May 31, 2020	MIS-C	10	8
					COVID-19	69	
Weisberg SP 2020	USA	\	4-17y	March–June 2020	MIS-C	15	6
					Severe COVID-19	14	
Weisberg SP 2021	USA	\	3-18y	March–June 2020	MIS-C	16	6
					Severe COVID-19	13	
Consiglio CR 2020	Rome/Italy/Sweden	\	0–19	March 17–May 15, 2020	MIS-C	13	6
				Sep 2017-June 2019	COVID-19	41	
Swann OV 2020	UK	Prospective	0-19y	Jan 17-July 17, 2020	MIS-C	52	8
					COVID-19	404	
Corwin DJ 2020	USA	Retrospective	0-21y	March 1–May 15, 2020	Severe MIS-C	5	8
					Moderate MIS-C "2020 KD"	8	
					Mild MIS-C	20	
Lee PY 2020	USA	Retrospective	1 m-17y	March 17–June 6, 2020	Severe MIS-C[b]	17	7
					Non-severe MIS-C[b]	9	
Pouletty M 2020	France	Retrospective	\	April 2020-	Severe MIS-C[b]	7	7
					Non-severe MIS-C[b]	9	
Jain S 2020	India	\	\	May 1–July 15, 2020	Severe MIS-C[b]	15	7
					Non-severe MIS-C[b]	8	
Davies P 2020	UK	Retrospective	0-18y	April 1–May 10, 2020	MIS-C with CAA	28	7
					MIS-C without CAA	50	
					Severe MIS-C[b]	36	
					Non-severe MIS-C[b]	42	
Whittaker E 2020	UK	Retrospective	3 m-17y	March 23–May 22, 2020	Severe MIS-C[b]	29	7
					Non-severe MIS-C[b]	29	
					MIS-C with CAA	8	
					MIS-C without CAA	50	
Jhaveri S 2020	USA	Retrospective	3-20y	April 24–May 16, 2020	MIS-C with CAA	4	8
					MIS-C without CAA	8	
Reiff DD 2021	USA	Retrospective	0-22y	April 1–September 1, 2020	MIS-C	21	7
					Severe COVID-19[a]	8	
					Non-severe COVID-19[a]	8	
Diorio C 2020	USA	Prospective	\	April 3–July 7, 2020	MIS-C	18	9
					Severe COVID-19[a]	11	
					Non-severe COVID-19[a]	21	
Rekhtman S 2020	USA	Prospective	0-18y	May 11–June 5, 2020	MIS-C	19	8
					COVID-19	12	
Ozsurekci Y 2021	Turkey	Retrospective	0-18y	March 26–November 3, 2020	MIS-C	30	7
					Severe COVID-19[a]	13	
Abrams JY 2021	USA	Retrospective	0-22y	March 11-Oct 10, 2020	Severe MIS-C[b]	648	7
					Non-severe MIS-C[b]	432	
Abdel-Haq N 2021	USA	\	3 m-17y	April 1–June 5, 2020	Severe MIS-C[b]	22	7
					Non-severe MIS-C[b]	11	
Vella LA 2021	USA	\	0-18y	April–June 2020	MIS-C	14	7
					COVID-19	16	
Girona-Alarcon M 2021	Spain	Prospective	\	March–June 2020	MIS-C	4	8
					Severe COVID-19[a]	16	

Notes: MIS-C, multisystem inflammatory syndrome in children; COVID-19, coronavirus disease 2019; CAA: coronary artery abnormality.
[a] 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.
[b] Severe MIS-C: MIS-C with shock, requiring ventilation or admission to the ICU, or with a fatal outcome.

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 2
The results of the meta-analysis

Case/control	SMD (95% *CI*)	*p*	Heterogeneity	
			p	I^2 (%)
MIS-C vs. COVID-19				
MIS-C vs. COVID-19 (BNP)	0.49 (0.17, 0.80)	0.002	0.196	27.9
MIS-C vs. non-severe COVID-19	1.13 (0.48, 1.77)	0.001	0.433	0.00
MIS-C vs. severe COVID-19	0.29 (−0.07, 0.65)	0.117	0.490	0.00
MIS-C vs. COVID-19 (Troponin)	0.13 (−0.07, 0.32)	0.212	0.883	0.00
MIS-C vs. non-severe COVID-19	0.24 (−0.06, 0.53)	0.118	0.301	16.4
MIS-C vs. severe COVID-19	0.04 (−0.23, 0.30)	0.782	1.000	0.00
MIS-C vs. COVID-19 (AST)	0.10 (−0.11, 0.31)	0.336	0.075	47.7
Severe MIS-C vs. non-severe MIS-C				
BNP	0.26 (0.04, 0.48)[a]	0.021	0.018	58.6
Troponin	0.05 (−0.06, 0.16)	0.387	0.591	0.00
AST	0.19 (−0.34, 0.71)	0.483	0.505	0.00
MIS-C with CAA vs. MIS-C without CAA				
BNP	−0.21 (−1.07, 0.64)	0.624	0.620	0.00
Troponin	−0.07 (−0.45, 0.31)	0.710	0.709	0.00

Notes: MIS-C, multisystem inflammatory syndrome in children; COVID-19, CORONAVIRUS DISEASE 2019; CAA: coronary artery abnormality; SMD: standard mean difference; BNP, brain natriuretic peptide; AST, aspartate aminotransferase.
[a] REM was used because of moderate heterogeneity (I^2 50–75%).

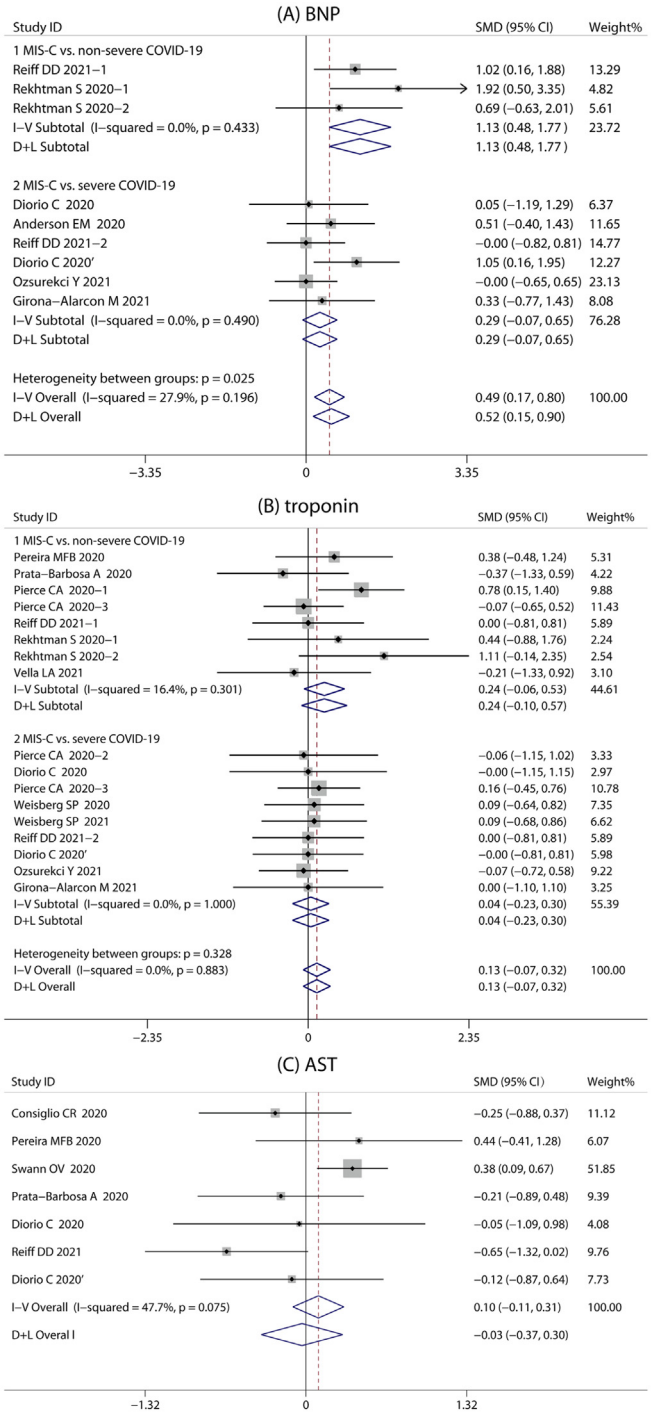

Fig. 2. Comparisons of MIS-C and COVID-19: (A) BNP; (B) troponin; (C) AST. The MIS-C patients showed higher BNP levels than patients with non-severe COVID-19, but the BNP levels were not significantly different between patients with MIS-C and severe COVID-19. There were no significant differences observed in the levels of troponin or AST between MIS-C patients and COVID-19 patients. AST: aspartate aminotransferase; BNP: B-type natriuretic peptide; COVID-19, coronavirus disease 2019; MIS-C, multisystem inflammatory syndrome in children.

that the BNP levels of MIS-C patients were higher than patients 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 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. [5] 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

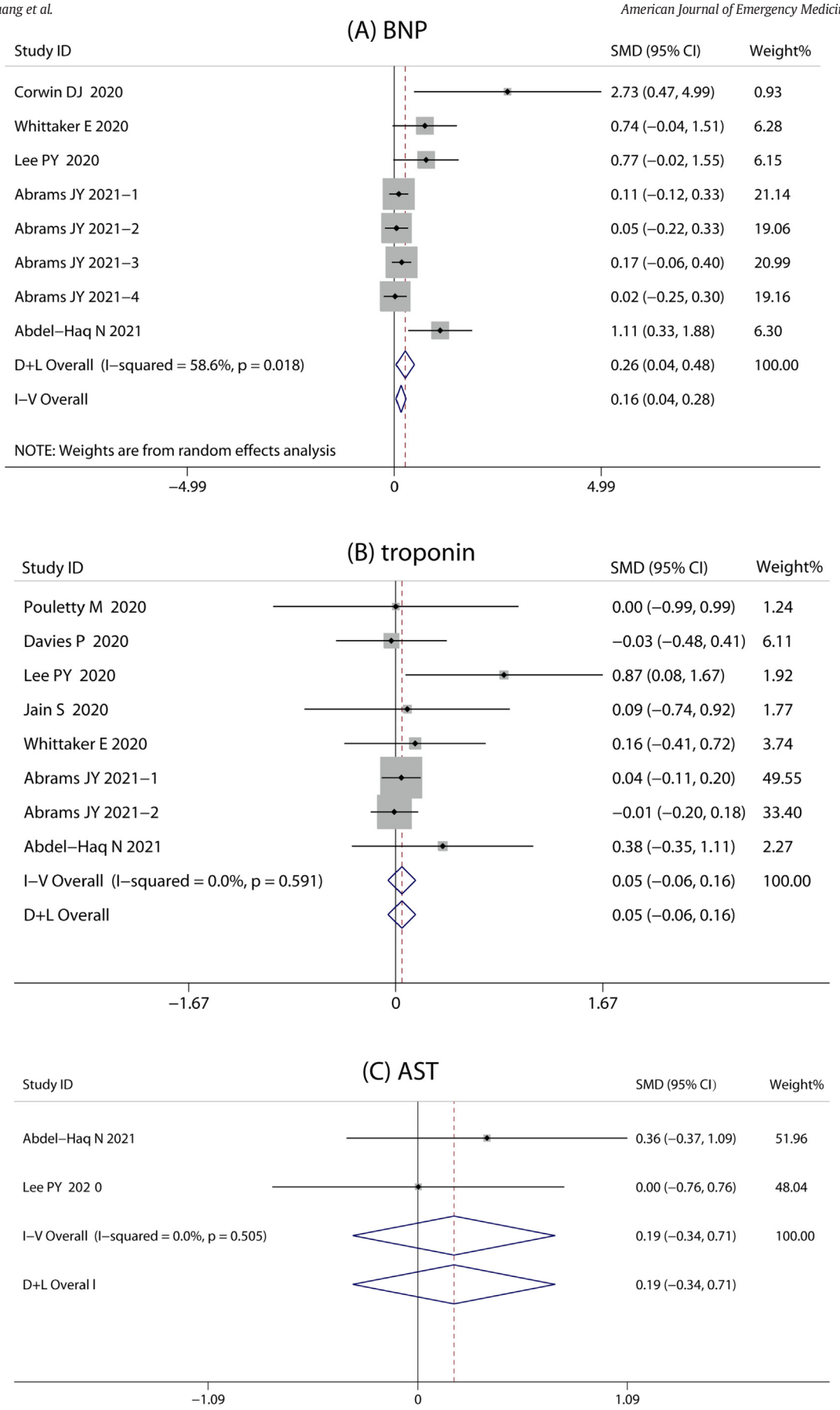

Fig. 3. Comparisons of severe and non-severe MIS-C: (A) BNP; (B) troponin; (C) AST. Patients with severe MIS-C exhibited higher levels of BNP than patients with non-severe MIS-C, but no differences were observed in troponin or AST levels. AST: aspartate aminotransferase; BNP: B-type natriuretic peptide; MIS-C, multisystem inflammatory syndrome in children.

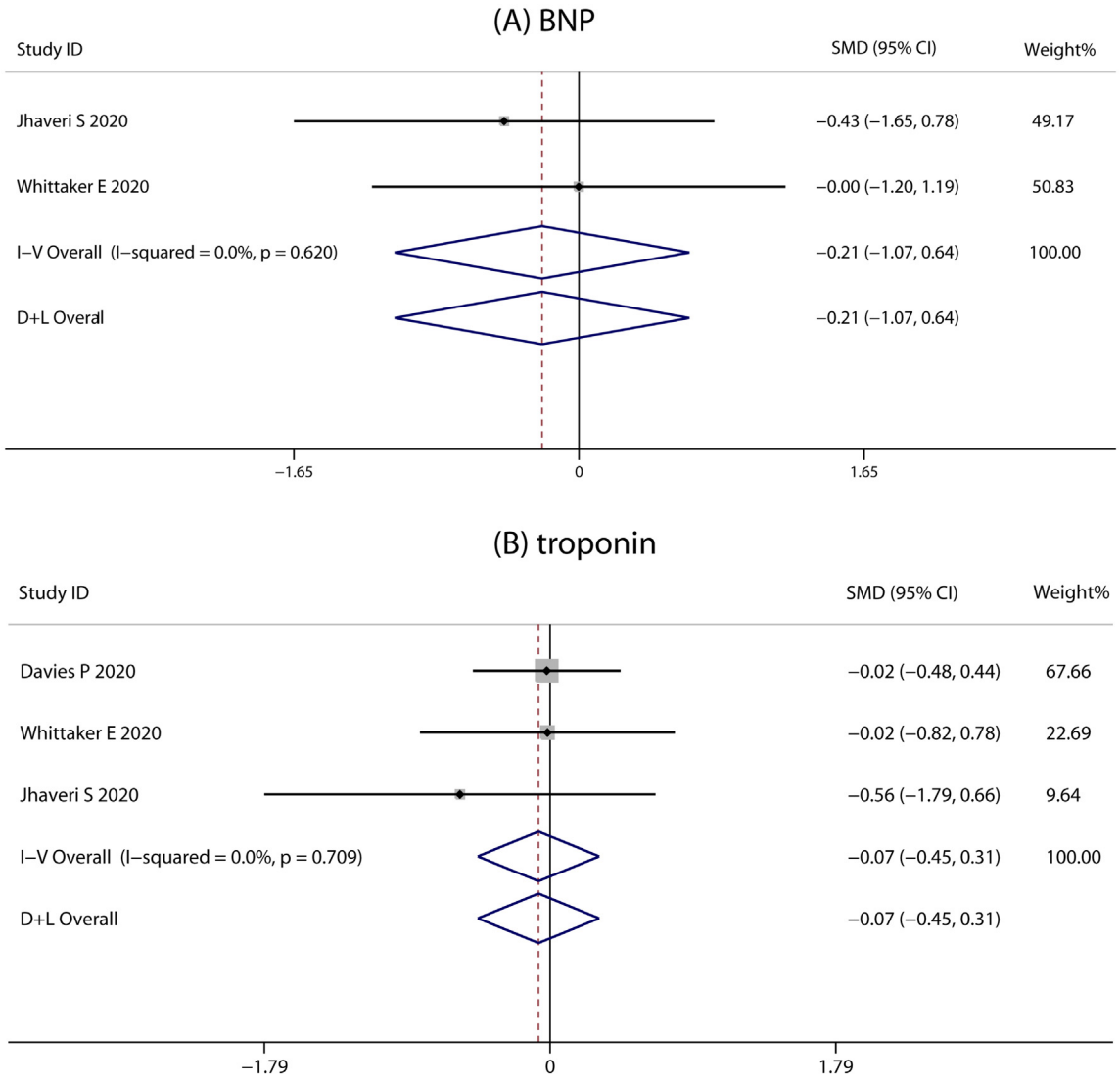

Fig. 4. Comparisons of MIS-C with CAA vs. MIS-C without CAA: (A) BNP; (B) troponin. There were no significant differences observed. BNP: B-type natriuretic peptide; CAA: coronary artery abnormality; MIS-C, multisystem inflammatory syndrome in children.

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.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations of interest

None.

Author contributions

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

Data availability statement

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

Acknowledgments

The authors thank Dr. Hongfen Yuan and Dr. Linwei Li for their scientific suggestions. We thank all of the participants in this study.

References

[1] Yasuhara J, Kuno T, Takagi H, Sumitomo N. Clinical characteristics of COVID-19 in children: a systematic review. Pediatr Pulmonol. 2020;55(10):2565–75. https://doi.org/10.1002/ppul.24991.
[2] Toubiana J, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoulvant F, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. BMJ (Clin Res Ed). 2020;369. https://doi.org/10.1136/bmj.m2094 m2094.
[3] Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020;395(10237):1607–8. https://doi.org/10.1016/S0140-6736(20)31094-1.
[4] Tam H, El Tal T, Go E, Yeung RSM. Pediatric inflammatory multisystem syndrome temporally associated with COVID-19: a spectrum of diseases with many names. CMAJ. 2020;192(38) E1093-E6. doi: 10.503/cmaj.201600. [Epub 2020 Sep 9].
[5] Lang JP, Wang X, Moura FA, Siddiqi AHK, Morrow DA, Bohula EA. A current review of COVID-19 for the cardiovascular specialist. Am Heart J. 2020;226:29–44. https://doi.org/10.1016/j.ahj.2020.04.025.
[6] Sperotto F, Friedman KG, Son MBF, VanderPluym CJ, Newburger JW, Dionne A. Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: a comprehensive review and proposed clinical approach. Eur J Pediatr. 2020. https://doi.org/10.1007/s00431-020-03766-6.
[7] Mair J, Jaffe A, Apple F, Lindahl B. Cardiac biomarkers. Dis Markers. 2015;2015 (370569). https://doi.org/10.1155/2015/370569 [Epub 2015 Apr 19].
[8] Zheng X, Zhang Y, Liu L, Yue P, Wang C, Zhou K, et al. N-terminal pro-brain natriuretic peptide as a biomarker for predicting coronary artery lesion of Kawasaki disease. Sci Rep. 2020;10(1):5130. https://doi.org/10.1038/s41598-020-62043-6.
[9] Atallah B, Mallah SI, AbdelWareth L, AlMahmeed W, Fonarow GC. A marker of systemic inflammation or direct cardiac injury: should cardiac troponin levels be monitored in COVID-19 patients? Eur Heart J Qual Care Clin Outcome. 2020;6(3):204–7. https://doi.org/10.1093/ehjqcco/qcaa033.
[10] Fitzgerald G, Kerley RN, Kiernan TJ. High-sensitivity troponin assays: development and utility in a modern health-care system. Expert Rev Cardiovasc Ther. 2019;17(10):763–70. https://doi.org/10.1080/14779072.2019.1675514 [Epub 2019 Oct 9].
[11] Gao L, Jiang D, Wen XS, Cheng XC, Sun M, He B, et al. Prognostic value of NT-proBNP in patients with severe COVID-19. Respir Res. 2020;21(1):83. https://doi.org/10.1186/s12931-020-01352-w.
[12] Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020;5(7):811–8. https://doi.org/10.1001/jamacardio.2020.1017.
[13] Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Accessed Oct 1 http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp; 2020.
[14] Diorio C, Henrickson SE, Vella LA, McNerney KO, Chase J, Burudpakdee C, et al. Multisystem inflammatory syndrome in children and COVID-19 are distinct presentations of SARS–CoV-2. J Clin Investig. 2020;130(11):5967–75. https://doi.org/10.1172/JCI140970.
[15] Anderson EM, Diorio C, Goodwin EC, McNerney KO, Weirick ME, Gouma S, et al. SARS-CoV-2 antibody responses in children with MIS-C and mild and severe COVID-19. medRxiv. 2020. https://doi.org/10.1101/2020.08.17.20176552.
[16] Corwin DJ, Sartori LF, Chiotos K, Odom John AR, Cohn K, Bassiri H, et al. Distinguishing multisystem inflammatory syndrome in children from Kawasaki disease and benign inflammatory illnesses in the SARS-CoV-2 pandemic. Pediatr Emerg Care. 2020;36(11):554–8. https://doi.org/10.1097/PEC.0000000000002248.
[17] Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA. 2020;324(3):259–69. https://doi.org/10.1001/jama.2020.10369.
[18] Lee PY, Day-Lewis M, Henderson LA, Friedman KG, Lo J, Roberts JE, et al. Distinct clinical and immunological features of SARS–CoV-2–induced multisystem inflammatory syndrome in children. J Clin Investig. 2020;130(11):5942–50. https://doi.org/10.1172/JCI141113.
[19] Jhaveri S, Ahluwalia N, Kaushik S, Trachtman R, Kowalsky S, Aydin S, et al. Longitudinal echocardiographic assessment of coronary arteries and left ventricular function following multisystem inflammatory syndrome in children. J Pediatr. 2020. https://doi.org/10.1016/j.jpeds.2020.08.002.
[20] Badue Pereira MF, Litvinov N, Lima Farhat SC, Eisencraft AP, Bento Cicaroni Gibelli MA, de Carvalho WB, et al. Severe clinical spectrum with high mortality in pediatric patients with COVID-19 and multisystem inflammatory syndrome. Clinics. 2020;75. https://doi.org/10.6061/clinics/2020/e2209.
[21] Prata-Barbosa A, Lima-Setta F, Santos GRD, Lanziotti VS, de Castro REV, de Souza DC, et al. Pediatric patients with COVID-19 admitted to intensive care units in Brazil: a prospective multicenter study. J Pediatr (Rio J). 2020;96(5):582–92. https://doi.org/10.1016/j.jped.2020.07.002.
[22] Pierce CA, Preston-Hurlburt P, Dai Y, Aschner CB, Cheshenko N, Galen B, et al. Immune responses to SARS-CoV-2 infection in hospitalized pediatric and adult patients. Sci Transl Med. 2020;12(564). https://doi.org/10.1126/scitranslmed.abe8120.
[23] Weisberg SP, Connors T, Zhu Y, Baldwin M, Lin WH, Wontakal S, et al. Antibody responses to SARS-CoV2 are distinct in children with MIS-C compared to adults with COVID-19. medRxiv. 2020. https://doi.org/10.1101/2020.07.12.20151068.
[24] Weisberg SP, Connors TJ, Zhu Y, Baldwin MR, Lin W-H, Wontakal S, et al. Distinct antibody responses to SARS-CoV-2 in children and adults across the COVID-19 clinical spectrum. Nat Immunol. 2020. https://doi.org/10.1038/s41590-020-00826-9.
[25] Pouletty M, Borocco C, Ouldali N, Caseris M, Basmaci R, Lachaume N, et al. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort. Ann Rheum Dis. 2020;79(8):999–1006. https://doi.org/10.1136/annrheumdis-2020-217960.
[26] Davies P, Evans C, Kanthimathinathan HK, Lillie J, Brierley J, Waters G, et al. Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: a multicentre observational study. Lancet Child Adolesc Health. 2020;4(9):669–77http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=32653054.
[27] Jain S, Sen S, Lakshmivenkateshiah S, Bobhate P, Venkatesh S, Udani S, et al. Multisystem inflammatory syndrome in children with COVID-19 in Mumbai. India Indian pediatr. 2020;57(11):1015–9https://www.embase.com/search/results?subaction=viewrecord&id=L632600472&from=export. doi: 10.07/s13312-020-2026-0. Epub 2020 Aug 11.
[28] Consiglio CR, Cotugno N, Sardh F, Pou C, Amodio D, Rodriguez L, et al. The immunology of multisystem inflammatory syndrome in children with COVID-19. Cell. 2020. https://doi.org/10.1016/j.cell.2020.09.016.
[29] Swann OV, Holden KA, Turtle L, Pollock L, Fairfield CJ, Drake TM, et al. Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: prospective multicentre observational cohort study. BMJ. 2020;370. https://doi.org/10.1136/bmj.m3249.
[30] Reiff DD, Mannion ML, Samuy N, Scalici P, Cron RQ. Distinguishing active pediatric COVID-19 pneumonia from MIS-C. Rheumatol Int. 2021;41(2):329–34. https://doi.org/10.1007/s00296-020-4728-9 [Epub 2020 Oct 18].
[31] Diorio C, McNerney KO, Lambert M, Paessler M, Anderson EM, Henrickson SE, et al. Evidence of thrombotic microangiopathy in children with SARS-CoV-2 across the spectrum of clinical presentations. Blood Adv. 2020;4(23):6051–63. https://doi.org/10.1182/bloodadvances.2020003471.
[32] Rekhtman S, Tannenbaum R, Strunk A, Birabaharan M, Wright S, Garg A. Mucocutaneous disease and related clinical characteristics in hospitalized children and adolescents with COVID-19 and multisystem inflammatory syndrome in children. J Am Acad Dermatol. 2021;84(2):408–14. https://doi.org/10.1016/j.jaad.2020.10.060.
[33] Ozsurekci Y, Gürlevik S, Kesici S, Akca UK, Oygar PD, Aykac K, et al. Multisystem inflammatory syndrome in children during the COVID-19 pandemic in Turkey: first report from the eastern Mediterranean. Clin Rheumatol. 2021:1–11. https://doi.org/10.1007/s10067-021-05631-9.
[34] Abrams JY, Oster ME, Godfred-Cato SE, Bryant B, Datta SD, Campbell AP, et al. Factors linked to severe outcomes in multisystem inflammatory syndrome in children (MIS-C) in the USA: a retrospective surveillance study. Lancet Child Adolesc Health. 2021;5(5):323–31. https://doi.org/10.1016/S2352-4642(21)00050-X.
[35] Abdel-Haq N, Asmar BI, Deza Leon MP, McGrath EJ, Arora HS, Cashen K, et al. SARS-CoV-2-associated multisystem inflammatory syndrome in children: clinical manifestations and the role of infliximab treatment. Eur J Pediatr. 2021;180(5):1581–91.
[36] Vella LA, Giles JR, Baxter AE, Oldridge DA, Diorio C, Kuri-Cervantes L, et al. Deep immune profiling of MIS-C demonstrates marked but transient immune activation compared to adult and pediatric COVID-19. Science Immunol. 2021;6(57). https://doi.org/10.1126/sciimmunol.abf7570.
[37] Girona-Alarcon M, Bobillo-Perez S, Sole-Ribalta A, Hernandez L, Guitart C, Suarez R, et al. The different manifestations of COVID-19 in adults and children: a cohort study

in an intensive care unit. BMC Infect Dis. 2021;21(1). https://doi.org/10.1186/s12879-021-05786-5.

[38] Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review. JAMA Cardiol. 2020;5(7):831–40. https://doi.org/10.1001/jamacardio.2020.1286.

[39] Del Greco G, Brady K, Clark B, Park H. A novel pediatric multisystem inflammatory syndrome during the covid-19 pandemic. Pediatr Emerg Care. 2020;36(10):500–4. https://doi.org/10.1097/PEC.0000000000002229.

[40] Kone-Paut I, Cimaz R. Is it Kawasaki shock syndrome, Kawasaki-like disease or pediatric inflammatory multisystem disease? The importance of semantic in the era of COVID-19 pandemic. RMD Open. 2020;6(2):06http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medc&AN=32611651.

[41] Baggish A, Drezner JA, Kim J, Martinez M, Prutkin JM. Resurgence of sport in the wake of COVID-19: cardiac considerations in competitive athletes. Br J Sports Med. 2020;54(19):1130–1. https://doi.org/10.1136/bjsports-2020-102516.

[42] Wang T, Du Z, Zhu F, Cao Z, An Y, Gao Y, et al. Comorbidities and multi-organ injuries in the treatment of COVID-19. Lancet. 2020;395(10228):e52. https://doi.org/10.1016/S0140-6736(20)30558-4 [Epub 2020 Mar 11].

[43] Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan. China JAMA Cardiol. 2020;5(7):802–10. https://doi.org/10.1001/jamacardio.2020.0950.

[44] Chen C, Zhou Y, Wang DW. SARS-CoV-2: a potential novel etiology of fulminant myocarditis. Herz. 2020;45(3):230–2. https://doi.org/10.1007/s00059-020-4909-z.

[45] Vlachakis PK, Tentolouris A, Tousoulis D, Tentolouris N. Current data on the cardiovascular effects of COVID-19. Hellenic J Cardiol. 2020;61(1):46–8. https://doi.org/10.1016/j.hjc.2020.04.001.

[46] Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci. 2020;63(3):364–74. https://doi.org/10.1007/s11427-020-1643-8 [Epub 2020 Feb 9].

[47] Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8(4):420–2. https://doi.org/10.1016/S2213-600(20)30076-X [Epub 2020 Feb 18].

[48] Cheung EW, Zachariah P, Gorelik M, Boneparth A, Kernie SG, Orange JS, et al. Multisystem inflammatory syndrome related to COVID-19 in previously healthy children and adolescents in New York City. JAMA. 2020;324(3):294–6. https://doi.org/10.1001/jama.2020.10374.