RESEARCH

Longitudinal Cardiac Outcomes of Multisystem Inflammatory Syndrome in Children: A Systematic Review and Meta-Analysis

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Abstract

There is a paucity of longitudinal data on cardiac outcomes in multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19. We aimed to investigate the longitudinal cardiovascular outcomes in MIS-C. PubMed and EMBASE were searched through May 2022. Observational studies were included, reporting mid-term (≥ 3 months) outcomes in children (aged < 21) with MIS-C. Data were extracted by two researchers. Longitudinal outcomes were synthesized by a one-group meta-analysis using a random-effects model. Eleven studies with a follow-up period (3 months to 1 year) were identified, including 547 MIS-C patients. The mortality was 2.5% (95% CI 1.3–4.9). The majority of left ventricular (LV) systolic dysfunction present in 46.8% (95% CI 32.7–61.3) in the acute phase resolved by 3 months, and the prevalence of LV systolic dysfunction was 1.7% (95% CI 0.5–5.7) and 2.1% (95% CI 0.8–5.4) at 3 month and 6 month follow-up, respectively. Additionally, the persistent LV systolic dysfunction in the small population was mild. However, coronary abnormalities such as coronary artery dilatation or aneurysms, seen in 23.7% (95% CI 17.7–31.1) at baseline, persisted in 4.7% (95% CI 1.5–14.3) at 3 months and 5.2% (95% CI 3.0–8.9) at 6 months. Mitral regurgitation (MR), which was observed in 56.6% (95% CI 27.7–81.6) at baseline, also persisted in 7.5% at 6 months. In conclusion, our study demonstrated largely favorable cardiac outcomes, suggesting resolution of LV systolic dysfunction in the majority of cases. However, coronary abnormalities and MR persisted in a subset of patients at mid-term follow-up.

Keywords COVID-19 · Multisystem inflammatory syndrome in children · Coronary abnormalities · Left ventricular dysfunction · Mitral regurgitation

Introduction

Coronavirus disease 2019 (COVID-19) has been a global pandemic since December 2019. Initial studies reported that children experienced mild manifestations of severe acute

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respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in contrast to adults [1]. However, in April 2020, a novel post-infectious hyperinflammatory syndrome associated with COVID-19, now termed as multisystem inflammatory syndrome in children (MIS-C) or pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2, was identified [2, 3].

The clinical features in the acute phase and short-term outcomes of MIS-C have been described previously. Cardiac involvement occurs in approximately 80% of children with MIS-C, including left ventricular (LV) dysfunction, coronary abnormalities, pericardial effusions, arrhythmias, and conduction abnormalities [4–9]. Up to 50% of MIS-C patients exhibit LV systolic and/or diastolic dysfunction, and 10–20% of cases develop coronary artery dilatation and/or aneurysms [2, 10, 11]. Previous reports suggest that most of the patients with severe cardiac involvement recovered from LV systolic dysfunction and coronary abnormalities in the acute phase [12–14]. Recently, several single-center studies have revealed that mid-term outcomes of MIS-C are largely reassuring [15–20]. However, the reported incidence of persistent cardiac manifestations, such as LV systolic dysfunction and coronary abnormalities, varies due to the small sample size in each study. In addition, longitudinal outcomes of various cardiac manifestations in MIS-C remain unclear, including persistent LV diastolic dysfunction and mitral regurgitation (MR).

Elucidating the prevalence and time-course of cardiac abnormalities at mid-term follow-up will help in understanding the long-term outcomes and determining the management plans for MIS-C. Thus, we conducted a systematic review and meta-analysis to clarify mid-term cardiovascular outcomes in patients with MIS-C.

Materials and Methods

Search Strategy

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines [21, 22]. All observational studies which included children with MIS-C associated with COVID-19 were identified using a 2-level search strategy. Databases including PubMed and EMBASE were searched through May 5th, 2022. Relevant studies were identified through a manual search of secondary sources including references of initially identified articles, reviews, and commentaries. All references were downloaded for consolidation, elimination of duplicates, and further analyses. Search terms included *COVID-19*, *SARS-CoV-2*, *coronavirus*, *MIS-C*, *multisystem inflammatory syndrome in children*, *PIMS*, *PIMS-TS*, *pediatric inflammatory multisystem syndrome*,

children, *child*, *pediatric*, *young people*, *long-term*, *mid-term*, *outcomes*, and *follow-up*. We did not apply language limitations.

Study Selection

The following inclusion criteria were applied: (1) the study design was an observational study that was published in a peer-reviewed journal, (2) the study population was children < 21 years of age, meeting the diagnostic criteria for MIS-C with evidence of SARS-CoV-2 infection, (3) the lengths of follow-up satisfied mid-term (≥ 3 months) evaluation. The diagnosis of MIS-C was based on the Center for Disease Control and Prevention definition or the Royal College of Paediatrics and Child Health diagnostic criteria for PIMS-TS [23, 24]. Studies reporting data at either 3 months, 6 months or 1 year follow-up were eligible, while studies with the lengths of follow-up < 3 months were excluded. Articles that do not contain original data of the patients such as guideline, editorial, and review were excluded from the secondary review.

Two independent authors (J.Y. and K.M.) reviewed the search results separately to select the studies based on the inclusion and exclusion criteria. Disagreements were resolved by consensus with a third author (T.K.).

Data Extraction and Quality Assessment

Two authors (J.Y. and K.M.) performed the data extraction independently. The following information was extracted: study details (first author, date of publication, study location, and study design), patient demographic and clinical characteristics (number of patients, age, gender, race/ethnicity, laboratory values, and treatments), and mid-term outcomes (death, echocardiographic and cardiac magnetic resonance [CMR] findings). Discrepancies regarding the extracted data were resolved through discussion and consensus with a third author (T.K.). Echocardiographic findings including LV function, coronary abnormalities, MR, and pericardial effusion were collected serially from baseline to 3 months, 6 months, and 1 year follow-up. LV systolic dysfunction was defined as left ventricular ejection fraction (LVEF) < 55%. LV diastolic dysfunction was defined as at least 2 parameters (E/A, e', or E/e') being abnormal. The mitral inflow E/A Doppler profile was considered abnormal if the E and A waves were fused or if the E/A ratio had a Boston Children's Hospital Z score > 2.0. The e' velocity and E/e' ratio, either septal or lateral, were considered abnormal if either had a Boston Children's Hospital Z score > 2.0. Coronary abnormalities were defined by z scores as follows: normal < 2, dilation 2 to < 2.5, aneurysm ≥ 2.5 [25]. The risk of bias for the prevalence studies for each retrospective cohort study

was assessed using the Newcastle–Ottawa Assessment Scale [26].

Statistical Analysis

We performed one-group meta-analysis in a random-effects model using the DerSimonian-Laird method for continuous values and Wald method for discrete values. Comprehensive Meta-Analysis version 2 (available from https://www.meta-analysis.com/index.php?cart=BTEJ5270189) and OpenMetaAnalyst version 12.11.14 (available from http://www.cebm.brown.edu/openmeta/) were used for statistical analysis. Continuous variables are expressed as the means ± standard deviations or medians (interquartile range), as appropriate for the data distribution. Categorical variables are expressed as frequencies and percentages. The I^2 statistic was used to quantify heterogeneity, with $I^2 > 50\%$ indicating substantial heterogeneity.

Results

A total of 574 articles were identified through the initial database searching and the removal of duplicated items. After title and abstract screening, 190 full-text articles were assessed for eligibility and 179 articles were excluded based on lack of inclusion criteria such as the article type (editorials, reviews, systematic reviews, and meta-analyses), population (adult patients with COVID-19, cases without meeting the case definition for MIS-C), and articles without mid-term or long-term outcomes. Finally, 11 observational studies [15–20, 27–31] were included in our meta-analysis (Fig. 1).

Study Characteristics

The study and patient characteristics are summarized in Table 1. Across all 11 studies, a total of 547 patients with MIS-C were included. All the included studies were published in 2021 and 2022. Among these 11 studies, 6 studies

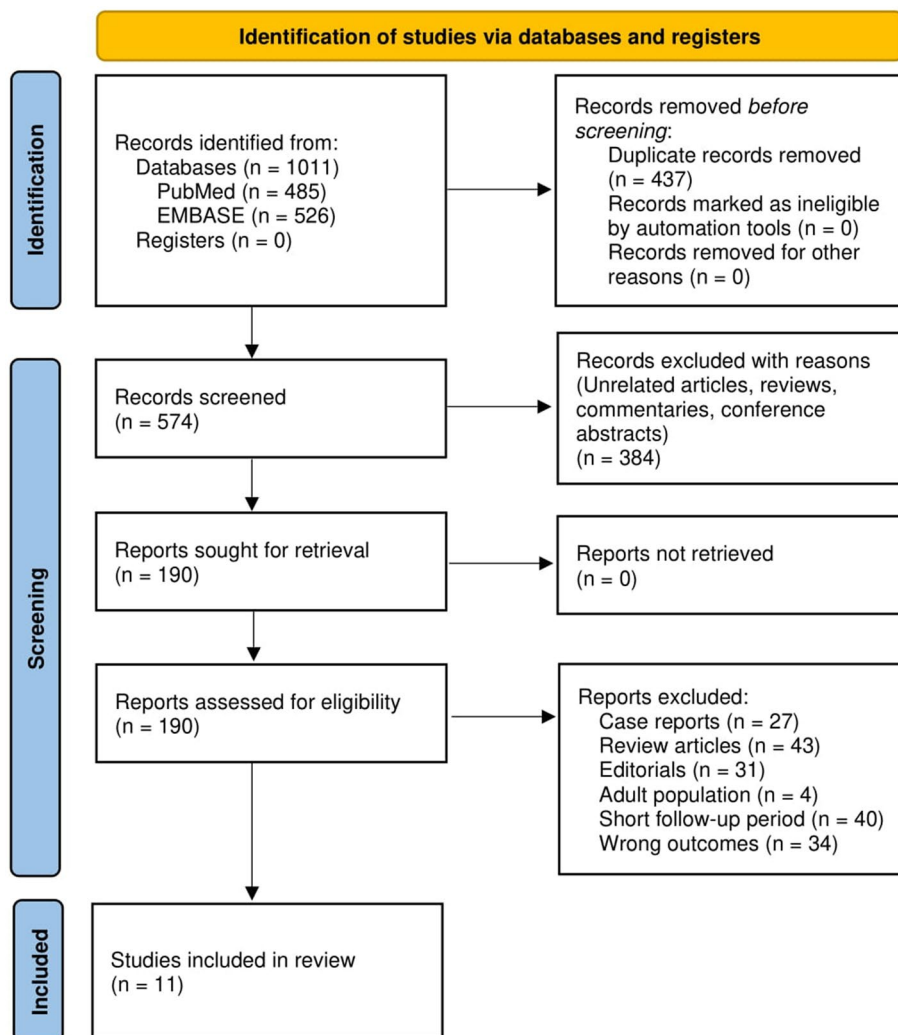**Fig. 1** PRISMA flow diagram of study selection

Table 1 Study and patient characteristics of the included studies

Study	Country	Publication date	Study design	Number of patients	Age, years	Male, n (%)	Hispanic/ Latino, n (%)	Black, n (%)	White, n (%)
Penner et al. [15]	UK	5/25/2021	Retrospective	46	10.2 (8.8–13.3)	30 (65)	1 (2)	16 (35)	9 (20)
Farooqi et al. [16]	USA	8/1/2021	Retrospective	45	9.4 ± 4.9	24 (53)	NA	10 (22)	21 (47)
Davies et al. [17]	UK	8/20/2021	Retrospective	68	NA	NA	NA	NA	NA
Capone et al. [18]	USA	10/1/2021	Retrospective	50	8.5 (5.4–11.5)	28 (56)	13 (26)	15 (30)	4 (8)
Barris et al. [19]	USA	10/21/2021	Retrospective	16	11.4 (5.9–13.2)	9 (56)	9 (56)	3 (19)	4 (25)
Kucera et al. [20]	UK	12/10/2021	Retrospective	80	9.1 (4.3–12.0)	54 (68)	NA	NA	NA
Matsubara et al. [27]	USA	2/11/2022	Retrospective	60	10.0 ± 4.3	36 (60)	9 (15)	29 (48)	16 (27)
Mitchell et al. [28]	USA	2/15/2022	Retrospective	50	8.3 (range 9 months – 17)	26 (52)	13 (26)	15 (30)	4 (8)
Awasthi et al. [29]	India	2/16/2022	Retrospective	40	7.0 (7.9–13.9)	26 (65)	NA	NA	NA
Dove et al. [30]	USA	2/28/2022	Retrospective	51	11.3 (7.9–13.9)	33 (65)	7 (14)	35 (69)	5 (10)
Aziz et al. [31]	Pakistan	3/24/2022	Retrospective	41	7.0 (range 0.8–16.0)	30 (73)	NA	NA	NA

Study	Asian, n (%)	Other, n (%)	Comorbidity, n (%)	WBC count, $\times 10^9$/L	Lymphocyte count, $\times 10^9$/L	Lymphopenia, n (%)	Hemoglobin, g/dL	CRP, mg/L	Ferritin, ng/mL	ALT, U/L
Penner et al. [15]	11 (24)	9 (20)	8 (17)	46	Minimum 0.7 (0.5–1)	NA	NA	28.1 (167–319)	915 (475–1650)	76 (48–126)
Farooqi et al. [16]	1 (2)	11 (11)	9 (20)	45	0.9 (0.5–2.1)	30 (66)	11.5 (11.1–12.3)	18.5 (0.75–25.8)	482 (284–634)	33 (21–50)
Davies et al. [17]	NA	NA	NA	68	NA	NA	NA	NA	NA	NA
Capone et al. [18]	6 (12)	21 (42)	NA	50	1.0 (0.6–1.5)	38 (76)	11.4 (10.5–12.1)	20.4 (12.2–29.1)	782 (366–1664)	NA
Barris et al. [19]	NA	NA	NA	16	NA	NA	NA	NA	NA	NA
Kucera et al. [20]	NA	NA	NA	80	Minimum 1.9 (1.2–3.8)	NA	Max 10 (6.1–13)	NA	Max 603 (356–1557)	74 (38–145)
Matsubara et al. [27]	2 (4)	13 (23)	NA	NA	0.5 (0.3–0.9)	NA	9 (7.9–10)	19.9 (15.8–25.8)	738 (447–1131)	NA
Mitchell et al. [28]	6 (12)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Awasthi et al. [29]	NA	NA	NA	NA	NA	26 (65)	NA	NA	NA	NA
Dove et al. [30]	3 (6)	NA	NA	NA	NA	NA	NA	NA	NA	NA

Table 1 (continued)

Study	Asian, n (%)	Other, n (%)	Comorbidity, n (%)	WBC count, ×10⁹/L	Lymphocyte count, ×10⁹/L	Lympho-penia, n (%)	Hemoglobin, g/dL	CRP, mg/L	Ferritin, ng/mL	ALT, U/L
Aziz et al. [31]	NA	NA	3 (7)	NA	NA	NA	NA	NA	NA	NA

Study	D-dimer, μg/mL	Troponin I, ng/mL	elevated troponin, n (%)	NT-proBNP, pg/mL	IVIG, n (%)	Corticosteroid, n (%)	Tocilizumab, n (%)	Anakinra, n (%)
Penner et al. [15]	4.945 (2.562–7.827)	NA	38 (86)	5218 (747–21,618)	38 (83)	25 (54)	NA	6 (13)
Farooqi et al. [16]	3.3 (2.2–4.5)	NA	NA	2582 (769–7280)	41 (91)	45 (100)	NA	5 (11)
Davies et al. [17]	NA	NA	NA	NA	52 (76)	51 (75)	NA	NA
Capone et al. [18]	2.248 (1.295–2.829)	NA	19 (38)	5023 (2708–12,766)	48 (96)	35 (75)	4 (8)	6 (12)
Barris et al. [19]	NA	NA	11 (69)	NA	13 (81)	3 (19)	14 (88)	2 (13)
Kucera et al. [20]	2.6 (1.181–5.603)	Max 0.021 (0.012–0.21)	37 (54)	Max 2858 (724–9639)	NA	NA	NA	NA
Matsubara et al. [27]	4.9 (2.4–7.8)	0.24 (0.03–0.91)	NA	NA	53 (90)	55 (92)	NA	NA
Mitchell et al. [28]	NA	NA	NA	NA	48 (96)	35 (70)	NA	NA
Awasthi et al. [29]	NA	NA	NA	NA	29 (73)	34 (85)	NA	NA
Dove et al. [30]	NA	NA	41 (87)	NA	42 (82)	48 (94)	NA	NA
Aziz et al. [31]	NA	NA	NA	NA	26 (70)	22 (59)	1 (2)	NA

Study	Infliximab, n (%)	Remdesivir, n (%)	Aspirin, n (%)	Anticoagulation, n (%)	Inotropes, n (%)	Mechanical ventilation, n (%)	ECMO, n (%)	ICU admission, n (%)
Penner et al. [15]	NA	NA	NA	35 (76)	22 (48)	16 (35)	1 (2)	NA
Farooqi et al. [16]	NA	1 (2)	45 (100)	NA	29 (64)	1 (2)	0 (0)	34 (76)
Davies et al. [17]	14 (21)	NA	NA	NA	NA	NA	NA	2 (3)
Capone et al. [18]	3 (6)	NA	46 (92)	23 (46)	31 (62)	NA	NA	26 (79)
Barris et al. [19]	NA	3 (19)	12 (75)	15 (94)	NA	NA	NA	NA
Kucera et al. [20]	NA	NA	NA	NA	22 (28)	NA	1 (1)	39 (49)
Matsubara et al. [27]	NA	NA	NA	NA	30 (50)	13 (22)	NA	42 (70)
Mitchell et al. [28]	NA	NA	NA	NA	29 (58)	NA	NA	33 (66)
Awasthi et al. [29]	NA	NA	32 (80)	NA	29 (73)	9 (23)	NA	34 (85)
Dove et al. [30]	NA	NA	NA	NA	29 (57)	NA	0 (0%)	41 (80)
Aziz et al. [31]	NA	NA	29 (71)	23 (56)	12 (29)	2 (5)	NA	9 (22)

Numbers represent n (%) for categorical variables, and mean ± standard deviation (SD), median [interquartile range (IQR)] for continuous variables

Abbreviation: *ALT* alanine aminotransferase; *CRP* C-reactive protein; *ECMO* extracorporeal membrane oxygenation; *ICU* intensive care unit; *IVIG* intravenous immunoglobulin; *LV* left ventricular; *LVEF* left ventricular ejection fraction; *NA* not available; *NT-proBNP* N-terminal proB-type natriuretic peptide; *UK* United Kingdom; *USA* United States of America; *WBC* white blood cell

were from the United States, 3 from the United Kingdom, and 2 from other countries (India and Pakistan). The follow-up timing varied up to 1 year; however, these studies all reported follow-up data in patients with MIS-C at 3 months or longer following initial diagnosis or discharge, including echocardiographic and CMR assessment. We synthesized outcomes at 3 months from 2 studies [27, 31] which explicitly included a follow-up at 3 months and 3 studies [17, 20, 30] which reported data at 100–105 days. We also synthesized outcomes at 6 months from 7 studies [16–19, 28, 29, 31] which included data at 6 months or 180 days follow-up. A summary of the risk of bias assessment for the prevalence studies for each retrospective cohort study is shown in Supplementary Table 1.

The pooled estimates from one-group meta-analysis in a random-effects model are presented in Table 2. The mean age at baseline was 9.5 [95% confidence interval (CI) 8.5–10.5; $I^2 = 79.8\%$] and males were 62.2% (95% CI 57.9–66.5; $I^2 = 0\%$). The pooled proportions of Hispanic, Black, White, and Asian cases were 18.5% (95% CI 8.1–28.9; $I^2 = 86.1\%$), 35.2% (95% CI 21.6–48.9; $I^2 = 87.4\%$), 18.2% (95% C, 9.6–26.9; $I^2 = 80.7\%$) and 8.0% (95% CI 3.1–12.9; $I^2 = 68.1\%$), respectively. Laboratory findings showed marked elevations in D-dimer, inflammatory markers including C-reactive protein and ferritin, and cardiac markers including N-terminal proB-type natriuretic peptide and troponin T (Table 2).

The pooled estimates regarding detailed information of treatment for MIS-C are shown in Table 2. The most common immunosuppressant was intravenous immunoglobulin (IVIG) (84.6%; 95% CI 78.4–90.7; $I^2 = 77.2\%$), followed by systemic corticosteroids (72.8%; 95% CI 61.2–84.3; $I^2 = 94.4\%$). A range of anti-inflammatory biologics and antiviral agents were used including tocilizumab, anakinra, infliximab, and remdesivir. The majority of the patients received aspirin (85.3%; 95% CI 74.6–96.1; $I^2 = 85.3\%$) and anticoagulation (68.3%; 95% CI 47.0–89.5; $I^2 = 90.3\%$). About half of the patients required inotropes (50.1%; 95% CI 31.3–68.8; $I^2 = 0\%$; $I^2 = 88.4\%$) and intensive care unit admission (46.7%; 95% CI 26.9–67.7; $I^2 = 91.8\%$; $I^2 = 94.9\%$). Overall, 17.8% (95% CI 0.0–49.7; $I^2 = 94.9\%$) required mechanical ventilation, and 1.4% (95% CI 0.5–4.3; $I^2 = 0\%$) needed extracorporeal membrane oxygenation (ECMO) (Supplementary Fig. 1 and 2). The mortality rate was 2.5% (95% CI 1.3–4.9; $I^2 = 0\%$) (Supplementary Fig. 3).

Ventricular Dysfunction

Longitudinal echocardiographic findings of the included study are summarized in Table 3. At baseline, LV systolic dysfunction, defined as LVEF < 55%, was identified in 46.8% (95% CI 32.7–61.3; $I^2 = 87.4\%$) (Fig. 2) and the mean LV ejection fraction was 54.1% (95% CI 49.4–58.7; $I^2 = 95.6\%$)

(Fig. 3). Three studies demonstrated that the prevalence of mild LV systolic dysfunction (LVEF 45–54%) was 62.8% (54/86) and the prevalence of moderate (LVEF 35–44%) or severe (LVEF < 35%) LV systolic dysfunction was 37.2% (32/86) at baseline. The longitudinal pooled prevalence of LV systolic dysfunction showed continued recovery in ventricular function from baseline to 6 months follow-up. The majority of the patients showed normalization of LV systolic dysfunction and the prevalence of LV systolic dysfunction was 1.7% (95% CI 0.5–5.7; $I^2 = 0\%$) at 3 months and 2.1% (95% CI 0.8–5.4; $I^2 = 0\%$) at 6 months (Fig. 2). All the persistent LV systolic dysfunction seen at 3 months and 6 months was mild, suggesting that there was no physiologically significant LV systolic dysfunction. At 3 months and 6 months follow-up, LVEF was 65.6% (95% CI 63.6–67.6; $I^2 = 83.5\%$) and 61.6% (95% CI 60.0–63.3; $I^2 = 81.9\%$), respectively (Fig. 3).

The incidence of LV diastolic dysfunction was calculated by summation because there were only 2 studies available [18, 28]. LV diastolic dysfunction was identified in 32% (32/100) at baseline and 4.1% (2/49) at 6 months.

Coronary Abnormalities

In the acute phase, the pooled prevalence of coronary abnormalities such as coronary artery dilation or aneurysms was 23.7% (95% CI 17.7–31.1; $I^2 = 68.5\%$). Many patients had resolution of coronary abnormalities in the acute period; however, coronary abnormalities were still observed in 4.7% (95% CI 1.5–14.3; $I^2 = 36.2\%$) of the patients at 3 months. Notably, coronary abnormalities persisted in 5.2% (95% CI 3.0–8.9; $I^2 = 0\%$) of the patients at 6 months (Fig. 4).

Mitral Regurgitation and Pericardial Effusion

At baseline, 56.6% (95% CI 27.7–81.6; $I^2 = 91.1\%$) had MR. Although MR resolved in some patients, MR persisted in 7.5% (95% CI 1.3–32.8; $I^2 = 73.2\%$) at 6 months (Fig. 5). The incidence of pericardial effusion was 32.1% (95% CI 15.8–54.3; $I^2 = 87.3\%$) in the acute phase. The majority of patients showed resolution of pericardial effusion seen in 2.5% (95% CI 0.6–9.4; $I^2 = 0\%$) at 6 months (Supplementary Fig. 4).

Discussion

The salient findings of our study can be summarized as follows: (1) The overwhelming majority of cases of LV systolic dysfunction present in the acute stages of MIS-C resolved completely by 3 months and the persistent LV systolic dysfunction in the small proportion of patients was very mild; (2) The prevalence of coronary abnormalities was 23.7% at

Table 2 Random-effects estimate (95% confidence interval) of the demographics, laboratory values, echocardiography findings, treatment and outcomes of the patients with MIS-C

	Random-effects estimate (95% CI)
Demographics	
Age, years	9.5 (8.5–10.5)
Male, %	62.2 (57.9–66.5)
Race/ethnicity	
Hispanic, %	18.5 (8.1–28.9)
Black, %	35.2 (21.6–48.9)
White, %	18.2 (9.6–26.9)
Asian, %	8.0 (3.1–12.9)
Other, %	26.3 (17.1–35.5)
Laboratory values	
White blood cell, $\times 10^9$/L	9.1 (8.1–10.1)
Lymphocyte count, $\times 10^9$/L	0.8 (0.4–1.2)
Platelet count, $\times 10^9$/L	169.5 (147.9–191.2)
Hemoglobin, g/dL	10.6 (9.3–12.0)
C-reactive protein, mg/L	217.3 (177.3–257.4)
Ferritin, ng/mL	707.9 (501.7–914.2)
ALT, U/L	60.3 (27.5–93.0)
D-dimer, µg/mL	3.5 (2.5–4.5)
Troponin T, ng/L	26.2 (10.2–42.2)
NT-proBNP, pg/mL	3875.8 (1938.1–5813.4)
Echocardiography findings	
LV systolic dysfunction or Myocarditis, %	46.8 (32.7–61.3)
LVEF, %	54.1 (49.4–58.7)
Coronary abnormalities, %	23.7 (17.7–31.1)
MR, %	56.6 (27.7–81.6)
Pericardial effusion, %	32.1 (15.8–54.3)
Treatment	
Intravenous immunoglobulin, %	84.6 (78.4–90.7)
Corticosteroids, %	72.8 (61.2–84.3)
Tocilizumab, %	31.4 (0.0–64.0)
Anakinra, %	12.1 (7.0–17.2)
Infliximab (TNF-α antagonist), %	8.0 (2.9–13.1)
Remdesivir, %	7.8 (0.0–23.0)
Aspirin, %	85.3 (74.6–96.1)
Anticoagulation, %	68.3 (47.0–89.5)
Inotropes, %	50.1 (31.3–68.8)
Mechanical ventilation, %	17.8 (0.0–49.7)
ICU admission, %	46.7 (26.9–67.7)
ECMO, %	1.4 (0.5–4.3)
Mortality, %	2.5 (1.3–4.9)

ALT alanine aminotransferase, *CI* confidence interval, *ECMO* extracorporeal membrane oxygenation, *ICU* intensive care unit, *LV* left ventricular, *LVEF* left ventricular ejection fraction, *MR*, mitral regurgitation, *NT-proBNP* N-terminal pro-B-type natriuretic peptide

baseline, while coronary abnormalities persisted in 4.7% and 5.3% of patients at 3 months and 6 months; (3) More than half of the patients had MR at baseline, which persisted in 7.5% at 6 months.

Our meta-analysis demonstrated that the majority of LV systolic dysfunction seen at baseline mostly resolved by 6 months and the persistent LV systolic dysfunction in the small proportion of patients was physiologically insignificant. Furthermore, Davies et al. [17] reported 1 year outcomes of 68 patients with MIS-C, showing that all of 39 patients (57.4%) with cardiac dysfunction at admission recovered by day 74. This finding suggests that midterm myocardial function outcomes are largely reassuring. Matsubara et al. found evidence of myocardial strain

Table 3 Longitudinal cardiovascular outcomes of the included studies

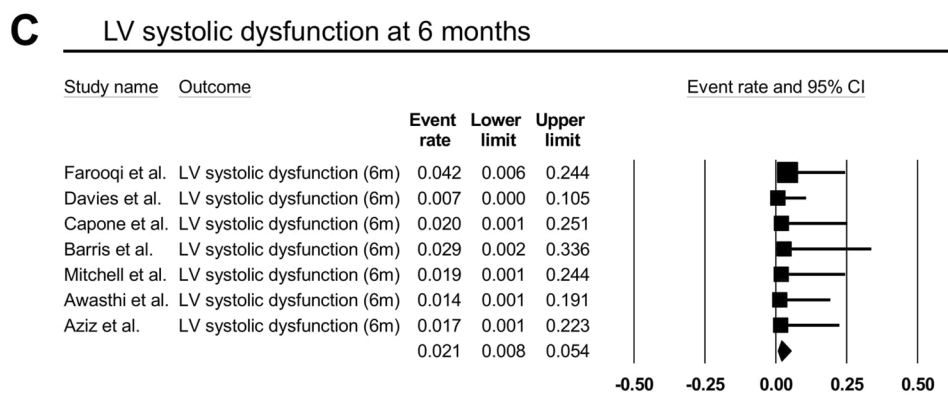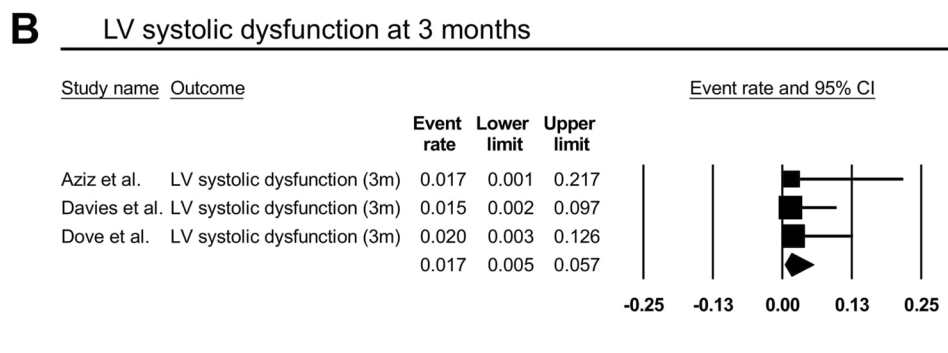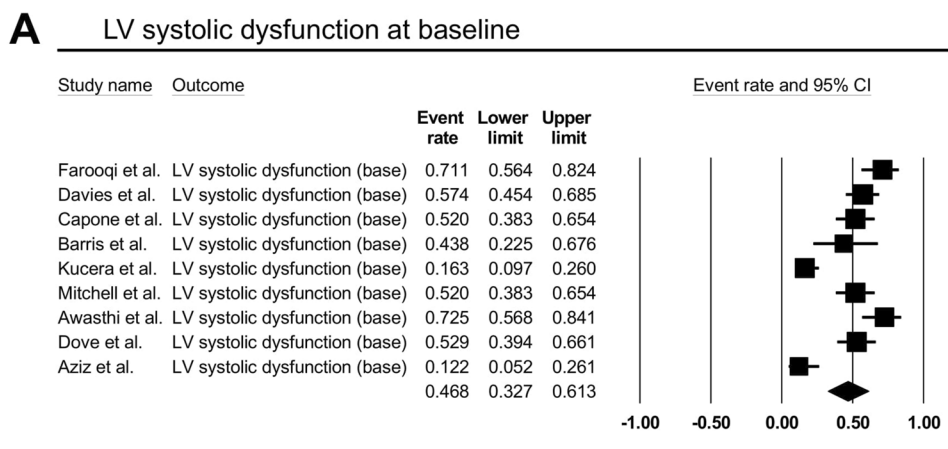| Study	Follow-up period	LV systolic dysfunction, n (%)			
		Baseline	3 months	6 months	1 year
Penner et al. [15]	6 weeks and 6 months after admission	NA	NA	NA	NA
Farooqi et al. [16]	1–4 weeks, 2 months (1–4) and 6 months (4–9) after discharge	34 (76); mild 24 (53), moderate to severe 10 (22)	NA	1 (4)	NA
Davies et al. [17]	1 year postadmission	39 (57)	1 (1)	0 (0)	0 (0)
Capone et al. [18]	~2 weeks, 8 weeks and 6 months after admission	26 (52); mild 15 (30), moderate 11 (22), severe 0 (0)	NA	0 (0)	NA
Barris et al. [19]	1 month and median 7.0 (6.0–8.4) months after admission	7 (44)	NA	0 (0)	NA
Kucera et al. [20]	Mean 103 days	13 (16)	NA	NA	NA
Matsubara et al. [27]	Subacute phase (within 1 week of the first echocardiogram), 1 month follow-up, and 3–4 month follow-up	NA	NA	NA	NA
Mitchell et al. [28]	2 weeks, 6–8 weeks (T2), and 6 months after treatment	26 (52); mild 15 (30), moderate 11 (22), severe 0 (0)	NA	0 (0)	NA
Awasthi et al. [29]	5 months (IQR 3–6) after discharge	29 (73)	NA	0 (0)	NA
Dove et al. [30]	105 days (IQR 93–151) after diagnosis	27 (53)	1 (2)	NA	NA
Aziz et al. [31]	1, 3, 6, 12 months after discharge	5 (12)	0 (0)	0 (0)	0 (0)

Study	LVEF, %				Coronary abnormalities, n (%)			
	Baseline	3 months	6 months	1 year	Baseline	3 months	6 months	1 year
Penner et al. [15]	NA	NA	NA	NA	15 (33)	NA	2 (4)	NA
Farooqi et al. [16]	54.5±8.3	NA	63.8±4.0	NA	7 (16)	NA	0 (0)	NA
Davies et al. [17]	NA	NA	NA	NA	19 (8)	6 (8)	6 (8)	2 (3)
Capone et al. [18]	54.0±9.0	NA	62.0±3.0	NA	26 (52)	NA	0 (0)	NA
Barris et al. [19]	54.0±9.0	NA	60.0 (58.0–63.0)	NA	3 (19)	NA	1 (6)	NA
Kucera et al. [20]	63.5 (58.0–68.0)	67.6 (58.0–63.0)	NA	NA	17 (22)	NA	NA	NA
Matsubara et al. [21]	55.0±10.0	35.0±3.0	NA	NA	4 (7)	0 (0)	NA	NA
Mitchell et al. [22]	54.0 (range 36–69)	NA	62.0 (range 57.0–70.0)	NA	12 (24)	NA	0 (0)	NA
Awasthi et al. [23]	45.0 (36.0–50.0)	NA	60.0 (55.0–65.0)	NA	9 (22)	NA	1 (3)	NA
Dove et al. [24]	53.9±13.5	65.4±5.2	NA	NA	10 (20)	NA	NA	NA
Aziz et al. [25]	NA	NA	NA	NA	10 (24)	1 (2)	1 (2)	0 (0)

Study	MR, n (%)				LV diastolic dysfunction, n (%)				Pericardial effusion, n (%)			
	Baseline	3 months	6 months	1 year	Baseline	3 months	6 months	1 year	Baseline	3 months	6 months	1 year
Penner et al. [15]	NA	NA	1 (2)	NA	NA	NA	NA	NA	1 (2)	NA	NA	NA
Farooqi et al. [16]	16 (36)	NA	1 (4.2)	NA	NA	NA	NA	NA	20 (44)	NA	0 (0)	NA
Davies et al. [17]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Capone et al. [18]	NA	NA	NA	NA	16 (32)	NA	1 (4)	NA	NA	NA	NA	NA
Barris et al. [19]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Kucera et al. [20]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Matsubara et al. [21]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Mitchell et al. [22]	42 (84)	NA	6 (24)	NA	16 (32)	NA	1 (4)	NA	24 (48)	NA	1 (4)	NA
Awasthi et al. [23]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Dove et al. [24]	23 (45)	NA	NA	NA	NA	NA	NA	NA	32 (63)	NA	NA	NA
Aziz et al.[25]	NA	NA	NA	NA	NA	NA	NA	NA	6 (15)	0 (0)	0 (0)	0 (0)

Numbers represent n (%) for categorical variables, and mean±standard deviation (SD), median [interquartile range (IQR)] for continuous variables

Abbreviations: *LV* left ventricular; *LVEF* left ventricular ejection fraction; *MR* mitral regurgitation; *NA* not available
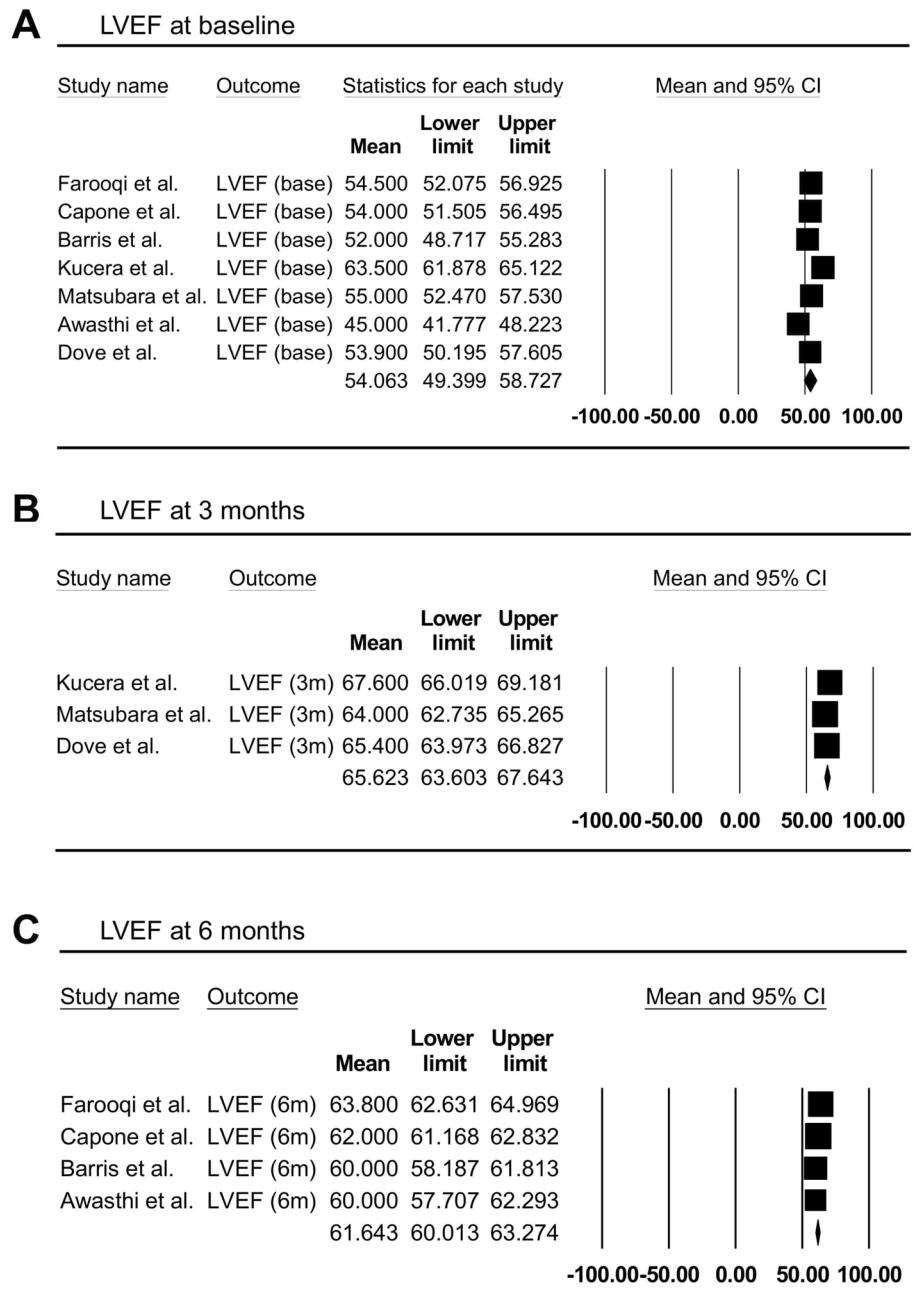
Fig. 2 Forest plots showing the pooled estimate of the incidence of LV systolic dysfunction over the follow-up period. **A** LV systolic dysfunction at baseline. **B** LV systolic dysfunction at 3 months. **C** LV systolic dysfunction at 6 months. *LV*, left ventricle

A LV systolic dysfunction at baseline

Study name	Outcome	Event rate	Lower limit	Upper limit
Farooqi et al.	LV systolic dysfunction (base)	0.711	0.564	0.824
Davies et al.	LV systolic dysfunction (base)	0.574	0.454	0.685
Capone et al.	LV systolic dysfunction (base)	0.520	0.383	0.654
Barris et al.	LV systolic dysfunction (base)	0.438	0.225	0.676
Kucera et al.	LV systolic dysfunction (base)	0.163	0.097	0.260
Mitchell et al.	LV systolic dysfunction (base)	0.520	0.383	0.654
Awasthi et al.	LV systolic dysfunction (base)	0.725	0.568	0.841
Dove et al.	LV systolic dysfunction (base)	0.529	0.394	0.661
Aziz et al.	LV systolic dysfunction (base)	0.122	0.052	0.261
		0.468	0.327	0.613

B LV systolic dysfunction at 3 months

Study name	Outcome	Event rate	Lower limit	Upper limit
Aziz et al.	LV systolic dysfunction (3m)	0.017	0.001	0.217
Davies et al.	LV systolic dysfunction (3m)	0.015	0.002	0.097
Dove et al.	LV systolic dysfunction (3m)	0.020	0.003	0.126
		0.017	0.005	0.057

C LV systolic dysfunction at 6 months

Study name	Outcome	Event rate	Lower limit	Upper limit
Farooqi et al.	LV systolic dysfunction (6m)	0.042	0.006	0.244
Davies et al.	LV systolic dysfunction (6m)	0.007	0.000	0.105
Capone et al.	LV systolic dysfunction (6m)	0.020	0.001	0.251
Barris et al.	LV systolic dysfunction (6m)	0.029	0.002	0.336
Mitchell et al.	LV systolic dysfunction (6m)	0.019	0.001	0.244
Awasthi et al.	LV systolic dysfunction (6m)	0.014	0.001	0.191
Aziz et al.	LV systolic dysfunction (6m)	0.017	0.001	0.223
		0.021	0.008	0.054

abnormalities despite normal LVEF, which suggests occult or subclinical systolic dysfunction [13]. Sanil et al. found persistent myocardial strain abnormalities at 10 weeks follow-up, with those having worse strain being more likely to experience hypotension, acute myocardial injury, inotropic requirement, cardiogenic shock, ECMO support, and longer hospital stay [32]. A recent study provided reassurance using sensitive deformation parameters that there was a rapid recovery of diastolic dysfunction by 3 months, suggesting no persistent subclinical dysfunction after. However, the assessment of diastolic function in children is limited since it has poor interobserver agreement and can vary according

to the volume status and valve competency, which makes the measurements unreliable and may have an adverse impact on interpretation [18]. Therefore, diastology is a concern in a subset of MIS-C patients, but more advanced functional imaging methods, such as strain, will better evaluate long-term findings. In addition to LV dysfunction, Farooqi et al. [16]. demonstrated that right ventricular (RV) dysfunction, seen in 35.6% of MIS-C patients at baseline, persisted in 6.5% and 4.2% of the patients at 1–4 months and 4–9 months follow-up, respectively. Ventricular systolic and diastolic dysfunction may be underestimated using only traditional echocardiographic measures. Furthermore, our study

Fig. 3 Forest plots showing the pooled estimate of LVEF over the follow-up period. **A** LVEF at baseline. **B** LVEF at 3 months. **C** LVEF at 6 months. *LVEF*, left ventricle ejection fraction
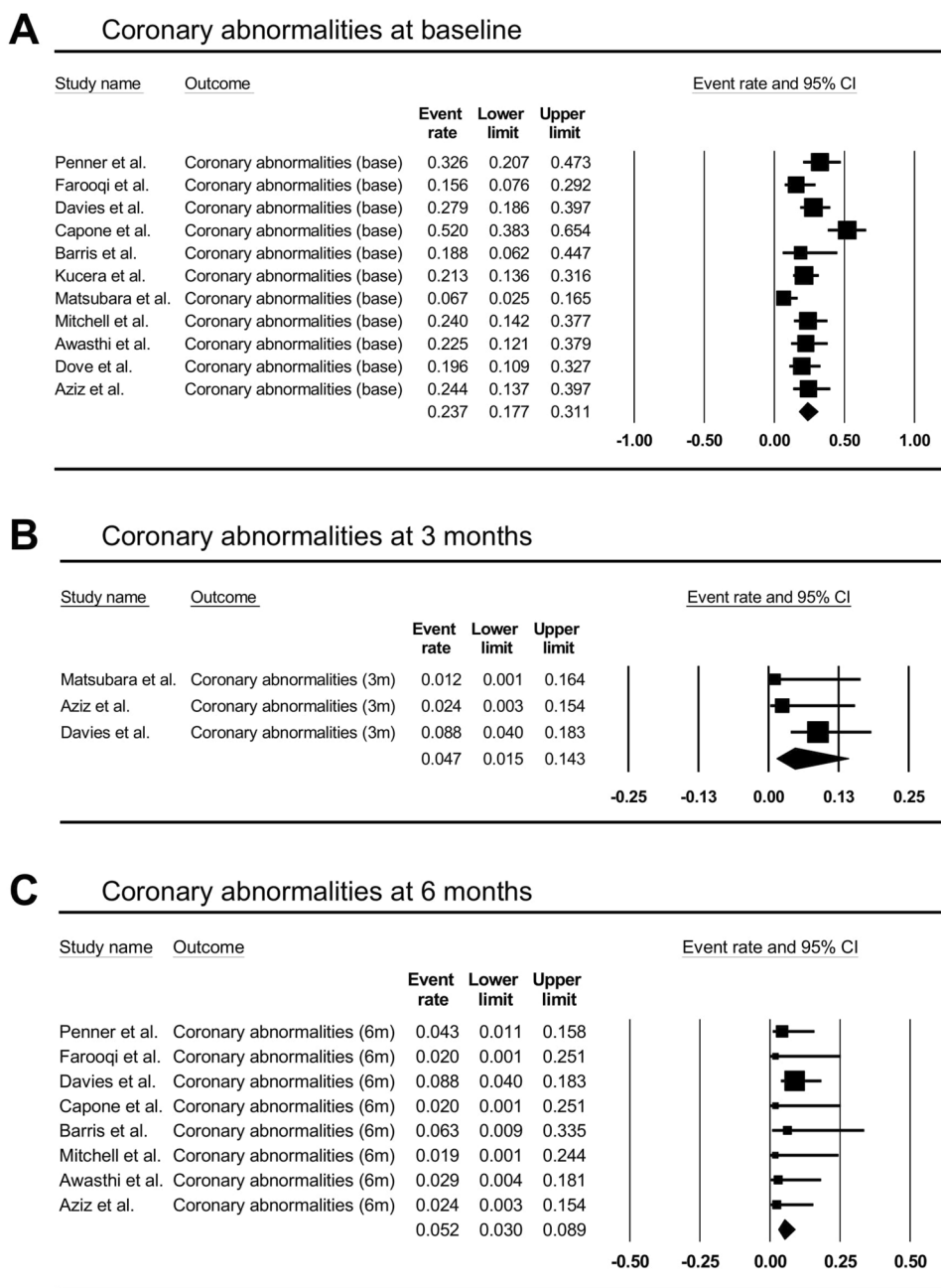
A   LVEF at baseline

Study name	Outcome	Statistics for each study			Mean and 95% CI
		Mean	Lower limit	Upper limit	
Farooqi et al.	LVEF (base)	54.500	52.075	56.925	
Capone et al.	LVEF (base)	54.000	51.505	56.495	
Barris et al.	LVEF (base)	52.000	48.717	55.283	
Kucera et al.	LVEF (base)	63.500	61.878	65.122	
Matsubara et al.	LVEF (base)	55.000	52.470	57.530	
Awasthi et al.	LVEF (base)	45.000	41.777	48.223	
Dove et al.	LVEF (base)	53.900	50.195	57.605	
		54.063	49.399	58.727	

-100.00 -50.00 0.00 50.00 100.00

B   LVEF at 3 months

Study name	Outcome				Mean and 95% CI
		Mean	Lower limit	Upper limit	
Kucera et al.	LVEF (3m)	67.600	66.019	69.181	
Matsubara et al.	LVEF (3m)	64.000	62.735	65.265	
Dove et al.	LVEF (3m)	65.400	63.973	66.827	
		65.623	63.603	67.643	

-100.00 -50.00 0.00 50.00 100.00

C   LVEF at 6 months

Study name	Outcome				Mean and 95% CI
		Mean	Lower limit	Upper limit	
Farooqi et al.	LVEF (6m)	63.800	62.631	64.969	
Capone et al.	LVEF (6m)	62.000	61.168	62.832	
Barris et al.	LVEF (6m)	60.000	58.187	61.813	
Awasthi et al.	LVEF (6m)	60.000	57.707	62.293	
		61.643	60.013	63.274	

-100.00 -50.00 0.00 50.00 100.00

demonstrated that more than half of the patients had MR at baseline, which persisted in 7.5% at 6 months. MIS-C patients have been reported to show MR more than Kawasaki disease (KD) [13]. However, the mechanisms and clinical implications of MR in MIS-C remain unclear. Long-term clinical implications of LV myocardial strain abnormalities, diastolic dysfunction, RV dysfunction, and MR are currently understudied and need further investigation using speckle-tracking echocardiography and CMR imaging.

In addition, the underlying mechanisms as well as an accurate diagnosis and optimal follow-up of myocardial dysfunction in MIS-C remains poorly understood. According to

the predominant hypothesis for the pathophysiology of MIS-C, a potential mechanism for myocardial dysfunction may be post-infectious myocarditis caused by a severe cytokine storm, which is supported by laboratory data such as elevated B-type natriuretic peptide and troponin, and reduced tissue deformation indices [13, 33, 34]. CMR remains the non-invasive reference standard for myocardial tissue characterization, particularly in myocarditis. However, there are only a limited number of CMR studies in children with MIS-C focusing on myocardial tissue characterization techniques and the extent of abnormalities seen varies across studies. Several studies have demonstrated the presence of

Fig. 4 Forest plots showing the pooled estimate of the incidence of coronary abnormalities over the follow-up period. **A** coronary abnormalities at baseline. **B** coronary abnormalities at 3 months. **C** coronary abnormalities at 6 months

A Coronary abnormalities at baseline

Study name	Outcome	Event rate	Lower limit	Upper limit	Event rate and 95% CI
Penner et al.	Coronary abnormalities (base)	0.326	0.207	0.473	
Farooqi et al.	Coronary abnormalities (base)	0.156	0.076	0.292	
Davies et al.	Coronary abnormalities (base)	0.279	0.186	0.397	
Capone et al.	Coronary abnormalities (base)	0.520	0.383	0.654	
Barris et al.	Coronary abnormalities (base)	0.188	0.062	0.447	
Kucera et al.	Coronary abnormalities (base)	0.213	0.136	0.316	
Matsubara et al.	Coronary abnormalities (base)	0.067	0.025	0.165	
Mitchell et al.	Coronary abnormalities (base)	0.240	0.142	0.377	
Awasthi et al.	Coronary abnormalities (base)	0.225	0.121	0.379	
Dove et al.	Coronary abnormalities (base)	0.196	0.109	0.327	
Aziz et al.	Coronary abnormalities (base)	0.244	0.137	0.397	
		0.237	0.177	0.311	

-1.00 -0.50 0.00 0.50 1.00

B Coronary abnormalities at 3 months

Study name	Outcome	Event rate	Lower limit	Upper limit	Event rate and 95% CI
Matsubara et al.	Coronary abnormalities (3m)	0.012	0.001	0.164	
Aziz et al.	Coronary abnormalities (3m)	0.024	0.003	0.154	
Davies et al.	Coronary abnormalities (3m)	0.088	0.040	0.183	
		0.047	0.015	0.143	

-0.25 -0.13 0.00 0.13 0.25

C Coronary abnormalities at 6 months

Study name	Outcome	Event rate	Lower limit	Upper limit	Event rate and 95% CI
Penner et al.	Coronary abnormalities (6m)	0.043	0.011	0.158	
Farooqi et al.	Coronary abnormalities (6m)	0.020	0.001	0.251	
Davies et al.	Coronary abnormalities (6m)	0.088	0.040	0.183	
Capone et al.	Coronary abnormalities (6m)	0.020	0.001	0.251	
Barris et al.	Coronary abnormalities (6m)	0.063	0.009	0.335	
Mitchell et al.	Coronary abnormalities (6m)	0.019	0.001	0.244	
Awasthi et al.	Coronary abnormalities (6m)	0.029	0.004	0.181	
Aziz et al.	Coronary abnormalities (6m)	0.024	0.003	0.154	
		0.052	0.030	0.089	

-0.50 -0.25 0.00 0.25 0.50

myocardial edema, with prevalence as high as 44–75% of patients with MIS-C [19, 35]. A recent publication by the CARDOVID Registry, which is one of the largest CMR-based studies in patients with MIS-C, identified 22/110 (20%) of patients with evidence of late gadolinium enhancement (LGE), with the vast majority meeting CMR criteria for myocarditis. Extent or quantity of LGE, which represents replacement fibrosis or acute myocardial necrosis, has been shown to be a risk factor for long-term outcomes in viral myocarditis data [36]. Short-term findings assessed by CMR demonstrated myocardial deformation indices were in the normal range within a few weeks after the onset of MIS-C;

however, lower strain parameters were found in a subset of children, suggestive of persistent subtle myocardial dysfunction [37]. Our echocardiography findings seem reassuring in terms of recovery from LV dysfunction; however, this may be due to underestimating true recovery as CMR can continue to show myocardial inflammation and decreased strain at follow-up. A recent statement from the American Heart Association proposed that CMR can be utilized to confirm the diagnosis of myocarditis in children and endomyocardial biopsy can be taken into consideration if necessary [38]. Markers of myocardial inflammation or edema by CMR are high signal intensity on T2-weighted imaging and markers

Fig. 5 Forest plots showing the pooled estimate of the incidence of MR over the follow-up period. **A** MR at baseline. **B** MR at 6 months. *MR*, mitral regurgitation
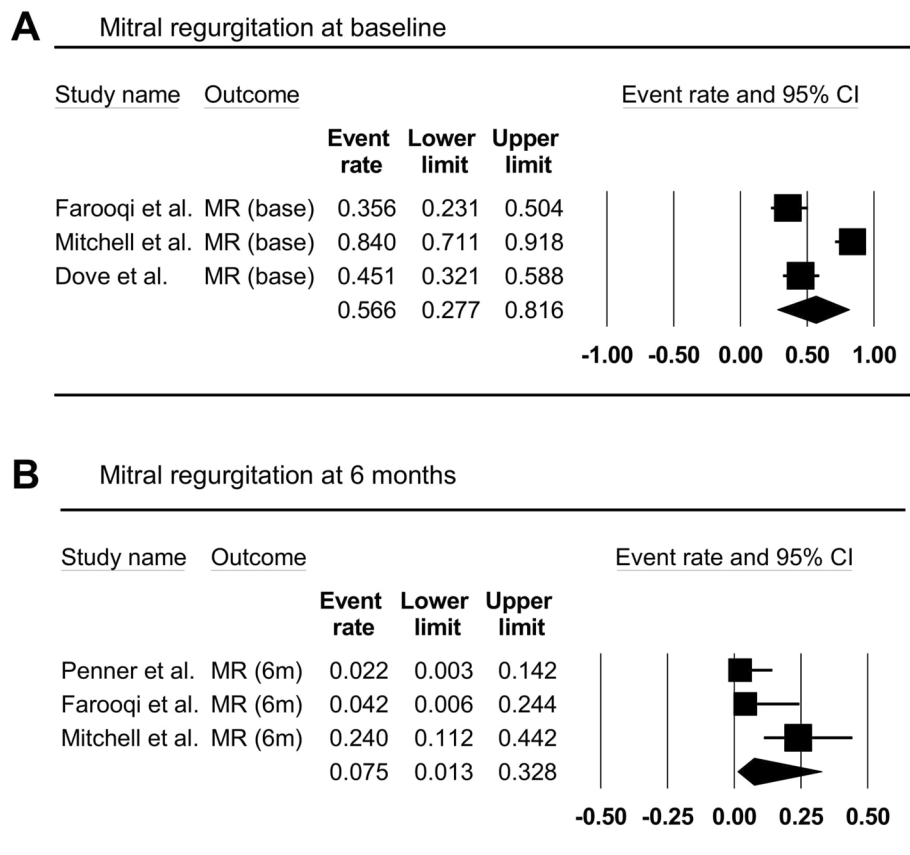
of myocardial fibrosis are increased native T1 and extracellular volume fraction. Hence, CMR is useful for diagnosis as well as follow-up evaluation of myocardial function in MIS-C. Further longitudinal studies by the combination of echocardiography and CMR would help refine the clinical course of full myocardial recovery and establish appropriate follow-up in children with MIS-C.

In our study, we exhibited many of coronary abnormalities regressed at follow-up period; however, coronary abnormalities noted at 3 months persisted until 6 months and would likely be present over the long-term. Previous studies showed mainly favorable early and mid- to long-term outcomes with recovery of coronary abnormalities [13, 18, 39]. One-year outcomes of 68 patients with MIS-C showed that all the 19 patients (27.9%) with coronary aneurysms at admission had resolution by day 400 [17]. In contrast, although infrequent, severe coronary artery involvement such as progression of giant coronary aneurysms has been described to date [2, 3, 40–43]. Some previous studies separated persistent coronary ectasia which is defined as coronary dilatation without a segmental aneurysm from coronary aneurysms [13]. Given the persistent coronary artery involvement in MIS-C, we highlight the need for continued caution and cardiac evaluation with serial echocardiography at regular follow-up period to investigate the

detailed characteristics of coronary abnormalities, including coronary dilatation, coronary ectasia, and coronary aneurysms. Future studies with standardized follow-up protocols, longer-term surveillance, and core laboratory interpretation are needed to identify the prevalence and progression of coronary abnormalities in MIS-C. Moreover, although MIS-C has some clinical similarities to KD, differences in long-term outcomes of coronary abnormalities between MIS-C and KD remain unclear. Persistent coronary artery aneurysms occur in about 5% of patients with KD, including about 1% developing giant coronary artery aneurysms [44]. Regression occurs in 75% of KD patients with coronary artery aneurysms and the initial diameter of coronary artery aneurysms has been shown to be predictive of outcomes [45, 46]. Further research is required to understand potentially variable long-term outcomes as well as pathophysiology of coronary abnormalities in MIS-C in comparison to KD as some of MIS-C patients also meet the diagnostic criteria of incomplete KD [5].

Arrhythmias and electrocardiographic changes have been reported in 30–70% of MIS-C patients [7, 47–49]. First-degree heart block was observed in 6–25% of patients more frequently than second- or third-degree heart block which was commonly associated with LV systolic dysfunction. Sinus bradycardia has also been reported [50, 51]. Patients

with persistent ventricular tachyarrhythmias had evidence of LV systolic dysfunction, requiring ECMO support [52, 53]. Electrocardiographic changes included low QRS amplitude, ST segment changes, QT prolongation, and T-wave abnormalities [48]. Long-term data on arrhythmias and electrocardiographic changes in MIS-C are warranted to understand persistence or recurrence of these abnormalities.

There are no randomized controlled trials assessing the efficacy of treatment in patients with MIS-C. Current treatment protocols are based on management experiences with KD because of the similarities between MIS-C and KD. IVIG has been used most commonly in our study as well as the previous studies in approximately 70–100% of patients with MIS-C [54–56]. We showed that corticosteroids were also used commonly in our study. As for corticosteroids therapy, a previous study revealed that patients who received combination therapy of IVIG and corticosteroids were less likely to have LV dysfunction at 1–2 days after initial treatment [54]. However, an international observational cohort study did not detect any significant differences in LV dysfunction or coronary abnormalities between IVIG alone, corticosteroids alone, or IVIG plus combination [56]. Based on the results of those studies, IVIG and/or corticosteroids therapy are favored as first-line treatment, which can contribute to the improvement of LV dysfunction and recovery from coronary abnormalities after the acute phase of MIS-C [57]. Biologic agents, such as interleukin-1, interleukin-6, and tumor necrosis factor-α blockers, can be used as second-line immunomodulatory treatment in MIS-C that is refractory to IVIG and corticosteroids [58, 59]. The clinical role of antiviral therapy with remdesivir is limited because of the lack of efficacy and safety data in children, and is utilized for severe acute COVID-19 [60]. Due to the risk of thrombosis with MIS-C, antiplatelet therapy and anticoagulants should be considered in MIS-C patients especially with LV dysfunction or coronary artery aneurysms [61].

This study had several limitations to be noted. First, the description of follow-up timing was variable and inconsistent between studies, which made it difficult to precisely compare the proportion of patients with residual cardiac abnormalities. Second, the available studies were observational studies, which are subject to methodological biases or reporting biases. Third, several variables, such as LV diastolic dysfunction and strain parameters, were not available across the included studies. In addition, the assessment of diastolic function in children is limited and can be unreliable due to poor interobserver agreement and the influence of the volumetric status or valve capacity. Finally, the number of included studies and the sample size were small, leading to substantial heterogeneity. There is still a paucity of available publications on longitudinal outcomes in MIS-C. Further studies with large cohorts of MIS-C and longer follow-up

periods will help understanding long-term outcomes of MIS-C to establish optimal treatment strategies.

Conclusions

Our meta-analysis demonstrated largely favorable mid-term cardiovascular outcomes, including low mortality rate and normalization of LV systolic dysfunction in the majority of MIS-C patients. However, there were persistent coronary abnormalities and MR in a subset of patients at 6 months follow-up. Further studies with systematic long-term follow-up data in larger cohorts of MIS-C patients are warranted to validate our findings.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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