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Cardiac manifestations of multisystem inflammatory syndrome of children after SARS-CoV-2 infection: a systematic review and meta-analysis

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Abstract

This systematic review and meta-analysis were conducted to evaluate the prevalence of cardiac manifestations associated with multisystem inflammatory syndrome in children worldwide. We conducted electronic searches in Ovid MEDLINE, Ovid EMBASE, and the World Health Organization COVID-19 Literature Database from the inception of the SARS-CoV-2 pandemic to 1 January, 2022. Three authors independently screened the abstracts to determine eligibility, assessed methodology in the full texts, and extracted the data.

We identified 2848 citations; 94 studies (14,932 patients) were included. The prevalence of vasopressors was 48.2% (95% CI 45.1%, 51.3%), left ventricular systolic dysfunction occurred in 37.2% (95% CI 34.1%, 40.3%), myocarditis in 34.1% (95% CI 30.5%, 37.8%), electrocardiographic dysrhythmias and abnormalities detected in 23.1% (95% CI 18.8%, 27.6%), coronary abnormalities identified in 18% (95% CI 16%, 20%), extracorporeal membrane oxygenation deployed in 2.2% (95% CI 1.7%, 2.8%), and mortality rate of 2.2% (95% CI 1.7%, 2.7%). A sensitivity analysis was performed after removing eleven studies with high bias, and the adjusted prevalence was not different than the original evaluation.

In this meta-analysis of the largest cohort of multisystem inflammatory syndrome in children patients to date, we established the most accurate prevalence of the most common cardiac manifestations. Providers will subsequently have more precise data to anticipate patient outcomes and approach discussions concerning the frequency of monitoring outside the acute hospital period.

In December 2019, a distinct clinical presentation of pneumonia was first described in China as being caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). By January 2020, the virus spread[1–5] with adults developing systemic hyperinflammation and myocardial injury.[6] children made up 2–6% of cases initially but were mostly asymptomatic. Some had mild respiratory symptoms, and the few with comorbidities required hospitalisation or intensive care.[7]

In April 2020, the first reports of paediatric systemic inflammatory syndrome related to severe SARS-CoV-2 emerged from the United Kingdom at the peak of the pandemic in Europe.[7–13] The syndrome consisted of hypotension, multiorgan involvement, and systemic inflammation. The following month, reports from the rest of Europe and North America validated the severity of this unfolding hyperinflammatory condition by comparing it to Kawasaki disease, toxic shock syndrome, and macrophage activation syndrome.[2,3,5,14–17] The Centers for Disease Control and Prevention published a case definition for disease surveillance and called the condition multisystem inflammatory syndrome in children.[18] The definition is based on age <21 years old, the presence of fever ≥38.0°C for ≥24 hours, increased inflammatory markers (such as ferritin, C-reactive protein, fibrinogen, procalcitonin), the involvement of two or more organ systems, COVID-19 infection or exposure within prior 4 weeks, and exclusion of other diagnoses.[19,20]

Initial reports confirm the development of myocarditis and/or left ventricular systolic dysfunction.[21] This includes coronary artery dilation and aneurysms,[22,23] cardiac conduction abnormalities, and up to a 12% rate of dysrhythmias.[23,24] In severe cases of multisystem inflammatory syndrome in children, patients were presenting in shock requiring fluid resuscitation, inotropic support, mechanical ventilation, and, in most severe cases, extracorporeal membrane oxygenation.[23] There have been numerous heterogenous small case series reporting cardiac

complications in multisystem inflammatory syndrome in children with the largest samples coming from Belay et al[25] (n = 1563), Bowen et al[26] (n = 2818), and Miller et al[27] (n = 4470). However, there has never been an attempt to combine these studies to establish the prevalence of these cardiac symptoms.

By determining the accurate prevalence, providers will better anticipate the outcome of their patients and approach discussions about the appropriate frequency of monitoring outside the acute period. Our objective was to perform a systematic review and meta-analysis of the multisystem inflammatory syndrome in children patients, focusing specifically on the associated cardiac sequelae and mortality.

Methods

Design

This is a systematic review and meta-analysis consisting of studies to determine the prevalence of different cardiac complications secondary to multisystem inflammatory syndrome in children. In summary, we included prospective and retrospective cohorts at single-centre and multi-centre facilities both in the United States and internationally. We conducted electronic searches of Ovid MEDLINE, Ovid EMBASE, and World Health Organization COVID-19 Literature Database from the inception of the SARS-CoV-2 pandemic to 1 January, 2022. Two authors independently screened the abstracts and full texts, extracted the data, and resolved disagreements by discussion with a third reviewer.

Types of studies

We included studies enrolling children and adolescents from ages 0 to 21 years of age with multisystem inflammatory syndrome in children-associated SARS-CoV-2 infection that discussed the most frequently associated cardiac manifestations. The search included information both from single and multi-centre institutions. It encompassed a diversified blend of retrospective and prospective data that were observational and contained cross-sectional, cohort, and case studies with greater than ten patients. Articles in languages other than English were considered eligible and translated via Google Translation.

We limited our review to studies assessing myocardial function via echocardiogram to define left ventricular systolic dysfunction as an ejection fraction ≤60%. Studies that discussed other echocardiographic measurements such as fractional shortening and tricuspid annular plane systolic excursion by M-mode, early and late mitral inflow peak velocities by spectral Doppler, and early diastolic septal and lateral mitral annular peak velocities were included but not the primary parameter evaluated. Simpson's biplane method was the most consistently reported measurement among previous reviews and implemented for this work. We used studies that classified coronary artery abnormalities as described by the Boston Children's Hospital z-score system. Normal was <2, dilation ≥2 to <2.5, and aneurysm ≥2.5. We also chose to report electrocardiographic dysrhythmias and abnormalities as a combined outcome since many articles did not report specific findings. Studies that defined myocarditis according to clinical presentation (shock, hypotension, chest pain, palpitations, or hypoxia) and diagnostic criteria were selected. Papers describing diagnostic criteria dependent upon electrocardiographic abnormalities (ST/T wave changes, ventricular dysrhythmias, and intraventricular conduction delay), elevated troponin or brain natriuretic peptide, functional/structural abnormalities on echocardiogram or cardiac magnetic resonance, and tissue characterisation by cardiac magnetic resonance per the Lake Louise criteria were incorporated.

We excluded clinical guidelines, systematic reviews, meta-analyses, editorials, and commentaries. Studies looking at multisystem inflammatory syndrome related to the adult population were also excluded, as well as articles discussing solely disease pathogenesis, molecular biology, immunology, other serotypes of coronavirus, or viral agents. Reports of multisystem inflammatory syndrome in children along with discussions of an emergency room course focus on radiological findings (x-rays, CT, or ultrasound), medication trials, case reports with <10 patients, or letters to the editor that were solely perspective or commentary pieces not describing specific cases of multisystem inflammatory syndrome in children were also excluded.

Types of participants

We included studies that enrolled children and adolescents (aged 0–21 years), diagnosed with multisystem inflammatory syndrome in children, and which reported myocardial dysfunction, conduction abnormalities, shock, and/or coronary disease. The summary table (Supplementary Table S1) gives an overview of the country of origin of the study, single or multi-centre, number of patients, number needing ICU, predominant comorbidity, and number of deceased patients.

Types of outcome measures

Our primary outcome was determining the prevalence of subjects requiring vasopressor support, left ventricular systolic dysfunction, electrocardiographic changes including dysrhythmias, coronary abnormalities (dilations and/or aneurysms), ECMO, and mortality. Our secondary outcome was identifying the prevalence of myocarditis by stratifying via method of diagnosis (Supplementary Table S3). Some studies incorporated cardiac MRI and identified myocarditis by assessing myocardial inflammation using the Lake Louise Criteria. In instances where MRI was not available, the remaining authors diagnosed myocarditis per criteria described within their manuscript (Denoted as Predetermined Criteria and Definition of Myocarditis According to Study in Supplementary Table S3). For the studies that did not characterise this measure, we defined myocarditis as left ventricular systolic dysfunction [ejection fraction < 55%], troponin, and/or brain natriuretic protein above the threshold of normal per the study, and any symptomatology [hypotension, shock, inotrope requirement, or oxygen requirements] (Denoted as Strict Criteria in Supplementary Table S3). The specific threshold per study for the definition of left ventricular systolic dysfunction and normal values used for troponin/brain natriuretic peptide/pro-brain natriuretic peptide are listed in Supplementary Table S3. Among all studies, dilation of a coronary artery was defined as a Z-score ≥2 to <2.5 and an aneurysm of coronary vessel as ≥2.5 per the Boston Children's Hospital z-score system.[28]

Search methods for identification of studies

For this systematic review, we performed a search in MEDLINE (PubMed), EMBASE (Ovid), and the WHO Global Research on Coronavirus Disease (COVID-19) Literature Database (https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/) from the inception of the SARS-CoV-2 pandemic to 1 January, 2022 (Supplemental Online Data). The search included keywords and controlled vocabulary for coronavirus/COVID-19

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and for the heart and select cardiac complications (Supplemental File 1). We imported the results to Covidence (version 1238, Melbourne, Australia), which detected duplicates.

Selection of studies

Two out of three reviewers (CC, MK, CFF) independently examined each potential study (as randomly assigned by Covidence) and decided on their inclusion in the review (Fig 1), based on its methods and outcomes. We performed this process without blinding of study authors, institutions, journals of publication, or results. We resolved disagreements by reaching consensus among review authors.

Data extraction and management

For each study included in the systematic review, two authors (CC & MK) independently extracted data. We resolved disagreements by discussion and another author (OK) providing the tie-breaking vote. We contacted all authors for their assistance in obtaining missing data pertinent to our analysis of primary outcomes. We also sought the authors' support with calculating the number of myocarditis cases in their study based on our strict clinical criteria.

Assessment of risk of bias in included studies

We evaluated the validity and design characteristics of each study looking for major potential biases such as study participation, study attrition, prognostic factor measurement, outcome measurement, study confounders, and statistical analysis.[29] Two authors reviewed and ranked each study's quality factor separately and defined studies as having low risk of bias only if they adequately fulfilled all the criteria.

Assessment of prevalence

We reported the prevalence and its 95% confidence interval as the number of patients with the outcomes of interest (vasopressor support, left ventricular systolic dysfunction, myocarditis, electrocardiographic dysrhythmias, coronary abnormalities including dilations and/or aneurysms, extracorporeal membrane oxygenation, and mortality over the total number of enrolled patients). To account for small proportions and interval confidences close to 0, we pooled the individual proportions using arcsine transformation.[30]

Assuming each study estimated a study-specific true effect, we used random-effect models to pool odds ratios. Such models assume no a priori knowledge about the association between the real, or apparent, prevalence; the differences between the studies are considered to be random. These models account for heterogeneity, with the centre of this distribution describing the average of the effects, and its width describing the degree of heterogeneity. We used the DerSimonian-Laird random-effect method in the presence of significant heterogeneity.[31]

Assessment of heterogeneity

We explored heterogeneity using the I^2 statistic. An I^2 statistic higher than 50% represented substantial heterogeneity.[32]

Sensitivity analysis

To further explore the effect of risk of bias, we conducted a sensitivity analysis, removing studies with a high risk of bias.

Statistical Analyses

Meta-analysis was undertaken using a random-effects model, conducted using the Open-Meta [Analyst] program (School of Public Health, Brown University, Providence, RI, USA). Forest plots of prevalence were calculated with 95% CI.

Results

Studies

We identified a total of 2858 references, of which 657 were duplicates and therefore removed from review, leaving a total of 2201 studies that were screened. A total of 1984 studies were not relevant to this review, leaving 217 full-text articles. From these, 94 met eligibility criteria (Fig 1). Of the articles, 71 (75.5%) were solely retrospective studies[1,3,5–12,15,17,19,20,22,24–28,33–81], 7 (7.4%) studies had a mix[13,18,82–86] of retrospective and prospective components, and 17 (17%) were prospective[2,4,16,21,87–98] studies. Fifty-six studies were from a single centre, and thirty-eight were from multiple centres. A summary of the included studies is presented in Supplementary Table 1.

Prevalence of overall results

Among the 86 studies that report vasopressor use, the prevalence is 48.2% (95% CI 45.1%; 51.3%), n = 14,593, $I^2 = 89.70\%$, Supplemental Figure S1(A). Of the 88 studies that report, left ventricular systolic dysfunction, the prevalence is 37.2% (95% CI 34.1%; 40.3%), n = 14,594, $I^2 = 90.2\%$, Supplemental Figure S2(A). Among the 80 studies that report myocarditis, the prevalence is 34.1% (95% CI 30.5%; 37.8%), n = 13,293, $I^2 = 92.6\%$, Supplemental Figure S3(A). Of the 59 studies that report electrocardiographic abnormalities, the prevalence is 23.1% (95% CI 18.8%; 27.6%), n = 11,470, $I^2 = 95.5\%$, Supplemental Figure S4 (A). Among the 90 studies that report coronary abnormalities, the prevalence is 18% (95% CI 16%; 20%), n = 14,707, $I^2 = 83.4\%$, Supplemental Figure S5(A). For the 77 studies that report extracorporeal membrane oxygenation use, the prevalence is 2.2% (95% CI 1.7%, 2.8%), n = 12,778, $I^2 = 53.8\%$, Supplemental Figure S6(A). Among the 90 studies that report mortality, the prevalence is 2.2% (95% CI 1.7%; 2.8%), n = 14,620, $I^2 = 43.8\%$, Supplementary Figure S7(A).

Assessment of the risks of bias

The overall risk of bias was estimated to be low. We assessed that the risk of bias was low in 60 studies (63.8%), moderate in 23 studies (24.4%), and high in 11 studies (11.76%). The full assessment is shown in Supplementary Table S2.

Sensitivity analysis based on the quality of evidence

For this sensitivity analysis, we removed the studies with a high risk of bias and included those with low and moderate risk of bias. Of the 77 studies that report vasopressor use, the prevalence is 49.1% (95% CI 45.8%; 52.3%), n = 14,280, $I^2 = 90.3\%$, Supplemental Figure S1(B). Among the 79 studies remaining that report left ventricular systolic dysfunction, the prevalence is 37.3% (95% CI 34.1%; 40.6%) n = 14,318, $I^2 = 90.8\%$, Supplemental Figure S2(B). Of the 74 studies that report myocarditis, the prevalence is 34.1% (95% CI 30.5%; 37.9%), n = 13,109, $I^2 = 93\%$, Supplemental Figure S3(B). Among the 56 studies that report electrocardiographic abnormalities, the prevalence is 21.4% (95% CI 17.3%; 25.8%), n = 11,363, $I^2 = 95.3\%$, Supplemental Figure S4(B). Of the 81 studies that report coronary abnormalities,

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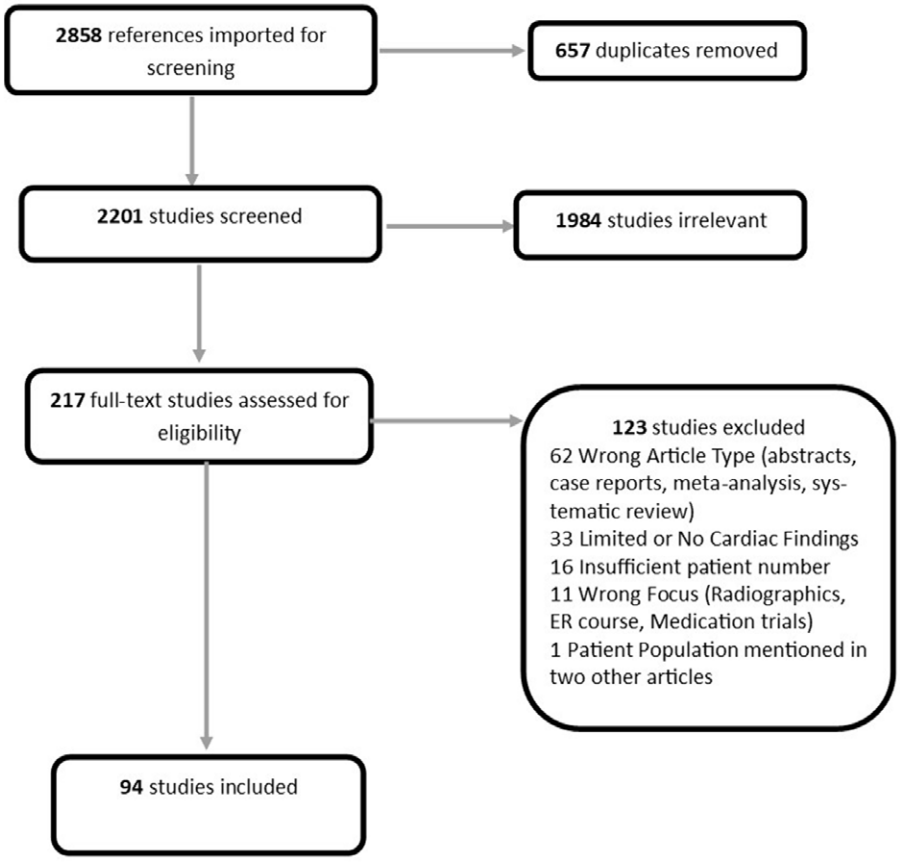

Figure 1. PRISMA study flow diagram, showing the total number of references that were screened, the reasons to exclude the references that made it to full-text screening, and the number of references that were included.

the prevalence is 18.2% (95% CI 16.2%; 20.4%), n = 14,422, $I^2 = 84.7\%$, Supplemental Figure S5(B). Among the 70 studies that report extracorporeal membrane oxygenation utility, the prevalence is 2.3% (95% CI 1.7%; 2.9%), n = 12,514, $I^2 = 57.7\%$, Supplemental Figure S6(B). Among the 78 studies that report mortality, the prevalence is 2.0% (95% CI 1.6%; 2.5%), n = 14,262, $I^2 = 38.3\%$, Supplementary Figure S7(B).

Assessment of myocarditis

Among the 94 studies available, only 80 could be used to extract information regarding the prevalence of myocarditis. Either some authors did not respond to our requests to provide their number of myocarditis cases or there was incomplete data to determine the prevalence. For 45 studies (Denoted as Strict Criteria in Supplementary Table 3), we categorised a posteriori the clinical criteria to determine the number of myocarditis. Twenty-four studies (Denoted as Predetermined Criteria in Supplementary Table 3) already ascertained cases of myocarditis in their respective populations based on criteria that included left ventricular systolic dysfunction on echocardiogram plus elevated troponin and/or brain natriuretic peptide. Four studies[22,38,57,97] within this subcategory further validated the diagnosis of myocarditis by requiring electrocardiographic changes such as ST-segment elevation/depression. Eight studies (Denoted as CMR in Supplementary Table 3) diagnosed myocarditis via cardiac resonance imaging using the Lake Louise criteria. Three studies[10,80,92] had zero cases of myocarditis. The specific definitions of left ventricular systolic dysfunction and parameters for normal troponin, brain natriuretic peptide, and pro-brain natriuretic peptide are mentioned in Supplementary Table S3.

Discussion

To address the heterogeneity of various small case series and cohorts, this systematic review aimed to evaluate the prevalence of common cardiac manifestations in afflicted critically ill children with multisystem inflammatory syndrome in children. To our knowledge, this is the first meta-analysis looking at the prevalence from such a robust sample (n = 14,932). Overall, the quality of evidence was good with 64% of studies having a low risk of bias and 24% a moderate risk of bias.

Severe multisystem inflammatory syndrome in children presents with shock requiring vasopressors to sustain haemodynamics. Early systematic reviews report a prevalence range from 40 to 52%[99,100] while single international studies show 70 to 80% utilisation.[11,33,82] This may be plausible as some middle and lower-income countries have higher comorbid patients, reduced disease recognition, and slower access to healthcare. In our analysis, vasopressors continue to be critical in shock management as the prevalence was 48.2% (95% CI 45.1%, 51.3%). In shock, cardiac dysfunction is frequently evaluated with an echocardiogram to assess left ventricular ejection fraction. Caution is necessary when interpreting this parameter because it is a volume-based measure that is preload dependent and subject to vasoactive use.[48,101] Myocardial tissue motion and deformation estimates with strain echocardiography are independent of these loading conditions, and indexes such as global longitudinal strain and early diastolic strain rate may be an option to grade ventricular dysfunction more accurately. This detects impaired function even when cardiac magnetic resonance proved myocarditis reveals a preserved left ventricular ejection fraction.[2,5,48,64,72] However, in keeping with consistency of measurements more commonly reported, we

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evaluated cardiac dysfunction via left ventricular systolic dysfunction. We reported a prevalence of 37.2% (95% CI 34.1%, 40.3%) compared to a previously described range of 32–58%.[23,99,100] This left ventricular systolic dysfunction requires outpatient follow-up with echocardiograms because it can persist even after 1 month from hospitalisation[46,84,91] with some residual left ventricular functional dysfunction[33,46,72,76,84,88,91,96] persisting 2–6 weeks after discharge.

Other non-invasive imaging such as cardiac magnetic resonance is useful for functional assessment and structural changes like in myocarditis.[83,102] Despite its sensitivity in detecting inflammation, its availability is limited[17,28,50,56,76,79,83,84] as evidenced by the few studies we identified. Twenty-four incorporated the criteria[102] where ≥1 clinical presentation and ≥1 diagnostic criteria were sufficient for clinical diagnosis (Predetermined Criteria in Supplemental Table 3). To improve the accuracy in our analysis, we elected to make criteria stricter by needing ≥2 diagnostic criteria: cardiac biomarkers (abnormal troponin and/or pro-brain natriuretic peptide) + left ventricular systolic dysfunction (ejection fraction <55%) in addition to the clinical presentation[102] (Strict Criteria in Supplemental Table 3). Our analysis therefore elicited a prevalence of 34.1% (95% CI 30.5%, 37.8%). Our results lie at the higher end of previous estimates, which reported a prevalence from 23 to 33%.[100,101] Even though children overall improve shortly after the diagnosis of multisystem inflammatory syndrome in children is made, long-term complications such as fibrosis, dilated cardiomyopathy, and arrhythmias may present thus warranting close monitoring.[10] Ventricular dysrhythmias in dilated cardiomyopathy are lethal complications of multisystem inflammatory syndrome in children-induced myocarditis in the latter stages but dysrhythmias overall can present early on with 7–60% of patients[23] having irritable foci. Despite the heterogeneity of studies, we were unable to perform further analyses looking at the prevalence of certain rhythms as the reporting of electrocardiographic information was inconsistent and infrequent. Those studies that were, are listed in Supplementary Table S3. From the studies that did cite this data, the calculated prevalence of electrocardiographic abnormalities was 23.1% (95% CI 18.8%, 27.6%). Despite the severity and potential for worsening progression, these dysrhythmias (including first-degree atrio-ventricular block) typically resolve within the first 2 weeks[1,22,101] before the 2-week follow-up.[9] The present literature describes only one report of three patients with persistent asymptomatic bradycardia lasting through the 2-month follow-up.[10]

Coronary abnormalities which can take months to resolve are the opposite of the swifter trajectory for healing seen in dysrhythmias. Resolution typically occurs in 79% of cases by 1 month[56] and in 100% of cases by 3 months.[71,103] In our patient cohort, the prevalence of coronary abnormalities was 18.0% (95% CI 16.0%; 20.0%) in comparison to the described 6–24%.[8,21,23,99–101] Some had residual aneurysms[53] and dilation after 2 weeks,[84] 4–6 weeks[71,88,96], 8 weeks[84,90], and by 3 months[96] post-discharge. We were unable to complete an analysis of the total cases of coronary dilations versus coronary aneurysms since some studies did not define them aside from the term "coronary abnormalities" or simply did not report them as findings. Of those in Supplementary Table S3, we tallied 717 total cases of coronary abnormalities with 300 coronary dilations (41.8%) and 367 coronary aneurysms (51.2%). Other variations of abnormalities included those describing arteries as hyperechoic, prominent, or lacking tapering. Regardless of the presentation, the evolution of the abnormality is imperative to monitor over the ensuing months as one patient had a stable medium coronary aneurysm (Z-score 9.8) 6 months out from discharge; these can become giant raising the risk of a myocardial infarction.[47,101]

Even though most patients recover rather uneventfully once medical therapies are initiated, some are affected with ventricular dysrhythmias, refractory shock, and/or acute heart failure.[7,23] These severe cases go can extend beyond vasopressor and mechanical ventilation management to necessitate extracorporeal membrane oxygenation support. Early in the pandemic, Belhadjer et al[33] published that 28% of patients at their centres required the intervention. Subsequently, Ahmed et al[99] published one of the first systematic reviews on multisystem inflammatory syndrome in children to mention that prevalence was closer to 4.4%. Our meta-analysis revealed a pool prevalence of 2.2% (95% CI 1.7%, 2.8%) [Supplementary Figure 6Sa]. This value is half as frequent likely because as more waves of COVID-19 have passed, there has been increased awareness of multisystem inflammatory syndrome in children, improvements of its management, and a decline in the severe outcomes of multisystem inflammatory syndrome in children.[27] As a result, reviews have observed a mortality of ~1–2%.[23,100,101] which is in concord with our prevalence of 2.2% (95% CI 1.7%, 2.7%) [Supplementary Figure 7Sa].

Strengths and Limitations

We evaluated 94 studies using a uniform definition of multisystem inflammatory syndrome in children thus providing a robust sample to calculate the precise prevalence of different cardiac manifestations. Additionally, we had a high proportion of articles with a low risk of bias and a high heterogeneity. Limitations include that most studies chosen involved retrospective data. And as for all meta-analyses, our findings were limited by the quality of evidence of the studies included. There was heterogeneity in how some outcomes were described and reported. For example, the definition of myocarditis was frequently based on clinical assessment and rarely on MRI. Due to differences in the definition of left ventricular systolic dysfunction and imaging strategies chosen, it is possible that not all patients with suspected myocarditis were systematically screened thus underestimating the true prevalence. Also, the use of brain natriuretic peptide or troponin in assessing myocardial involvement can be misleading as both can increase from sepsis. Additionally, each paper referenced a different range of normal depending on the institution's lab. The extent of our findings from electrocardiography is also hindered by the lack of consistent reporting from multiple groups.

Conclusions

In a meta-analysis and systematic review of multisystem inflammatory syndrome in children literature, we assessed the most common cardiac manifestations of these critically ill children. We determined a prevalence of cardiac complications from a population of 14,932 patients. Among those admitted to a critical care unit for multisystem inflammatory syndrome in children, half required vasoactive support, one-third had left ventricular systolic dysfunction, one-third had myocarditis, one quarter had electrocardiographic abnormalities, one-sixth had coronary abnormalities, and 2% required extracorporeal support with an overall mortality rate of 2%. Further research is still critical in determining the appropriate long-term follow-up and consequences, especially in those with coronary abnormalities and myocarditis which might persist for months. Appropriate cardiac re-examinations with

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specific imaging modalities may ensure the safety of children in otherwise apprehensive families as these cardiac sequelae resolve.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/S104795112300015X

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Conflicts of interest. None.

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