SYSTEMATIC REVIEW

Systemic inflammatory syndrome in COVID-19–SISCoV study: systematic review and meta-analysis

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BACKGROUND: There has been a recent upsurge in the cases of Multisystem inflammatory syndrome in children (MIS-C) associated with Coronavirus disease (COVID-19). We performed a systematic review and meta-analysis on the demographic profile, clinical characteristics, complications, management, and prognosis of this emerging novel entity.

METHODS: Using a predefined search strategy incorporating MeSH terms and keywords, all known literature databases were searched up till 10th July 2020. The review was done in accordance with PRISMA guidelines and registered in PROSPERO (CRD4202019757).

RESULTS: Of the 862 identified publications, 18 studies comprising 833 patients were included for meta-analysis. The socio-demographic profile showed male predilection ($p = 0.0085$) with no significant racial predisposition. A higher incidence of gastrointestinal symptoms (603/715, 84.3%), myocarditis (191/309, 61.8%), left ventricular dysfunction (190/422, 45.0%), pericardial (135/436, 31.0%) and neurological symptoms (138/602, 22.9%) was reported. Serological evidence of SARS-CoV-2 had higher sensitivity compared to rtPCR (291/800, 36.4% vs 495/752, 65.8%; $p < 0.001$). Coronary artery anomaly (CAA) was reported in 117/681 in 9 publications (17.2%). A total of 13 (1.6%) fatalities were reported.

CONCLUSION: Clinicians need to be vigilant in identifying the constellation of these symptoms in children with clinical or epidemiologic SARS-CoV-2 infection. Early diagnosis and treatment lead to a favorable outcome.

IMPACT: Key message

- This review analyses the demographic profile, clinical spectrum, management strategies, prognosis, and pathophysiology of MIS-C among children with SARS-CoV-2 infection.
- The stark differences of MIS-C from Kawasaki disease with respect to demographics and clinical spectrum is addressed.
- Over-reliance on rtPCR for diagnosis can miss the diagnosis of MIS-C.

New addition to existing literature

- The first systematic review and meta-analysis of published literature on MIS-C associated with COVID-19.

IMPACT:

- The article will serve to spread awareness among the clinicians regarding this emerging novel entity, so that diagnosis can be made early and management can be initiated promptly.

INTRODUCTION

Having acquired the status of the pandemic by the World Health Organisation, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has continued to wreak havoc throughout the globe, creating new records of casualties and death tolls almost daily. On the brighter side, children have reported a relatively lesser incidence of the disease. The first reported childhood infection with SARS-CoV-2 dates back to January 2020, in a family of six members with a history of travel to Wuhan, China.[1] Currently, as the numbers show, children <18 years constitute only 1.7% of the cases in the USA[2] and 2% of a large observational cohort in the UK.[3,4] Kawasaki disease shot into the limelight yet again after a cluster of cases in the pediatric age group emerged across various parts of the world. Bergamo, a place in Italy, with a very high

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burden of COVID-19 cases reported a 30 fold rise in the incidence of this rare pediatric vasculitis syndrome.[5,6] Since then, there has been a flurry of case reports, case series and observational studies over a short span of time in various parts of the world amidst this ever-growing pandemic, shedding light on yet another dimension of SARS-CoV-2, previously unheard of.

KAWASAKI-COVID-19—THE CONNECTION

Kawasaki disease (KD) represents a relatively uncommon but potentially severe pediatric vasculitis syndrome that affects multiple systems. Coronary artery abnormality (CAA) is considered to be one of the most dreaded complications. It was first described in 1967 by a Japanese pediatrician, Dr. Tomisaku Kawasaki, as acute vasculitis with mucocutaneous lymph node syndrome.[7] Bacterial infections like *Staphylococcus aureus*, *Streptococcus pyogenes* and *Yersinia pseudotuberculosis* have been implicated in the etiopathogenesis of KD. However, the causal association could not be proved based on advanced modern molecular studies.[8] A prospective study of KD in the Netherlands showed a mean annual incidence of 5.8/100,000 among children less than five years of age.[9] Chang et al. in 2013 showed a higher rate of viral isolation in 226 patients of Kawasaki disease in which enterovirus was the most common followed by adenovirus, human rhinovirus, and coronavirus.[10] The rapidly increasing reports of this multisystem inflammation with definite temporal association with SARS-COV-2 infection led researchers of United Kingdom Royal College of Pediatric and Child Health (UKRCPCH) to formulate an interim case definition, which was provisionally assigned the name of Pediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PIMS-TS).[11] To facilitate early recognition of these cases, the World Health Organization (WHO) and the Centre for Disease Control and Prevention (CDC, United States) also came up with case definitions to track the disease early in its natural course and deploy measures for early effective management. See Supplement Appendix for case definitions.[12,13]

NEED FOR THE STUDY

As the number of reports of multisystem inflammatory disease in children associated with COVID-19 keeps uprising to significant numbers, a systematic review with meta-analysis combining all the available literature of this disease entity was felt as a need to the hour to provide an in-depth understanding of the clinico-demographic profile, management strategies, and prognosis.

METHODS

Research question

To analyze the demographic profile, clinical characteristics, management strategies, prognosis, and finally assess the hypothetical pathophysiological pathways of the multisystem inflammatory syndrome in children (MIS-C) less than 21 years of age temporally associated with SARS-CoV-2 infection.

Protocol and registration

This systematic review with meta-analysis was constructed in accordance with the framework of Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) (see PRISMA checklist in Supplementary Appendix). The protocol was registered under the International Prospective Register of Systematic Reviews (PROSPERO) (CRD4202019757).

Data sources and searches

We searched the database platforms of MEDLINE, WHO COVID-19 database, LitCOVID, Google Scholar, Science direct, Web of Sciences, ProQuest, Springer library, Wiley online library, Taylor and Francis online, preprints from medRxiv and bioRxiv using the search terms "COVID 19", "SARSCOV2", "Multisystem inflammatory syndrome in children", "MIS-C", "Pediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2" and "PMIS-TS" for all the articles on 26th June 2020, which was subsequently updated with periodical searches till 10th July 2020. The search was performed by two independent reviewers using appropriately chosen relevant Medical subject headings (MeSH) terms and keywords. The complete list of search terms is provided in the Supplementary Appendix. Shadow search of the reference lists was done manually by independent reviewers at multiple points of time till 10th July 2020 to avoid missing key articles. The search was restricted to articles in the English language.

Study selection based on inclusion and exclusion criteria

The identified articles were reviewed critically based on title, date, place, sample size, authors, and the type of study by two independent reviewers (Dhar D and Samim M). All the abstracts were screened and stratified based on their type and sample size. The following inclusion criteria were taken into account for quantitative analysis of data: (1) case series with 10 or more sample size, (2) cohort studies and (3) retrospective observational studies, and (4) research letter or correspondence articles having data on patient characteristics. The articles which were excluded from quantitative analysis comprised case reports, viewpoints, perspectives, letter to the editors, case series with <10 patients, correspondence articles lacking patient data, and articles focusing only on pathogenesis. The two reviewers independently analyzed the included publications by full-text reading and screening of Supplementary Appendices. In case of discrepancy, a unanimous decision was attained through web-based conference discussions. The inter-rater reliability assessment of the included articles was guided by kappa statistics.[14] However, owing to the relative novelty of the disease entity, the excluded articles were considered in the qualitative assessment to provide valuable insights into the depths of our clinical problem.

Data extraction and quality assessment

Data extraction was performed by two reviewers, independently, from the studies included for quantitative analysis. The extracted data were segregated into demographic parameters which included sample size, sex distribution, median age, racial distribution as defined in each study; clinical parameters comprising gastrointestinal symptoms, neurological symptoms, pericardial disease, myocarditis and left ventricular dysfunction (defined by ejection fraction <50%); parameters on complications comprising requirement of vasopressor support, invasive ventilatory support, the incidence of coronary artery abnormalities and mortality; management strategies which included use of Intravenous immunoglobulin, corticosteroids and need for second-line immunomodulators; and finally, COVID-19 status defined based on rtPCR and serological evidence (IgG, IgM, and IgA).

Risk of bias

Two reviewers assessed the robustness of each of these studies by using the National Institute of Health quality assessment tool for case series and observational cohort studies. Each study was evaluated for underlying potential flaws in methodology including sources of bias like patient selection, attrition, detection, confounding factor, and causality association. Any discrepancy was sorted by group discussion between reviewers and further confirmed by a third independent reviewer. The studies were then assigned "good", "fair", and "poor" status based on the responses. In view of the relative scarcity of data, it was unanimously decided by the board of authors to maintain a low threshold of inclusion for a study.

Data synthesis and statistics

The extracted data were tabulated in Microsoft Office Excel spreadsheet based on defined variables. Categorical variables
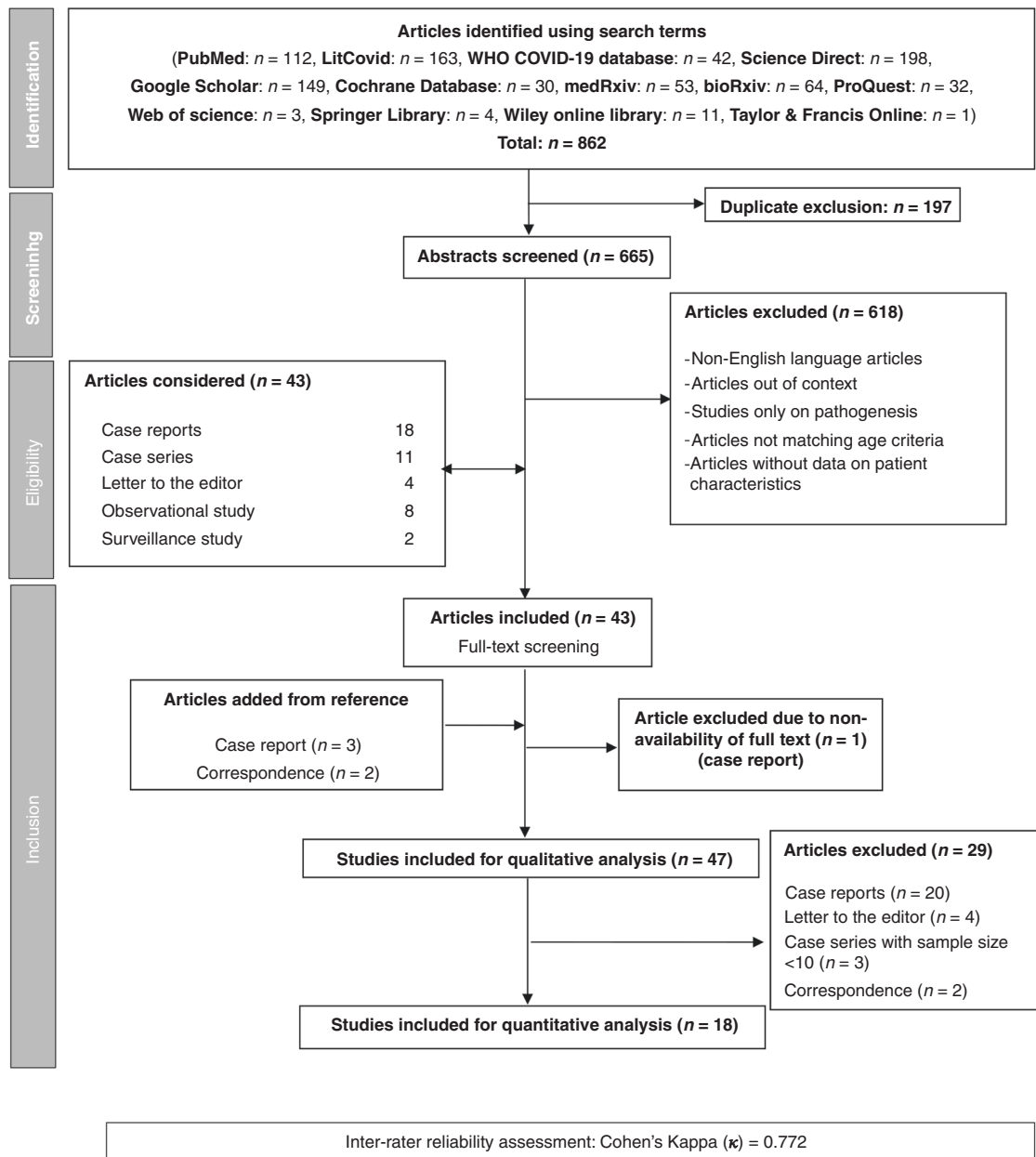
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Identification

Articles identified using search terms
(**PubMed**: $n = 112$, **LitCovid**: $n = 163$, **WHO COVID-19 database**: $n = 42$, **Science Direct**: $n = 198$,
Google Scholar: $n = 149$, **Cochrane Database**: $n = 30$, **medRxiv**: $n = 53$, **bioRxiv**: $n = 64$, **ProQuest**: $n = 32$,
Web of science: $n = 3$, **Springer Library**: $n = 4$, **Wiley online library**: $n = 11$, **Taylor & Francis Online**: $n = 1$)
Total: $n = 862$

Screeninhg

Duplicate exclusion: $n = 197$

Abstracts screened ($n = 665$)

Articles excluded ($n = 618$)

-Non-English language articles
-Articles out of context
-Studies only on pathogenesis
-Articles not matching age criteria
-Articles without data on patient
 characteristics

Eligibility

Articles considered ($n = 43$)

Case reports	18
Case series	11
Letter to the editor	4
Observational study	8
Surveillance study	2

Articles included ($n = 43$)
Full-text screening

Inclusion

Articles added from reference

Case report ($n = 3$)
Correspondence ($n = 2$)

**Article excluded due to non-availability of full text ($n = 1$)
(case report)**

Studies included for qualitative analysis ($n = 47$)

Articles excluded ($n = 29$)

Case reports ($n = 20$)
Letter to the editor ($n = 4$)
Case series with sample size <10 ($n = 3$)
Correspondence ($n = 2$)

Studies included for quantitative analysis ($n = 18$)

Inter-rater reliability assessment: Cohen's Kappa (κ) = 0.772

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram.

were represented with percentages. Median value with interquartile range was used to designate continuous variables. The included publications were subjected to heterogeneity assessment. Pooled estimates with 95% confidence intervals were calculated using random-effects (REML) model after obtaining the effect sizes for each parameter. Cochrane's Q and I^2 statistics were implemented to estimate the heterogeneity quantitatively, based on the method described by Higgins et al.[15] I^2 values of 25, 50, and 75% were tentatively assigned an as low, moderate, and high degree of heterogeneity that is not attributable to chance alone. Negative values of I^2 were considered equivalent to zero. p-values for each of the I^2 data were calculated by using χ^2 test with ($n - 1$) degrees of freedom ($n =$ number of studies) and graphically depicted using Forest plot (Fig. 1). To look for Publication bias, funnel plot was constructed. Asymmetry of Funnel plot with meta-bias analysis was carried out by applying Egger's regression test.[16] The Begg and Mazumdar's nonparametric rank correlation test was applied to assess the correlation

between the ranks of effect sizes and the ranks of their variances.[17] The heterogeneity and publication bias was computed using STATA - MP version 16.0. For descriptive analysis, the results were then plotted in the component bar diagram (refer to Fig. 2). All the variables could not be defined in every included study due to the unavailability of data. Finally, the individual independent groups were subjected to one-way ANOVA with the Bonferroni criterion.[18] The obtained p-value of <0.05 was considered statistically significant. Box and whisker plot was designed using the estimated median with their interquartile range (refer to Fig. 2). The statistical analysis was done using a custom code written in MATLAB. In-depth analysis of any association of the independent variables concerning the severity parameters like Kawasaki disease shock syndrome (KDSS), the requirement of vasopressor support, and left ventricular dysfunction with low ejection fraction cardiac failure could not be carried out due to dearth of patient-specific information in the included publications.
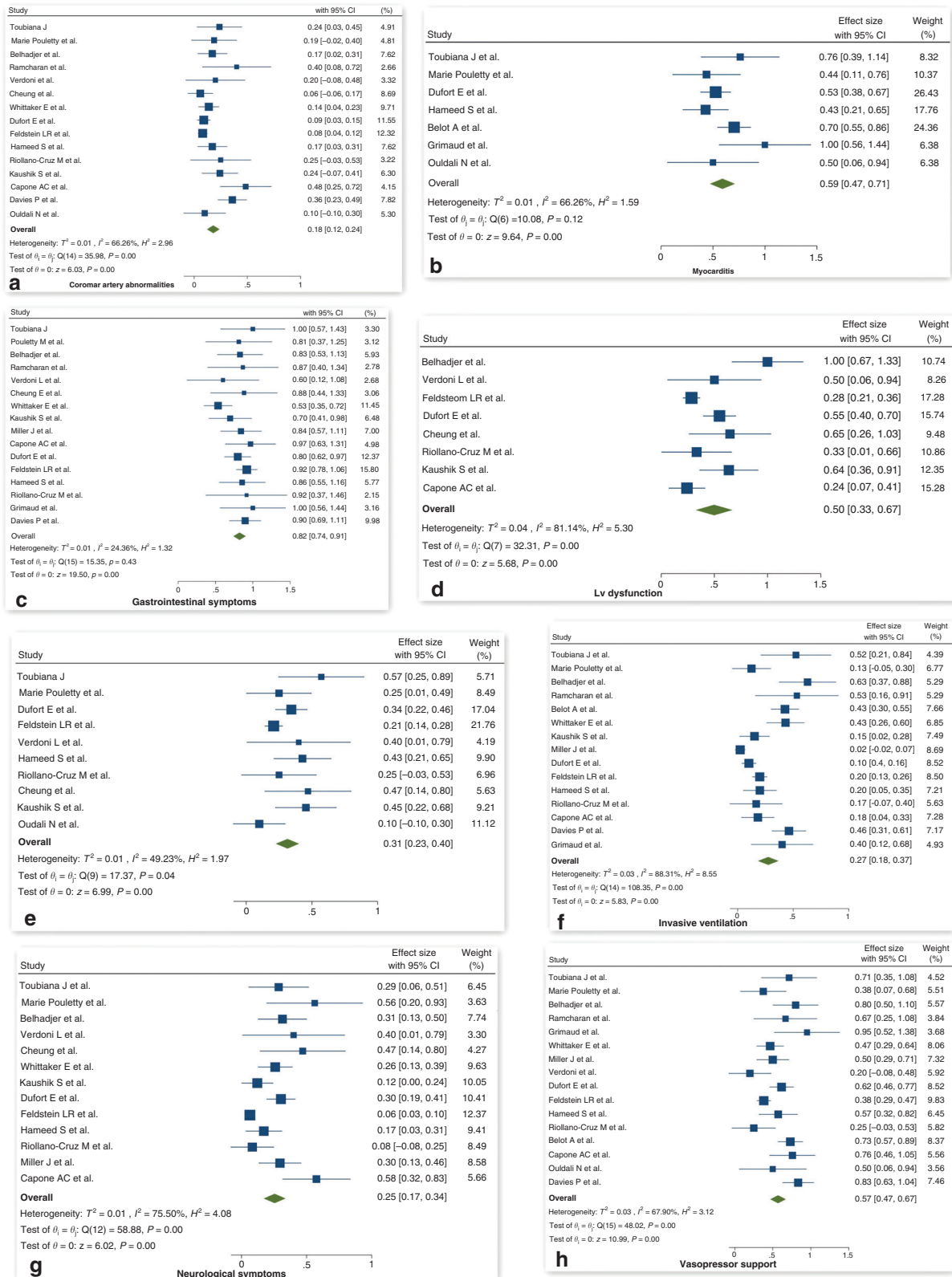
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Fig. 2 Forest plots of various clinical manifestations of the selected studies. a Coronary artery abnormalities in MIS-C across the studies represented by Forest plot. **b** Myocarditis in MIS-C across the studies represented by Forest plot. **c** Gastrointestinal symptoms in MIS-C across the studies represented by Forest plot. **d** Left ventricular dysfunction in MIS-C across the studies represented by Forest plot. **e** pericardial disease in MIS-C across the studies represented by Forest plot. **f** Need for invasive ventilator support in MIS-C across the studies represented by Forest plot. **g** Neurological symptoms in MIS-C across the studies represented by Forest plot. **h** Need for vasopressor support in MIS-C across the studies represented by Forest plot.
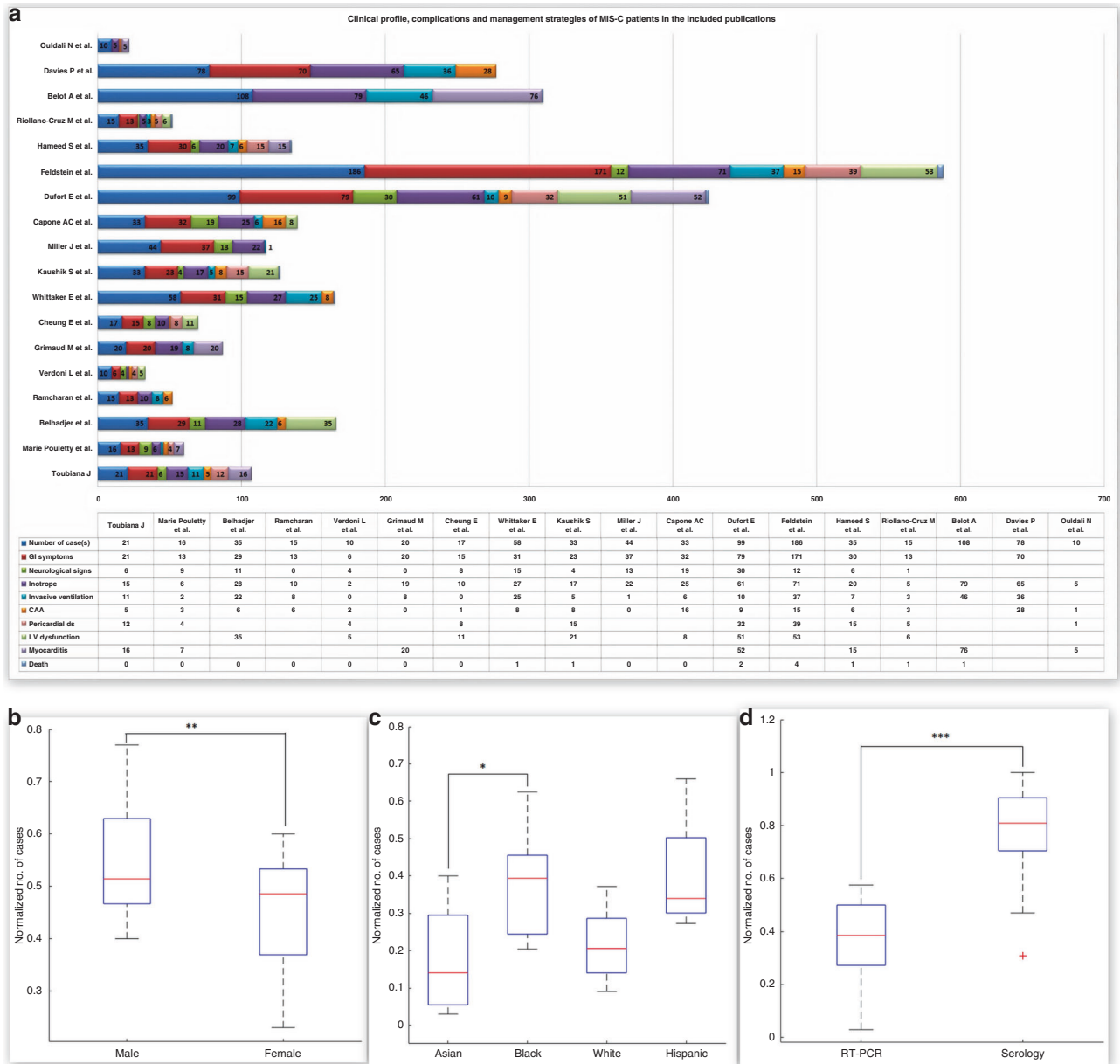
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	Toubiana J	Marie Pouletty et al.	Belhadjer et al.	Ramcharan et al.	Verdoni L et al.	Grimaud M et al.	Cheung E et al.	Whittaker E et al.	Kaushik S et al.	Miller J et al.	Capone AC et al.	Dufort E et al.	Feldstein et al.	Hameed S et al.	Riollano-Cruz M et al.	Belot A et al.	Davies P et al.	Ouldali N et al.
Number of case(s)	21	16	35	15	10	20	17	58	33	44	33	99	186	35	15	108	78	10
GI symptoms	21	13	29	13	6	20	15	31	23	37	32	79	171	30	13		70	
Neurological signs	6	9	11	0	4	0	8	15	4	13	19	30	12	6	1			
Inotrope	15	6	28	10	2	19	10	27	17	22	25	61	71	20	5	79	65	5
Invasive ventilation	11	2	22	8	0	8	0	25	5	1	6	10	37	7	3	46	36	
CAA	5	3	6	6	2	0	1	8	8	0	16	9	15	6	3		28	1
Pericardial ds	12	4			4		8		15			32	39	15	5			1
LV dysfunction			35		5		11		21		8	51	53		6			
Myocarditis	16	7				20							52		15	76		5
Death	0	0	0	0	0	0	0	1	1	0	0	2	4	1	1			

Fig. 3 Clinico-demographic characteristics of the included studies. a Component bar diagram depicting clinical profile, complications, and management strategies of MIS-C in the included studies. **b** Box and Whisker plots depicting median with interquartile range of male vs female distribution. **c** Box and Whisker plots depicting median with interquartile range of racial distribution (Blacks- including Afro-Caribbean, Asians, Whites and Hispanics). **d** Box and Whisker plots depicting median with interquartile range of the rtPCR for SARS-CoV2 infection vs serological evidence.

RESULTS

Study characteristics

Our search strategy yielded a total of 862 articles out of which 665 abstracts were screened after the exclusion of duplicated articles. 618 articles were excluded based on exclusion criteria, yielding a total of 47 publications after add-ons from reference lists. Finally, 18 articles, comprising 8 case series,[19–26] 8 observational studies (prospective and retrospective)[27–34], and 2 surveillance study[35,36] with a total of 833 patient records were considered for quantitative analysis (refer to Fig. 3). Inter-reader reliability, assessed using Cohen's κ, was found to be 0.772, which is equivalent to a moderate level of agreement.[14] Dual reviewer quality assessment for assessment of the risk of bias on the NIH scale showed all the studies to be in the "fair" category (as depicted in Table 1). Heterogeneity assessment from Cochrane's Q, I^2 statistics, p-values

for respective I^2, and Forest plot is described in Table 2, Section A and Fig. 1. The degree of asymmetry of funnel plot was assessed using Egger's and Begg's test. Egger's regression test for meta-bias analysis showed a bias coefficient of 4.40 with a 95% CI of 0.997–2.919, $p = 0.0007$ suggesting significant evidence for the presence of a small study effect. Kendall's score obtained from Begg's test was 44 with a standard error of 20.158, z of 2.13, and p of 0.0329, depicting a significant publication bias.

Clinico-demographic analysis

Patient demographics. Analysis of 833 patient records showed a sex ratio of 1.31. The median age was 8.9 ± 1.9 years. Among the various racial groups, occurrence of MIS-C in black (including Afro-Caribbean), white, Hispanic and Asian ethnicity was 198/579 (34.2%) in 11 publications;[19–28,30,31,33,35] 114/530 (21.5%) in 8

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Table 1. Quality ratings of included studies according to the National Institute of Health Quality assessment tool for case series and observational cohort studies.

Case series[a]	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Reviewer 1	Reviewer 2
Verdoni et al.[19]	Yes	Yes	NR	NA	NA	Yes	No	Yes	Yes	Fair	Fair
Cheung et al.[20]	Yes	Yes	NR	NA	NA	Yes	No	Yes	Yes	Fair	Fair
Whittaker et al.[21]	Yes	Yes	NR	NA	NA	Yes	No	Yes	Yes	Fair	Fair
Kaushik et al.[22]	Yes	Yes	NR	NA	NA	Yes	No	Yes	Yes	Fair	Fair
Miller et al.[23]	Yes	Yes	NR	NA	NA	Yes	No	Yes	Yes	Fair	Fair
Capone et al.[24]	Yes	Yes	NR	NA	NA	Yes	No	Yes	Yes	Fair	Fair
Dufort et al.[25]	Yes	Yes	NR	NA	NA	Yes	No	Yes	Yes	Fair	Fair
Hameed et al.[26]	Yes	Yes	NR	NA	NA	Yes	No	Yes	Yes	Fair	Fair

Observational cohort studies[b]	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Reviewer 1	Reviewer 2
Toubiana et al.[27]	Yes	Yes	NA	Yes	NA	No	No	NA	Yes	No	Yes	No	NA	No	Fair	Fair
Marie Pouletty et al.[28]	Yes	Yes	NA	Yes	NA	Yes	No	NA	Yes	No	Yes	No	NA	Yes	Fair	Fair
Belhadjer et al.[29]	Yes	Yes	NA	Yes	NA	Yes	No	NA	Yes	No	Yes	No	NA	NA	Fair	Fair
Ramcharan et al.[30]	Yes	Yes	NA	Yes	NA	Yes	No	NA	Yes	No	Yes	No	NA	Yes	Fair	Fair
Grimaud et al.[31]	Yes	Yes	NA	Yes	NA	Yes	Yes	NA	Yes	No	Yes	No	NA	No	Fair	Fair
Feldstein et al.[35]	Yes	Yes	NA	Yes	NA	Yes	Yes	NA	Yes	No	Yes	No	NA	No	Fair	Fair
Belot et al.[36]	Yes	Yes	NA	Yes	No	Yes	Yes	NA	Yes	No	Yes	NA	NA	No	Fair	Fair
Riollano-Cruz et al.[32]	Yes	Yes	NA	Yes	NA	Yes	Yes	NA	Yes	No	Yes	No	NA	No	Fair	Fair
Davies et al.[33]	Yes	Yes	NA	Yes	NA	Yes	Yes	NA	Yes	No	Yes	No	NA	No	Fair	Fair
Ouldali et al.[34]	Yes	Yes	NA	Yes	NA	Yes	Yes	NA	Yes	No	Yes	No	NA	NA	Fair	Fair

NR not reported, *CD* cannot determine, *NA* not applicable.

[a]Q1. Was the study question or objective clearly stated? Q2. Was the study population clearly and fully described, including a case definition? Q3. Were the cases consecutive? Q4. Were the subjects comparable? Q5. Was the intervention clearly described? Q6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants? Q7. Was the length of follow-up adequate? Q8. Were the statistical methods well-described? Q9. Were the results well-described?

[b]Q1. Was the research question or objective in this paper clearly stated? Q2. Was the study population clearly specified and defined? Q3. Was the participation rate of eligible persons at least 50%? Q4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? Q5. Was a sample size justification, power description, or variance and effect estimates provided? Q6. For the analyses in this paper, where the exposure(s) of interest measured prior to the outcome(s) being measured? Q7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? Q8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as a continuous variable)? Q9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? Q 10. Was the exposure(s) assessed more than once over time? Q 11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? Q 12. Were the outcome assessors blinded to the exposure status of participants? Q 13. Was loss to follow-up after baseline 20% or less? Q 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

articles;[20–25,32,33,35] 106/308 (34.8%) in 5 articles[22–24,32,35] and 58/349 (16.6%) in 9 publications[20–22,24,25,27,28,30,33], respectively. One-way ANOVA revealed a male predilection ($p = 0.0085$) for developing MIS-C in children with SARS-CoV-2 infection. The racial distribution pattern showed no definite predisposition. However, when compared between groups, children of the black population had a significantly greater risk when compared to Asians ($p = 0.020$). Co-morbidity profile projected overweight/obesity and chronic lung disease as the dominant pre-existing morbidity with a prevalence of 106/405 (28.6%) in 7 publications[22–25,29,32,35] and 13/101(14.9%) in 4 studies,[22,24,25,29] respectively. See Table S1 in Supplementary Appendix.

Clinical presentations and complications. In addition to the Kawasaki-like presentations, COVID-19 patients had gastrointestinal symptoms as the predominant feature that got reflected in all the included publications. Meta-analysis of 17 studies[19–32,35] estimated an association of gastrointestinal symptoms with PMIS-TS in 603/715, (84.3%) of the subjects, with low evidence of heterogeneity ($I^2 = 24.36\%$, $p = 0.43$). This was followed by myocarditis, which was reported in 7 publications[25–28,31,34,36] summing up to 191/309, (61.8%)

of children, with a moderate degree of heterogeneity ($I^2 = 37.14$, $p = 0.12$). There were 2 dedicated retrospective studies on acute myocarditis ($n = 20$) and acute heart failure ($n = 35$) by Grimaud et al.[31] and Belhadjer et al.[29], respectively. Left ventricular dysfunction (ejection fraction < 50%) was reported in 190/422 (45.0%) of the subjects encompassing 8 publications[19,20,22,24,25,29,32,35] with high heterogeneity ($I^2 = 81.14\%$, $p < 0.01$). Pericardial disease comprising echocardiographic pericardial effusion and pericarditis was reported in 135/436 (30.9% of patients across 10 studies),[19,20,22,25–28,32,34,35] meta-analysis of which showed low heterogeneity ($I^2 = 49.23\%$, $p = 0.04$). Neurological symptoms which included meningeal signs, headache, confusion, irritability was reported in 138/602 (22.9%) of patients in 13 publications,[19–29,32–36] with a high degree of heterogeneity ($I^2 = 75.50\%$, $p < 0.01$). Coronary artery abnormalities were detected in 117/681 (17.2%) of the study subjects in the 16 included articles,[19–22,24–35] with moderate heterogeneity, ($I^2 = 66.26\%$, $p < 0.01$). Acute kidney injury was reported in 40/176 (22.7%) of children with MIS-C in 3 studies.[23–25]

SARS-CoV-2 diagnostics. Reverse transcriptase-polymerase chain reaction (rtPCR) from nasopharyngeal, tracheal, and feces sample

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Table 2. Section A: Heterogeneity assessment of the studies included for meta-analysis. Section B: Qualitative analysis—Description of the studies included for meta-analysis. Section B: Qualitative analysis—Description of the studies not included in the quantitative analysis (case reports, case series with less than 10 sample size, correspondence, and letter to the editors).

Section A

Parameters	No. of studies	No. of patients (total no.)	Pooled estimates in proportion (95% of CI)	Cochrane's Q	Heterogeneity (I^2 %)	p-value for I^2
Gastrointestinal symptoms	16	603/715	0.82(0.74–0.91)	15.35	24.36	0.43
Left ventricular dysfunction	8	190/422	0.50 (0.33–0.67)	32.21	81.14	<0.01
Pericardial disease	10	135/436	0.34 (0.23–0.40)	17.37	49.23	0.04
Neurological symptoms	13	138/602	0.25 (0.17–0.34)	58.88	75.50	<0.01
Myocarditis	7	191/309	0.59 (0.47–0.71)	10.08	37.14	0.12
Need for vasopressor support	16	458/783	0.57 (0.47–0.67)	48.02	67.90	<0.01
Need for invasive ventilation	16	226/813	0.27 (0.18–0.37)	108.35	88.31	<0.01
Coronary artery anomalies	16	117/681	0.18 (0.12–0.24)	35.98	66.26	<0.01

Section B

Study	Type	Demographics	COVID-19 diagnosis	Patient characteristics	Treatment	Outcome	Place
Veena et al.[56]	Case report	6 month, female	SARS-CoV-2 rtPCR was positive	Classic	IVIg	Recovered	California, USA
				Kawasaki			
Abdul Rauf et al.[57]	Case report	5 year, male	SARS-CoV-2 rtPCR was negative (repeated twice), diagnosed on the basis of contact history	Abdominal pain, gastrointestinal symptoms, myocarditis, and shock	IVIg, aspirin, steroids, empirical antibiotics	Recovered	Kerala, India
Labé et al.[58]	Case report	3 year, male	PCR negative. CT scan suggestive	glossitis, generalized exanthema bilateral palmar edema, desquamation of the extremities was, and cervical lymphadenopathy. No respiratory complaints	Fever 8 days, IVIg	Recovered	Argenteuil, France
Dolinger et al.[59]	Case report	Known Chron's disease patient on TNF blockade	SARS-CoV-2 PCR was positive	erythematous maculopapular facial rash, abdominal pain, absence of respiratory symptoms	Fever for 5 days with Infliximab	Recovered	New York, USA
Greene et al.[60]	Case report	11 year, female	SARS-CoV-2 PCR was positive				New York USA

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Table 2. continued

Section B

| Study / Demographics / COVID-19 diagnosis / Outcome	Type	Patient characteristics	Place	Treatment
SARS-CoV-2 PCR was positive; Recovered		Fever, rash, and pharyngitis on the first visit followed by distributive shock with multi-organ dysfunction after 48 h.		Empirical antibiotics, IVIg, tocilizumab, anticoagulation
Chiu et al.[61]; 10-year-old male; SARS-CoV-2 PCR was positive; Critically ill	Case report	Prolonged fever, conjunctivitis, rash, myocarditis	Boston, USA	Inotropic support
Yozgat[62]; 3 year, girl; COVID-19 PCR negative, radiology suggestive; Recovered	Letter to the editor	Persistent fever, hypotension, mucosal lesions, and coronary echogenicity	Istanbul, Turkey	IVIg and aspirin
Deza Leon et al.[63]; 6 year, female; SARS-CoV-2 rtPCR was positive; Recovered	Letter to the editor	Loss of consciousness, fever, blanchable maculopapular rash	Michigan, USA	IVIg, aspirin
Rodriguez-Gonzalez et al.[64]; 6 month, male; SARS-CoV-2 PCR was positive; Recovered	Case report	Fever, cyanosis, cardiogenic shock, pulmonary hypertension. No other features of MIS-C	Cadiz, Spain	Inotropic support, tocilizumab, hydroxychloroquine, azithromycin, methylprednisolone
Rivera-Figueroa et al.[65]; 5-year male; SARS-CoV-2 PCR was positive; Recovered	Case report	Incomplete Kawasaki with small global pericardial effusion but no CAA	Mississipi, USA	IVIg and aspirin
Ng et al.[66]; 3 cases, SARS-CoV-2 PCR was positive in 1 patient, SARS-CoV2 negative in 2; Recovered	Case report	Abdominal pain, tachycardia, hypotension, conjunctivitis, rash	Leicester, UK	IVIg, methylprednisolone, and aspirin. 2 patients needed inotropic suppprt
Regev et al.[67]; 16-year-old male	Case report	Atypical Kawasaki disease, abdominal involvement cardiac dysfunction, small vessel vasculitis, and severe hypocomplementemia, ARDS	Israel	

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Table 2. continued

Section B

Study / Demographics / COVID-19 diagnosis / Outcome	Type	Patient	Place / characteristics / Treatment
Hutchison et al.[68] 14 years, male Negative for rtPCR, positive serological evidence Recovered	Case report	MIS-C	New York, USA presentation with headache, confusion, and irritability Corticosteroids, IVIg, anticoagulation rtPCR positive for nasopharyngeal swab Recovered	IVIg, aspirin with methylprednisolone, inotropes
Wolfe et al.[69] 2 cases, 4-year male and 3-year female Positive for rtPCR for 1 patient Recovered	Case report	Fever, rash, IVIg,	New York, USA abdominal pain, erythematous rash in both children steroid, and aspirin
Rosenzweig et al.[69] 2 cases, 16 years male and 14 years female Serology positive. Other child-rtPCR positive Recovered	Letter to the editor	1st child: flu-like illness and ITP. Other child:	New York, USA mixed AIHA Child 1–Corticosteroids Child 2—warm PRBC transfusion, rituximab
Wacker et al.[70] 1 case, 10-year old male Serology based Recovered	Case report	Fever, GI IVIg,	Switzerland symptoms, Shock, LAD, and RCA dilatation of long segment corticosteroids, Anakinra
Nguyen et al.[71] Fever, sore throat, diarrhea Parenteral antibiotics	Case report	USA 1	case, 10-year female rtPCR negative, serology positive Recovered
Vari et al.[72] Eczema, fever, abdominal pain, left Coronary dilatation IVIg and aspirin	Case report	USA 1	case, 14-year multiracial male rtPCR negative, serology positive Recovered
Bapst et al.[73] 1 case, 13 year rtPCR negative, serology positive	Case report	Fever,	Switzerland odynophagia, erythema multiforme. Other infections excluded. Echocardiography normal Recovered
Giannattasio et al.[74]	Letter to the editor	–	Naples, Italy

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Table 2. continued

Section B

Study	Type	Demographics	COVID-19 diagnosis	Outcome	Patient characteristics	Place	Treatment
		1 case, 9-year male	Serology positive	Recovered	Fever, abdominal pain, acute kidney injury, acute myocardial injury. No respiratory symptoms, no conjunctival involvement		Azithromycin, methylprednisolone. Doxycycline later due to increased QT interval
Klocperk et al.[75]	Case report	Fever, headache, abdominal pain, diffuse erythematous rash, no respiratory symptoms	rtPCR from nasopharyngeal swab positive	Recovery	Fever, case, 8-year-old	Italy 1	IVIg and corticosteroids
Saeed et al.[76]	Case report	Case 1: fever, abdominal pain, maculopapular rash, hypotensive shock Case 2: fever, diarrhea, altered consciousness, poor LV function	rtPCR positive for both cases	Recovery	cases, 10-year old girl and 13-year-old girl	Iran 2	Hydrocortisone, ascorbic acid, Thiamine, IVIg
Licciardi et al.[77]	Case report	Fever, profuse diarrhea, mucocutaneous involvement	Serology positive for both patients, negative for rtPCR	Recovered	2 cases	Italy	IVIg and corticosteroids
Chiotos et al.[78]	Case series	6 cases (5 female, 1 male) rtPCR positive 3/6 cases, Serology positive for 5/5 tested cases. 5 out of 6 were discharged. One patient remained in Pediatric ICU			Fever, diarrhea, shock, and variable presence of rash, conjunctivitis, extremity edema, and mucous membrane changes.	Philadelphia, PA	IVIg and methylprednisolone
Alexandre Belot et al.[36]	Nationwide Surveillance study as a Brief Communication	108 Kawasaki disease associated with COVID-19	All cases were either positive for SARS-CoV-2 rtPCR or based on serology		Kawasaki-like disease (61%), myocarditis (70%), MAS (23%), seritis (22%)	France	Intensive care unit admission (67%)
Temima Waltuch et al.[79]	Case series	4 children 5 years to 13 years	All were negative for rtPCR but positive on serology.	All recovered	– Overlap features of KD and TSS. 3 out of 4 had asymptomatic COVID-19 infection	New York, US	Tocilizumab was initiated in all patients to inhibit cytokine storm. Anakinra depending on the clinical context
Shelley Riphagen et al.[80]	Correspondence	8 children			IVIg, Unrelenting fever, conjunctivitis, generalized extremity pain variable rash, peripheral edema, and with marked gastrointestinal symptoms.	London, UK	

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Table 2. continued

Section B

Study	Type	Demographics	COVID-19 diagnosis	Outcome	Patient characteristics	Place	Treatment
			2/8 were tested positive for by PCR. One patient was positive for Adenovirus and Herpes virus. Rest likely from exposure	7 recovered, 1 patient died	patients, 4 out of 8 received Methylprednisolone, inotropes		IVIg all
Blondiaux et al.[81]	Case series	4 children (1 male, 3 female), median age 9.5 years	All were tested negative for rtPCR. All were positive on serology	Recovered	myocarditis with GI symptoms, required ICU admission	Paris, France	All had IVIg and corticosteroids
Dallan et al.[82]	Correspondance	3 cases: case 1—12 year, Hispanic male Case 2: 10year old mixed race boy Case 3: 10year old male	Case 1: rtPCR positive for SARS-CoV2 Case2: rtPCR negative Case3: Serology positive for SARS-CoV2	2 children recovered and case 3 was improving	odynophagia, pruritic maculopaular rash Case 2: fever, abdominal pain, odynophagia, hypotensive shock Case 3: fever, abdominal pain, MDS, mesenteric adenitis with dilated LAD and RCA	Geneva, Switzerland Fever,	Case 1: symptomatic management Case 2: hydroxychloroquine, azithromycin Case3: hydroxychloroquine, azithromycin, anakinra

KD Kawasaki disease, TSS toxic shock syndrome, MAS macrophage activation syndrome, IVIg intravenous Immunoglobulin, rtPCR real-time reverse transcriptase polymerase chain reaction, RCA right coronary artery, LAD left anterior descending artery, AIHA autoimmune hemolytic anemia, ITP immune thrombocytopenic purpura.

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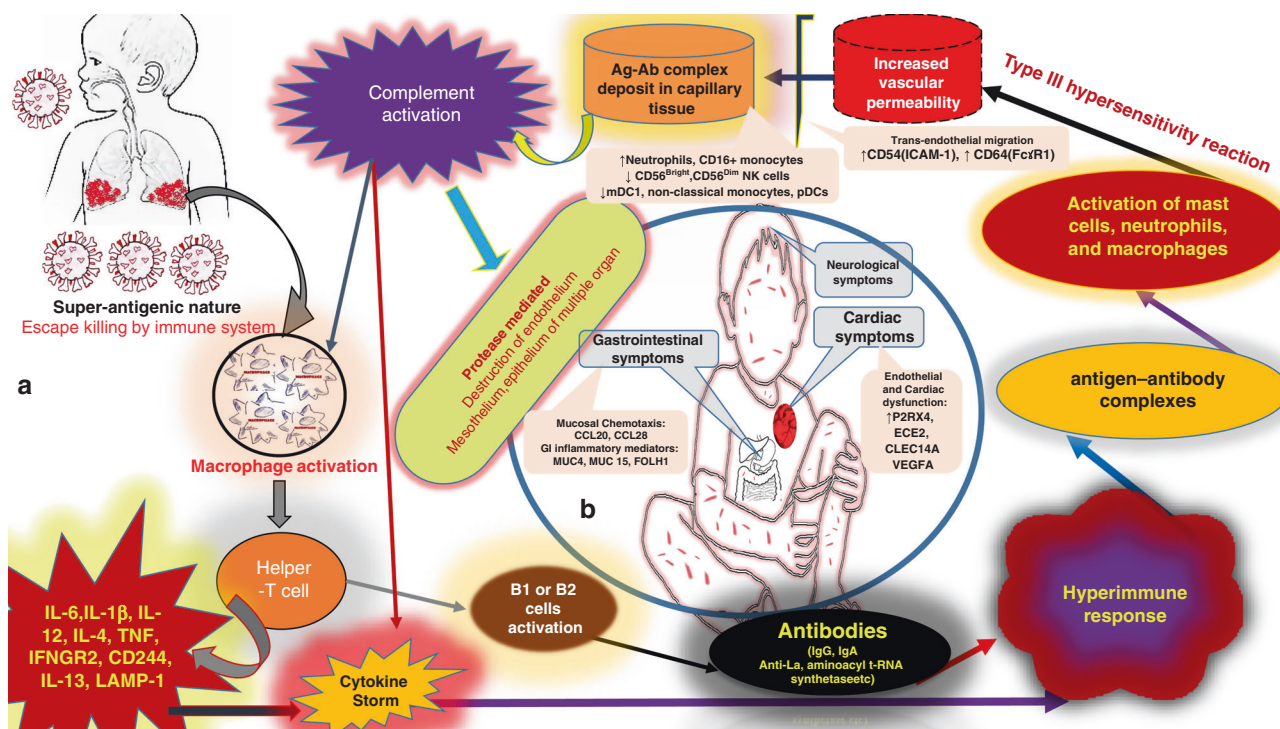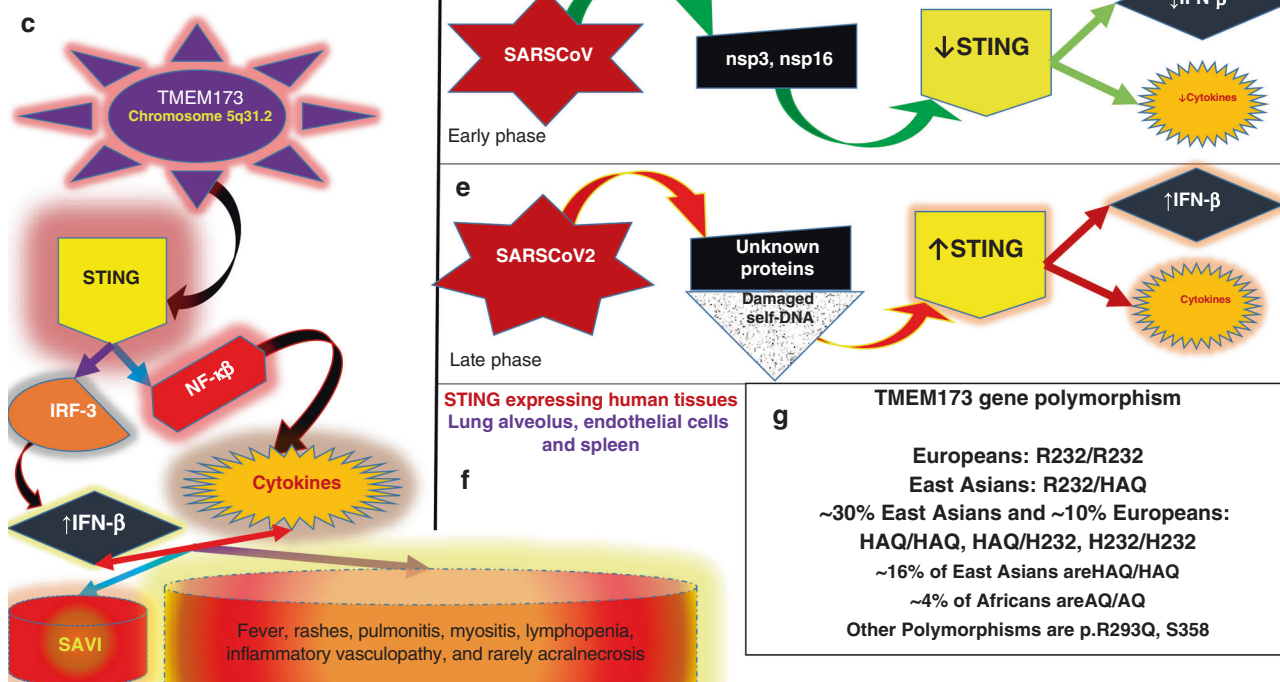
specimen showed positivity in 291/797 (36.5%) patients across 18 publications compared to serology for SARS-CoV-2 antibodies (IgG, IgA, IgM) which had a much higher positivity rate of 495/749 (66.1%) of the tested patients ($p < 0.001$). COVID-19 was diagnosed based on the epidemiological context in the absence of evidence by rtPCR and serology for SARS-CoV-2 antibodies in 154/678 study subjects in 10 publications (22.7%).

Management strategies. Meta-analysis showed vasopressor support was needed by 458/783 (61.1%) children in the study population in 16 publications,[19,21–36] with evidence of high heterogeneity ($I^2 = 67.90\%$, $p < 0.01$). Invasive ventilation support was needed by 226/813 (27.8%) study subjects in 16 articles, with a high degree of heterogeneity ($I^2 = 88.31$, $p < 0.01$). Intravenous immunoglobulin and aspirin were used as the first line of therapy in the majority of the patients in all the published literature. Corticosteroids were administered to 349/695 (50.2%) subjects.[19–25,27–29,31,33–36] Retreatment with intravenous immunoglobulin was required in 66/266 subjects (24.8%).[24,27,28,33,35] Second-line immunomodulators comprising anakinra, tocilizumab were used in 84/577 (14.6%) of the study subjects.[19,25–27,30,32]

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Fig. 4 Depicting the proposed pathogenesis of MIS-C with COVID-19 (the proposed pathogenesis is a constellation of various hypotheses referred accordingly). a The early phase of SARS-CoV-2 infection is devoid of any immune response. As the disease progresses to the late phase, owing to its superantigenic property, the virus evades destruction by phagocytes. The mass proliferation of the virus subsequently triggers dysregulated activation of macrophages and initiates a hyperimmune response mediated by helper T cells. This subsequently leads to a tremendous efflux of IL-6, IL-1ß, IL-12, LAMP-1, IFNGR2, and CD244. The humoral response, mediated by the proliferation of B1 or B2 cells leads to the overproduction of antibodies (IgG, IgA, Anti-La, aminoacyl t-RNA synthetase). The antigen-antibody complexes, thus formed mediates a Type III hypersensitivity reaction resulting in further activation of mast cells, neutrophils, macrophages, secretion of CD54 (ICAM-1), CD64 (FcγR1), CD16$^+$ monocytes, and activation of complement pathways. At the same time, there is a decrease in levels of CD56 bright and CD56 dim NK cells, pCDc, mDC1 and non-classical monocytes. The resultant inflammatory milieu causes protease-mediated endothelial, mesothelial, and epithelial inflammation with subsequent tissue damage leading to systemic symptoms. **b** Depicting the pathogenesis of the most commonly encountered organ systems involved in MIS-C. Gastrointestinal symptoms, attributed mostly to mucosal chemotaxis, are mediated by CCL20 and CCL28. This leads to elevation of the several inflammatory markers in blood like MUC4, MUC15, and FOLH1. Cardiac symptoms are attributed to inflammatory mediators of endothelial dysfunction such as P2RX4, ECE2, CLEC14A, and VEGFA. **c** Delineates the role of STING (stimulator of interferon gene) pathway. Transmembrane protein 173 (TMEM173), located in chromosome 5q31.2, a ~7-kb-long gene encodes the STING protein. STING can be activated by cytosolic DNA (damaged self-DNA) and RNA viruses leading to activation of NFκß, IRF-3, and subsequently overproduction of interferon ß and cytokines. This results in STING-associated vasculopathy with onset in infancy (SAVI) like manifestations characterized by fever, rash, pulmonitis, myositis, lymphopenia, inflammatory vasculopathy, and rarely acral necrosis. **d** Role of STING pathway in SARS-CoV pathogenesis in the early phase "During its early phase of SARS-CoV was shown to cause downregulation of the STING pathway through nsp3, nsp 16". **e** While the role of the STING pathway in the early phase of SARS-CoV-2 infections remains unknown, COVID-19, in its late phase, leads to excessive upregulation of STING protein which results in massive stimulation of NF-κß and IRF-3, thereby causing a huge surge in the levels of interferon ß and cytokines. **f** The human tissues expressing STING protein include alveoli of the lung, endothelial cells, and spleen. **g** Depicts the various polymorphisms of TMEM173 gene.

Prognosis

A total of 13 fatalities were reported among 833 study subjects (1.6%) across 8 published literature.[21,22,25,26,32,33,35,36] Sub-group analysis of all the deaths revealed massive ischemic infarctions of the brain with or without hemorrhage was the cause of death in 4/13 deaths in 4 of the articles. Out of the 4 deaths in the study by Feldstein et al., 2 were due to underlying clinical conditions (asthma and neurological co-morbidities) while one of the patients was negative with respect to both rtPCR and serology. Detailed mortality data was lacking in the rest of the studies. The study by Ramcharan et al.[30] had follow-up data on 12 of the MIS-C patients, in which all the subjects had normal CT angiographic imaging.

Review of the studies excluded from meta-analysis

Data from the case reports, letters to the editors, correspondence articles, brief communication articles, and case series with less than 10 sample sizes, which were excluded from meta-analysis, are summarized in Table 2, Section B.

DISCUSSION

Previous studies have shown a connection between Kawasaki disease and viral infections. Turnier et al. in a retrospective study showed that 192 out of 222 (86%) included patients had evidence of upper respiratory tract viral infection detected by PCR.[37] The common virus detected was enterovirus/rhinovirus. However, there was no difference in the clinical profile in the groups without viral infection. Esper et al. in 2005, in his case–control study, showed an association between "New Heaven Coronavirus" (HCoV-NH) by rtPCR and Kawasaki disease in 8 out of 11 patients compared to controls (1 out of 22) rendering a *p*-value of 0.0015.[38] Thus, perhaps the link between SARS-CoV-2 and MIS-C is not that surprising after all. Frequent clustering of simultaneous familial Kawasaki disease, as has been reported in several case reports and series, serves to reinforce this connection which we are witnessing now.[39]

Pathophysiology: the evidence so far

While the pathophysiology behind the late appearance of MIS-C associated with SARS-CoV-2 remains unproven, Rowley H has provided valuable insights, according to which, there may be the role of post-infectious IgG-mediated enhancement effect.[40] This post-infectious immune dysregulation harbors at the core of pathomechanisms of SARS-CoV-2. Virus escapade from the futile efforts of phagocytes and its superantigenic character contributes to a hyperimmune response from the helper T cells and activation

of macrophages, culminating in a potentially life-threatening cytokine storm.[41] At the same time, humoral immune response, mediated by B1 or B2 cells result in the overproduction of IL-6, IL-1ß, IL-12, LAMP-1, IFNGR2, CD244, IgG, IgA, IgM, anti-La, anti aminoacyl t-RNA synthetase, and others.[42,43] This paves the way for the formation and deposition of antigen-antibody complexes in the perivascular spaces which leads up to a massive increase in vascular permeability, activation of the complement system, chemotaxis of neutrophils, activation of CD16+ monocytes, decrease in NK cells, pCDc, mDC1, and non-classical monocytes. The resultant inflammatory milieu as a result of this type III hypersensitivity reaction draws forth secretion of CD54 (ICAM-1), CD64, and protease-mediated endothelial, mesothelial, and epithelial inflammation along with tissue damage that manifests as systemic symptoms.[44] The fact that the majority of children with MIS-C were tested negative for SARS-CoV-2 rtPCR and instead were positive on serology serves as a crude marker of this hypothesis. However, no reported worsening of illness following convalescent plasma therapy so far somewhat contradicts this view on pathogenesis. High dose Immunoglobulin prior to serological testing could well be an important confounding factor that might have led to false-negative serological test among some of the patients.[5] Computational models have also demonstrated the possibility of superantigenic property derived from the unique structural motif of SARS-CoV-2, which acts as a trigger for inflammatory cascade, climaxing to an event akin to Toxic Shock Syndrome.[45] Cheng et al. have further demonstrated stronger interaction between human T cells and the virus with a rare mutation (D838Y/N/E) in the European strain of SARS-CoV-2. The higher prevalence of gastrointestinal symptoms as noted in our review can be accounted for by significant expression of Angiotensinogen converting enzyme receptor 2 (ACE-2) in the differentiated enterocytes. The study by Lamers et al. using human small intestinal organoids (hSIO) demonstrated a high affinity of SARS-CoV and SARS-CoV-2 virus to enterocytes.[46] Gastrointestinal inflammation can be attributed to mucosal chemotaxis mediated by CCL20, CCL28, and is evident by elevation of the inflammatory markers in blood like MUC4, MUC15, and FOLH1. Similarly, myocarditis has been attributed to the affinity of SARS-CoV-2 to the ACE-2 receptors in the cardiomyocytes.[47] Pericardial involvement has been linked with either direct invasion of the SARS-CoV2 or due to proinflammatory milieu induced by the virus.[47,48] Inflammatory markers of endothelial dysfunction like P2RX4, ECE2, CLEC14A, VEGFA have been linked to cardiac involvement.[42] Refer to Fig. 4 for further details.

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Role of the STING pathway

While the early phase in the pathogenesis of SARS-CoV2-mediated MIS-C largely remains unexplored, extrapolation of knowledge from SARS-CoV pathomechanisms hints at a possible role of the STING pathway (stimulator of interferon-gamma). STING protein, encoded by TMEM173 (transmembrane protein) and expressed in alveoli, endothelial cells, and spleen can be activated by DNA debris of host cells, degraded mitochondrial DNA as well as RNA viruses. ACE-2 activation mediated by SARS-CoV-2 has also been found to upregulate this pathway. Subsequently, there is a massive release of interferon ß and cytokines resulting from activation of NF-κß and IRF-3. This leads to STING-associated vasculopathy with onset in infancy (SAVI) like manifestations[49,50] typified by fever, lung injury, vascular inflammation, myositis, dermatologic manifestations, acral necrosis, and arterial aneurysms. Polymorphisms of TMEM173 among various racial subgroups perhaps account for the variations in clinical presentation and severity of the disease manifestations.

Kawasaki-MIS-C: the mismatch

While the connection between the two disease entities is still hypothetical, the differences albeit, are glaring. The median age of children in this review, 8.9 ± 1.9 years, is quite different from the typical age group in which Kawasaki disease usually manifests. The 5-year National surveillance study of the Netherlands by Take et al. has shown median age of 2.4 years.[9] The data from all over the globe have suggested an overwhelming predominance of the disease among the under-fives.[51–55] In contrary to the widespread prevalence of Kawasaki disease in the Asian continent, the prevalence of MIS-C has not been that striking even though the number of cases of COVID-19 has also been quite significant in this part of the globe. In fact, in this review, the blacks had a significantly greater incidence compared to the Asians. A majority of the reported cases meeting the criteria of MIS-C didn't meet the American Heart Association (AHA) criteria for complete Kawasaki disease, another pointer of mismatch between these two clinical conditions. The frequent occurrences of gastrointestinal symptoms, neurological features, myocarditis, left ventricular dysfunction with a relative sparing effect on renal functions as evidenced from this review throw striking daylight on the genuine differences in clinical presentations of these two clinical entities.

Key aspects of the review

From the evidence gathered from this systematic review and meta-analysis, we suggest this unique combination of Kawasaki-like illness with a definite consortium with gastrointestinal symptoms, neurologic manifestations including meningeal signs, myocarditis with or without left ventricular dysfunction, and symptomatic or echocardiographic pericardial involvement, be assigned a different nosology called Systemic inflammatory syndrome in COVID-19 or SISCoV. This will enable faster characterization of this clinical entity, the inclusion of relevant investigations, and appropriate evidence-based management thereby preventing fatalities.

Research gaps

The wide geographic distribution of the studies, observational design, and lack of follow-up are some of the key factors reducing the robustness of this review. As the objectives differed among various studies, the data representation was less adequate in some of the variables. A dearth of detailed patient-wise distribution in many of the published articles including their Supplementary Appendices was a significant hindrance to the use of advanced statistical analysis. The natural course of the coronary artery abnormalities remains an unexplored frontier which will only be revealed in due course of time through follow-up studies.

CONCLUSION

With the emergence and subsequent uprise of MIS-C, there needs to be strict vigilance among children presenting to the emergency department or Pediatric Intensive Care Unit. A high index of suspicion should be maintained in patients reporting gastrointestinal symptoms, evidence of circulatory failure, central nervous system symptoms, left ventricular dysfunction, and symptomatic or echocardiographic pericardial effusion even if rtPCR for SARS-CoV-2 is negative. It is important to abide by the guidelines for diagnosis and management laid by WHO, UKRCPCH, and CDC. Early management with intravenous immunoglobulins and aspirin has been found to have a favorable outcome. Certain groups of patients require retreatment with IVIg, while others require initiation of second-line immunomodulation. A baseline evaluation for coronary artery abnormalities forms an essential component for future surveillance. Fatalities due to MIS-C are usually rare especially when suspected early, diagnosed promptly, investigated rationally, and treated methodically.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the formulation of this study. Authors D.D., T.D., M.M.S, H.P., A.C., N.P., S.M.S, P.K., A.P., and A.G. were involved in conceptualization. Review of literature review, data extraction, and data synthesis were done by D.D., M.M.S, N.P., S.R., A.G., and A.P. Quality assessment of the studies were done by D.D., M.M.S, H.P, N.P., C.S.R, and M.K. Statistical analyses were carried out by T.D. and A.C. Drafting, and framing of images was done by D.D. and M.M.S. Analysis and interpretation of results were carried out by D.D., M.M.S, T.D., H.P, C.S.R, M.K., and S.R. All authors played an active role in the revision of the manuscript. Final approval was obtained from all authors prior to submission of the manuscript.

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