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COVID-19 Associated Multisystem Inflammatory Syndrome: A Systematic Review and Meta-analysis

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ABSTRACT

The prevalence of multisystem inflammatory syndrome in children (MIS-C) has increased since the coronavirus disease 2019 (COVID-19) pandemic started. This study was aimed to describe clinical manifestation and outcomes of MIS-C associated with COVID-19.

This systematic review and meta-analysis were conducted on all available literature until July 3rd, 2020. The screening was done by using the following keywords: ("novel coronavirus" Or COVID-19 or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or coronavirus) and ("MIS-C" or "multisystem inflammatory" or Kawasaki). Data on gender, ethnicity, clinical presentations, need for mechanical ventilation or admission to intensive care unit (ICU), imaging, cardiac complications, and COVID-19 laboratory results were extracted to measure the pooled estimates.

Out of 314 found articles, 16 articles with a total of 600 patients were included in the study, the most common presentation was fever (97%), followed by gastrointestinal symptoms (80%), and skin rashes (60%) as well as shock (55%), conjunctivitis (54%), and respiratory symptoms (39%). Less common presentations were neurologic problems (33%), and skin desquamation (30%), MIS-C was slightly more prevalent in males (53.7%) compared to females (46.3%).

The findings of this meta-analysis on current evidence found that the common clinical presentations of COVID-19 associated MIS-C include a combination of fever and mucocutaneous involvements, similar to atypical Kawasaki disease, and multiple organ dysfunction. Due to the relatively higher morbidity and mortality rate, it is very important to diagnose this condition promptly.

Keywords: Coronavirus; Kawasaki disease; Multisystem inflammatory syndrome in children; Severe acute respiratory syndrome coronavirus 2

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INTRODUCTION

An outbreak of a newly emerging infectious disease was reported in Wuhan city, China in the last days of

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2019. The disease was caused by a novel beta coronavirus called 2019-nCoV.[1] Later the name was changed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which caused the coronavirus disease 2019 (COVID-19).[2]

Most affected individuals were adults. The most common presentations were fever, dry cough, and fatigue. Other less common symptoms were nausea, vomiting, diarrhea, sputum production, headache, seizure, etc.[3-6] Few cases of COVID-19 were reported in childhood age, with milder presentations compared to adults.[2] Children with the critical disease were younger than one-year-old or had preexisting conditions. In the first months of 2020, several reports of a Kawasaki-like disease were published in some populations.[7] Clinical evidence suggested that this disorder was associated with SARS-CoV-2. In May 2020, the center for disease control and prevention (CDC) of the United State named this condition as COVID-19 associated multisystem inflammatory syndrome (MIS-C).

Kawasaki disease is a childhood-onset inflammatory syndrome. If Kawasaki disease is not treated with intravenous immune globulin (IVIG), it can cause coronary artery abnormalities in up to 25 percent of the patients. The exact etiology of Kawasaki disease is unknown, but there is some evidence that particular infectious agents can trigger this condition, especially in genetically susceptible individuals.[8] Similarly, the exact mechanism of COVID-19 associated MIS-C is unknown. Possible mechanisms for multiple organ involvement might include direct viral insult, a consequence of hypoxia-related to lung injury, or due to hyper inflammatory state and high levels of cytokines.[9] Furthermore, data are scarce on different presentations of MIS-C. In this study, we aimed to describe the clinical manifestations of a multisystem inflammatory syndrome associated with COVID-19.

MATERIALS AND METHODS

Search Strategy

Databases including Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science (ISI), EMBASE, PubMed, and Google Scholar were searched for published relevant papers in the past year until July 3rd, 2020. The screening was performed by evaluating titles and abstracts. Screened papers were imported to EndNote X9 citation manager to exclude duplicates. The search terms that were used to include the relevant studies were (“novel coronavirus” or COVID-19 or SARS-CoV-2 or coronavirus) and ("MIS-C" or "multisystem inflammatory" or Kawasaki)

Inclusion and Exclusion Criteria

All articles, regardless of the design, study level (levels 1-4), and language, that assessed the clinical manifestations of COVID-19 associated MIS-C were included. Abstracts of non-English articles were translated into the English language and were included in the study. Papers that included adults or lacked epidemiological information were excluded.

Data Extraction and Statistical Analysis

Two authors (N.M. and A.B.) performed all stages of the meta-analysis independently. Clinical manifestations including signs, symptoms, laboratory data, and imaging results were extracted and were used for the measurement of pooled estimates (Table 1-3). Single-arm Meta-analysis was performed using the comprehensive meta-analysis version 3 software.[10] This analysis took study effects into account and considered the studies as single groups with events and sample sizes, and the results were calculated by a random-effect method. For analysis of intensive care unit (ICU) admission rates, we excluded data from studies that were only on the pediatric intensive care unit (PICU) patients. Data were presented; using a 95% confidence interval, while the I^2 statistic and Cochran’s Q test were used to assess statistical heterogeneity. Cochran’s Q is computed by summing the squared deviations of each study's estimate from the overall estimate. Forest plots were used to illustrate the prevalence with a 95% confidence interval. *p-values* were obtained by comparing the statistic based on χ^2 distribution with k-1 degrees of freedom (k is the number of studies).

Statistical tests for heterogeneity were performed to determine if the included studies had similar rates of clinical manifestations. *p-value*s smaller than 0.05 in Cochran’s Q test would reject the null hypothesis that there is no heterogeneity between studies. Moreover, I^2 revealed that the extent to which the studies varied was due to heterogeneity rather than chance or sampling error. Following the rule of thumb, I^2 values larger than 40% were considered as substantial heterogeneity. Since heterogeneity was present in all fields, a random-effects model was used to conduct the meta-analysis.

Table 1. Characteristics of the included studies

First Author, Publication Year	Country	Study type	Number of patients	Sex		Race/ethnicity/ancestry				Comorbidities	
				male	female	White	Black	Asian	Hispanic	Asthma	Overweight (BMI > 25)
Eva W. Cheung et al, 2020	U.S.A	Letter	17	8	9	8	4	1			
Kathleen Chiotos et al, 2020	U.S.A	case series	6	1	5	2	2				0
Julie Toubiana et al, 2020	France	prospective observational	21	9	12						
Tristan Ramcharan et al, 2020	U.K	retrospective observational	15	11	4						
Marion Grimaud et al, 2020	France	case series	20	10	10						
Marie Pouletty et al, 2020	France	cohort	16	8	8					2	4
Zahra Belhadjer et al, 2020	France	case series	35	18	17					3	6
Jonathan Miller et al, 2020	U.S.A	cohort	44	20	24	9	9		15		16
Christine A. Capone et al, 2020	U.S.A	cohort	33	20	13	3	8	3		5	15
Shubhi Kaushik et al, 2020	U.S.A	cohort	33	20	13	3	13	1	15	5	2
Eléonore Blondiaux et al, 2020	France	case series	4	1	3						1
Elizabeth Whittaker et al, 2020	England	case series	58	25	33	12	22	18			
Lucio Verdoni et al, 2020	Italy	cohort	10	7	3						
L.R. Feldstein et al, 2020	U.S.A	case series	186	115	71	35	46		57		45/153
Elizabeth M. Dufort et al, 2020	U.S.A	case series	99	53	46	29/78	31/78	4/78			29
Khuen Foong Ng et al, 2020	U.K	case series	3	2	1		2	1			1

Table 2. Extracted variables from the included studies

First Author, Publication Year	Clinical description													
	Fever	Gastrointestinal*	Skin rash	desquamation	Conjunctivitis	Cheilitis	Lymphadenopathy	Edema	Shock**	Neurologic***	Respiratory****	Myalgia	Arthralgia	Acute kidney injury
Eva W. Cheung et al, 2020	17	15	12	3	11	9	6		13	8	7	6		
Kathleen Chiotos et al, 2020	6	6	2		2	3	0	2	6	1	4			4
Julie Toubiana et al, 2020	21		16	4	17	16	12						2	
Tristan Ramcharan et al, 2020	15	13										4		
Marion Grimaud et al, 2020	20	20	10		6	5	2							
Marie Pouletty et al, 2020	16	13	13		15	14	6	11		9	2		1	
Zahra Belhadjer et al, 2020	35	29		20			21			11	23			
Jonathan Miller et al., 2020	44	37	31		23				22	13	11			7
Christine A. Capone et al, 2020	33	32							25	19	17			23
Shubhi Kaushik et al, 2020	31	23	14		12					4	11			
Eléonore Blondiaux et al, 2020	4		4		2		1							
Elizabeth Whittaker et al, 2020	58	31	30		26		9	9	29	15	12			13
Lucio Verdoni et al, 2020	10	6			7	6	1			2				
L.R. Feldstein et al, 2020	186		110		103		18							
Elizabeth M. Dufort et al, 2020	99	79	59		55		6	9	10	30	40	17	4	10
Khuen Foong Ng et al, 2020	3	3	2		3		2				2			

*abdominal pain, vomiting, and/or diarrhea; **requiring vasopressors; *** headache, stiff neck, vision change; ****cough, dyspnea

Table 3. Extraction of variables from included studies

First Author, Publication Year	Ventilation		Admission to ICU	History of COVID-19 sick contact	Echocardiography					Chest radiography or computed tomography abnormalities*	Positive microbiological findings	
	Non-invasive	Invasive			Normal Left ventricular function	Decreased Left ventricular function	myocarditis	Coronary dilation/aneurysm	Pericardial effusion		Nasopharyngeal SARS-CoV-2 RT-PCR	Positive serum serology
Eva W. Cheung et al, 2020		0	15	11	6	11			8		8	9
Kathleen Chiotos et al, 2020	2	3		0	2	4		1		5	3	5/5
Julie Toubiana et al, 2020		11	17		5	16	16	5	12	8in18	8	19
Tristan Ramcharan et al, 2020		4	10	3	3	12		7	8	7in14	2	12
Marion Grimaud et al, 2020	11	8										
Marie Pouletty et al, 2020			7	12			7	3		5	9in16	7/8
Zahra Belhadjer et al, 2020	11	22						6				
Jonathan Miller et al, 2020											15	31
Christine A. Capone et al, 2020	17		26		14	19					9/33	6/30
Shubhi Kaushik et al, 2020	12	5		5	11/32	21/32			15/32	11	11	27
Eléonore Blondiaux et al, 2020		1			1	3		0	1	3	0	4
Elizabeth Whittaker et al, 2020		25						8			15	40/46
Lucio Verdoni et al, 2020				5	5	5		2	4	5	2	8
L.R. Feldstein et al, 2020			148								73	85
Elizabeth M. Dufort et al, 2020	23	14	79				52	9			50/98	76/77
Khuen Foong Ng et al, 2020								3	2	3	1	3

*Ground glass opacity, interstitial abnormalities, and local patchy shadowing

Table 4. Quality assessment of the included studies based on NIH study quality assessment tools for observational cohort and cross-sectional studies

	Julie Toubiana et al, 2020	Tristan Ramcharan et al, 2020	Marie Pouletty et al, 2020	Jonathan Miller et al, 2020	Christine A. Capone et al, 2020	Shubhi Kaushik et al, 2020	Lucio Verdoni et al, 2020
1. Clearly stated research question or objective	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Clearly specified study population	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. The participation rate of eligible persons equal tohigher than 50%	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. All the subjects were selected or recruited from the same or similar populations (including the same period)? Use of prespecified inclusion and exclusion criteria to be applied uniformly to all participants	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Stating justification for sample size, power description, or variance and effect estimates	No	No	No	No	No	No	No
6. The exposure(s) of interest was measured before the measured outcome(s)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Sufficient timeframe sufficient to reasonably expect to see the possible association between exposure and outcome	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Examining the different levels of the exposures that that can vary in amount or level, as related to the outcome (e.g., categories of exposure, or exposure measured as a continuous variable)	NA	NA	NA	NA	NA	NA	NA
9. Clear, valid, and reliable exposure measures (independent variables) consistently across all study participants	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. More than a one-time assessment of the exposure(s)	NA	NA	NA	NA	NA	NA	NA
11. Clearly defined, validated, reliable outcome measures (dependent variables) consistently across all study participants	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Blinded outcome assessors blinded to the exposure status of participants	NA	NA	NA	NA	NA	NA	NA
13. Less than 20% loss to follow-	Yes	Yes	Yes	Yes	Yes	Yes	Yes

up after baseline							
14. Statistical adjustment for the key potential confounding variables in the assessment of the relationship between exposure(s) and outcome(s)?	NA	NA	NA	NA	NA	NA	NA
Quality Rating (Good, Fair, or Poor)	Good	Good	Good	Good	Good	Good	Good

CD, cannot determine; NA, not applicable; NR, not reported

Table 5. Quality assessment; using NIH study quality assessment tools for case series studies

	Kathleen Chiotos et al, 2020	Marion Grimaud et al, 2020	Zahra Belhadjer et al, 2020	Eléonore Blondiaux et al, 2020	Elizabeth Whittaker et al, 2020	L.R. Feldstein et al, 2020	Elizabeth M.Dufort et al, 2020	KhuenFoong Ng et al, 2020
1. Clear study question or objective	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Clear description of the study population, including a case definition?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Consecutive cases	NR	NR	NR	NR	NR	NR	NR	NR
4. Comparability of the subjects	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Clear description of the intervention	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Clearly defined, validated and reliable outcome measures implemented consistently across all study participants	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Adequate length of follow-up	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Good description of the statistical methods	NA	Yes	Yes	NA	Yes	Yes	Yes	NA
9. Good description of results	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Quality Rating (Good, Fair, or Poor)	Good	Good	Good	Good	Good	Good	Good	Good

CD, cannot determine; NA, not applicable; NR, not reported

Methodological Quality Assessment

The methodology quality of the studies was assessed by two reviewers independently; using the NIH study quality assessment tools (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) for cohort, cross-sectional, and observational studies as well as case series. Disagreements were resolved by a third reviewer or consensus-based discussion (Tables 4 and 5).

RESULTS

Study Characteristics

Out of 314 papers found on July 3rd, 2020, 16 papers were included for data extraction (Figure 1).

Seven studies were conducted in the U.S.A,[9,11-16] five studies in France[17-21], three studies in the U.K[22-24], and one study in Italy (Table 1).[7] All the included papers were published in English. Overall, these studies included 600 patients and comprised of 328 males and 272 females.

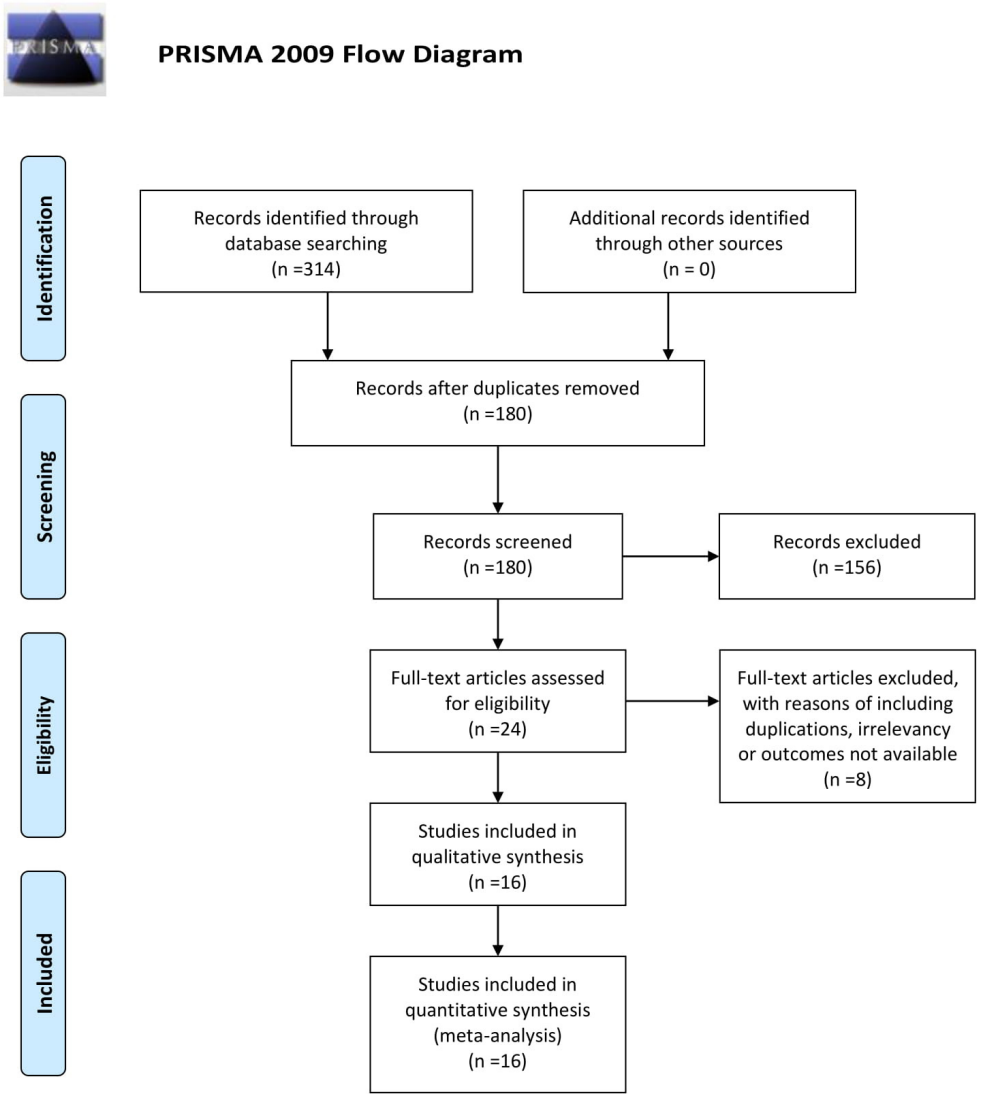

Figure 1. PRISMA flow diagram

Sex, Race and Ethnicity Distribution in Multisystem Inflammatory Syndrome Associated with Coronavirus Disease 2019

The random-effects model on the 16 included studies indicated that 53.7% (95% CI, 49%-59%) of the patients were male (Table 6A), and 46.3% (95% CI, 41%-51%) were female (Table 6B). Cochran's *Q* test showed 18% heterogeneity among the included studies, which was not significant (Q-value=18, $p=0.24$, I^2=18).

The Random-effects model revealed that after

inclusion of various number of studies that reported ethnicity separately, 23% of the patients were White (95% CI, 15%-32%). There was a 69% heterogeneity, which was significant (Q-value=22, *p=0.002*, I^2=69)(Table 6C). Thirty-one percent of the patients were Black (95% CI, 25%-38%) with 39.86% heterogeneity, which was not significant (Q-value=13, *p=0.10*, I^2=39.86)(Table 6D). Ten percent of the patients were Asian (95% CI, 4%-26%) with 76% heterogeneity which was significant (Q-value=21, *p=0.001*, I^2=76) (Table 6E). Thirty-four percent of patients were Hispanic (95% CI, 27%-42%) with 27% heterogeneity, which was not significant (Q-value=2, *p=0.25*, I^2=27) (Table 6F).

Prevalence of Clinical Manifestations in COVID-19 Associated MSI-C Based on the Random-effects Model

After including 10 studies, 28% (95% CI, 21%-36%) of the patients were overweight. Cochran's *Q* test showed 42% heterogeneity among the included studies, which was not significant (Q-value=15, *p=0.079*, I^2=42) (Table 7A).

After including 4 studies, 13% (95% CI, 8%-20%) of the patients had asthma. Cochran's *Q* test showed 0% heterogeneity among studies, which was not significant (Q-value=0.87, *p=0.83*, I^2=0)(Table 7B).

Table 6. Forest plots of Sex, Race, and ethnicity distribution in coronavirus disease 2019 (COVID-19) associated multisystem inflammatory syndrome; using the binary random-effects method. Blue squares represent an individual study's effect; the square's size varies to reflect a particular study's weight. The blue horizontal lines represent CI's. The red diamond represents the overall or summary. A: Male sex ratio in 16 studies. B: Female sex ratio in 16 studies. C: White ethnicity ratio in 8 studies. D: Black ethnicity ratio in 9 studies. E: Asian ethnicity ratio in 6 studies. F: Hispanic ethnicity ratio in 3 studies

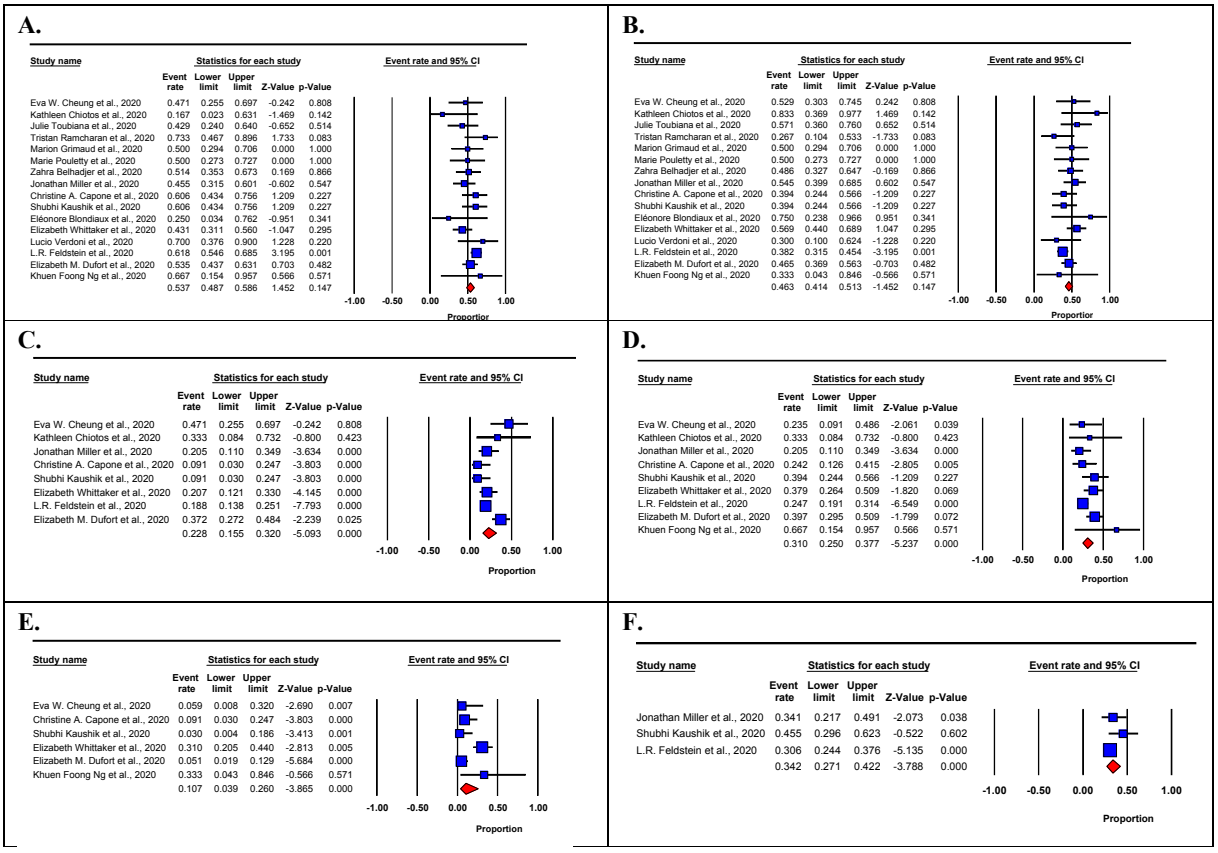

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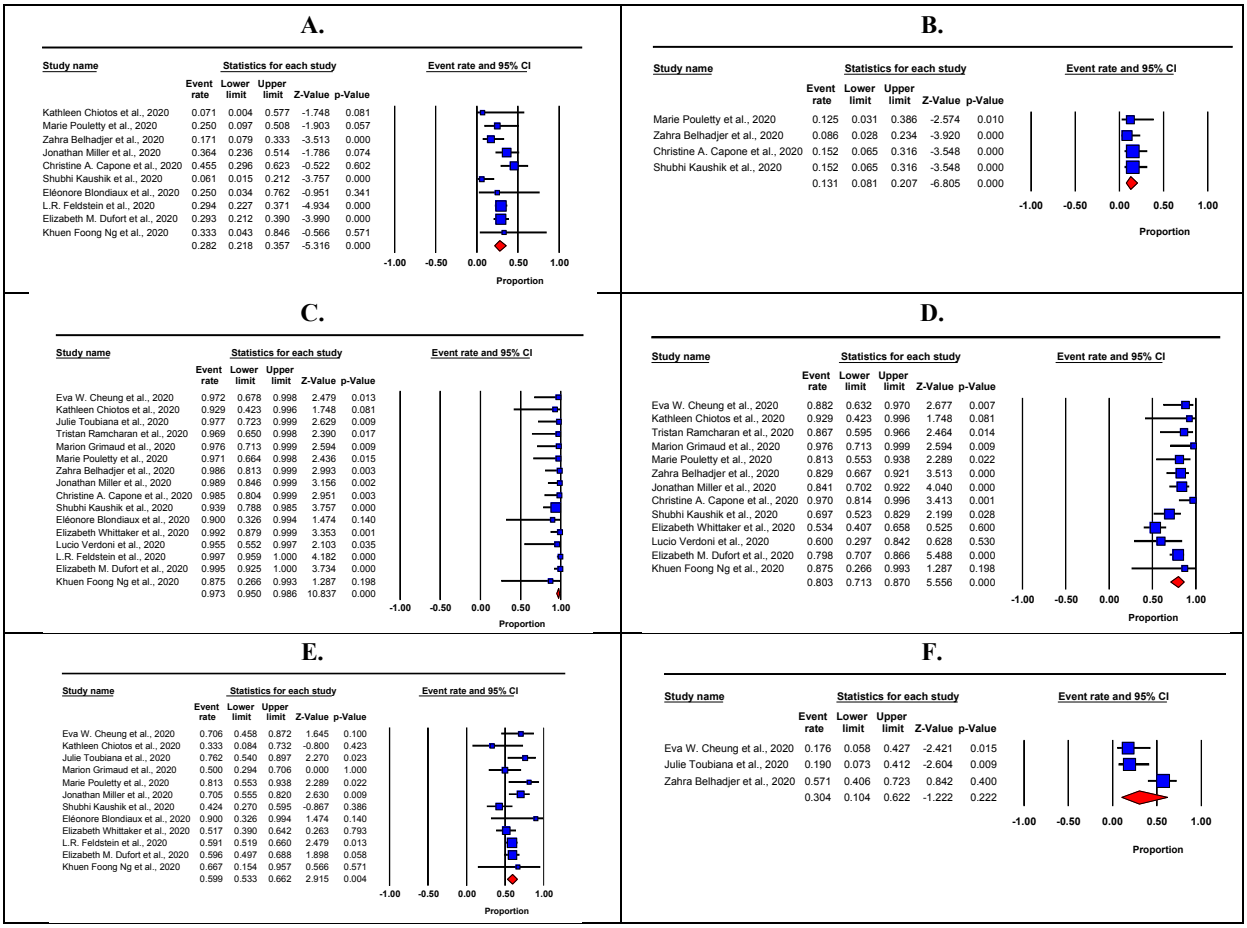
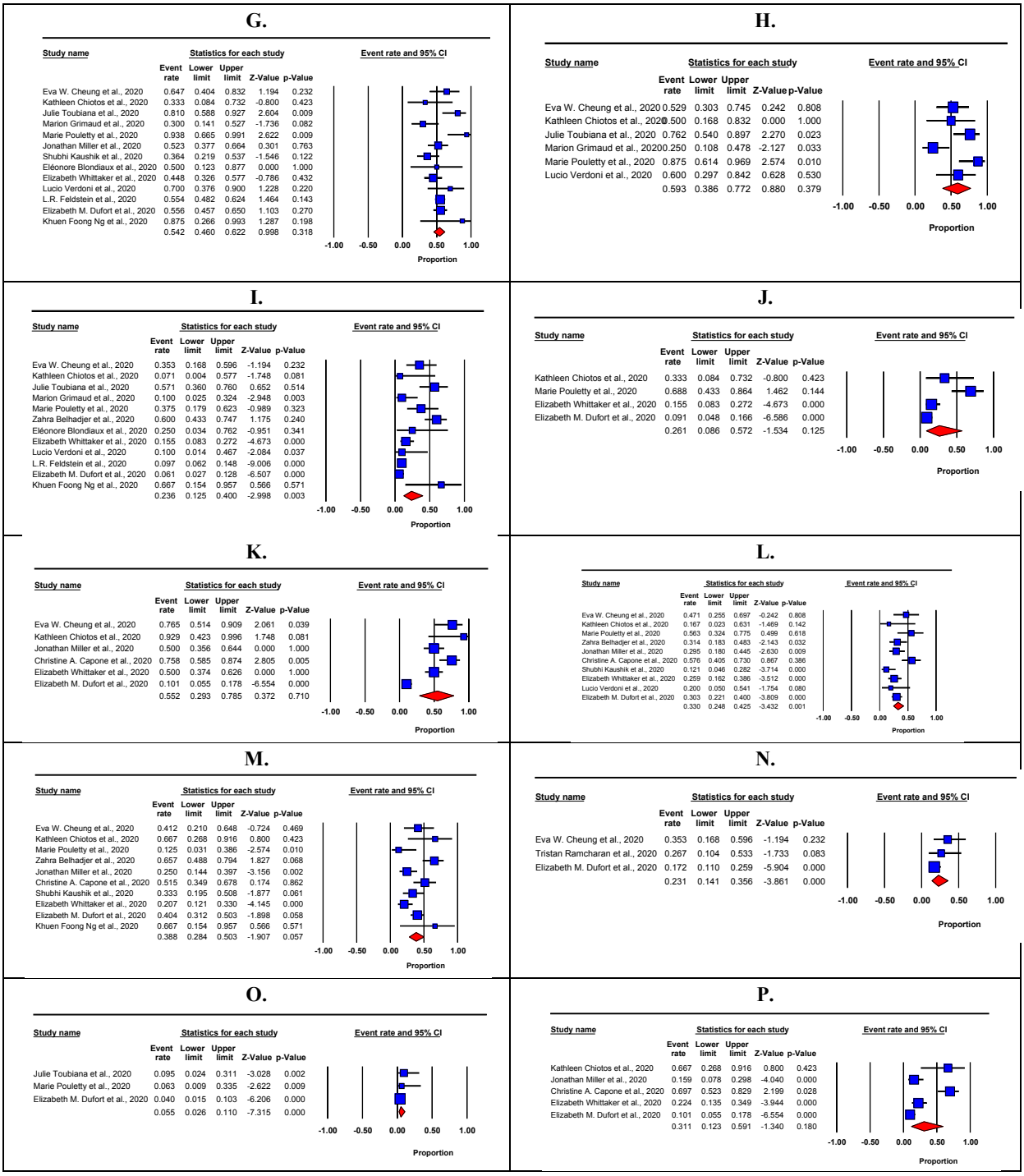
Table 7. Forest plots of clinical manifestations of coronavirus disease 2019 (COVID-19); associated multisystem inflammatory syndrome; using the binary random-effects method. Blue squares represent an individual study's effect; the square's size varies to reflect a particular study's weight. The blue horizontal lines represent CI's. The red diamond represents the overall or summary. A: Obesity prevalence in 10 studies. B: Asthma prevalence in 4 studies. C: Fever prevalence in 16 studies. D: Gastrointestinal symptoms prevalence in 13 studies. E: Skin rash prevalence in 12 studies. F: Skin desquamation prevalence in 3 studies. G: Conjunctivitis prevalence in 13 studies. H: Cheilitis prevalence in 6 studies. I: Lymphadenopathy prevalence in 12 studies. J: Edema prevalence in 4 studies. K: Shock prevalence in 6 studies. L: Neurologic symptoms prevalence in 10 studies. M: Respiratory symptoms prevalence in 10 studies. N: Myalgia prevalence in 3 studies. O: Arthralgia prevalence in 3 studies. P: Acute kidney injury prevalence in 5 studies





After including 16 studies, 97.3% (95% CI, 95%-99%) of the patients had a fever. Cochran's *Q* test showed 0% heterogeneity among studies, which was not significant (Q-value=9.72, *p=0.84*, I^2=0) (Table 7C).

After including 13 studies, 80% (95% CI, 71%-87%) of the patients had gastrointestinal symptoms, i.e. abdominal pain, vomiting, or diarrhea. Cochran's *Q* test

showed 63% heterogeneity among studies, which was significant (Q-value=32, *p=0.001*, I^2=63) (Table 7D).

After including 12 studies, 59.9% (95% CI, 53%-66%) of the patients had a skin rash. Cochran's *Q* test showed 36% heterogeneity among studies, which was not significant (Q-value=17, *p=0.10*, I^2=36) (Table 7E).

After including 3 studies, 30% (95% CI, 10%-62%) of the patients had skin desquamation. Cochran's *Q* test showed 81% heterogeneity among studies, which was significant (Q-value=10.8, *p=0.004*, I^2=81) (Table 7F).

After including 13 studies, 54% (95% CI, 46%-62%) of the patients had conjunctivitis. Cochran's *Q* test showed 54% heterogeneity among studies, which was significant (Q-value=26.0, *p=0.01*, I^2=54) (Table 7G).

After including 6 studies, 59% (95% CI, 38.6%-77.2%) of the patients had cheilitis. Cochran's *Q* test showed 67% heterogeneity among studies, which was significant (Q-value=15.21, *p=0.009*, I^2=67) (Table 7H).

After including 12 studies, 23.6% (95% CI, 12.5%-40%) of the patients had lymphadenopathy. Cochran's *Q* test showed 85% heterogeneity among studies, which was significant (Q-value=74.24, *p=<0.001*, I^2=85) (Table 7I).

After including 4 studies, 26% (95% CI, 8.6%-57%) of the patients had edema. Cochran's *Q* test showed 87.7% heterogeneity among studies, which was significant (Q-value=24, *p<0.001*, I^2=87.7) (Table 7J).

After including 6 studies, 55% (95% CI, 29%-78%) of the patients had a shock. Cochran's *Q* test showed 91% heterogeneity among studies, which was significant (Q-value=56.7, *p<0.001*, I^2=91) (Table 7K).

After including 10 studies, 33% (95% CI, 25%-42%) of the patients had neurologic symptoms, including headache, stiff neck, or vision change. Cochran's *Q* test showed 59.84% heterogeneity among studies, which was significant (Q-value=22.41, *p=0.008*, I^2=59.84) (Table 7L).

After including10 studies, 38.8% (95% CI, 28%-50%) of the patients had respiratory symptoms, including cough or dyspnea. Cochran's *Q* test showed 69.84% heterogeneity among studies, which was significant (Q-value=29.84, *p<0.001*, I^2=69.84) (Table 7M).

After including3 studies, 23% (95% CI, 14%-35.6%) of the patients had myalgia. Cochran's *Q* test showed 36.7% heterogeneity among studies, which was not significant (Q-value=3.16, *p=0.20*, I^2=36.7) (Table 7N).

After including 3 studies, 5.5% (95% CI, 2.6%-11%) of the patients had arthralgia. Cochran's *Q* statistics showed 0% heterogeneity among studies, which was not significant (Q-value=1.05465020694151, *p=0.59*, I^2=0) (Table 7O).

After including 5 studies, 31% (95% CI, 12%-59%) of the patients had acute kidney injury. Cochran's *Q* test showed 90.6% heterogeneity among studies, which was significant (Q-value=42.95, *p<0.001*, I^2=90.68) (Table 7P).

Cardiovascular Manifestations and Need for ICU Admission in COVID-19 Associated MIS-C Based on Random-effects Model

After including 8 studies, 34.7% (95% CI, 27.1%-43.1%) of the patients had normal left ventricular function. Cochran's *Q* test showed 0% heterogeneity among studies, which was not significant (Q-value=4.47, *p=0.72*, I^2=0) (Table 8A).

After including 8 studies, 65.3% (95% CI, 56.9%-72.9%) of the patients had decreased Left ventricular function. Cochran's *Q* statistics showed 0% heterogeneity among studies which was not significant (Q-value=4.47, *p=0.72*, I^2=0) (Table 8B).

After including of 3 studies, 56.9% (95% CI, 40.3%-72.2%) of the patients had Myocarditis. Cochran's *Q* test showed 56.2% heterogeneity among studies, which was not significant (Q-value=4.57, *p=0.10*, I^2=56.2) (Table 8C).

After including 10 studies, 19.9% (95% CI, 12.6%-30%) of the patients had coronary artery dilation. Cochran's *Q* test showed 52% heterogeneity among studies, which was significant (Q-value=18.8, *p=0.027*, I^2=52) (Table 8D).

After including 7 studies, 49.1% (95% CI, 39.5%-58.9%) of the patients had pericardial effusion. Cochran's *Q* test showed 0% heterogeneity among studies, which was not significant (Q-value=2.3, *p=0.89*, I^2=0) (Table 8E).

After including 6 studies, 37% (95% CI, 26%-49%) of the patients required non-invasive ventilation. Cochran's *Q* test showed 62% heterogeneity among studies, which was significant (Q-value=13, *p=0.02*, I^2=62.0) (Table 8F).

After including 10 studies, 32% (95% CI, 20%-48%) of the patients required invasive ventilation. Cochran's *Q* test showed 78.88% heterogeneity among

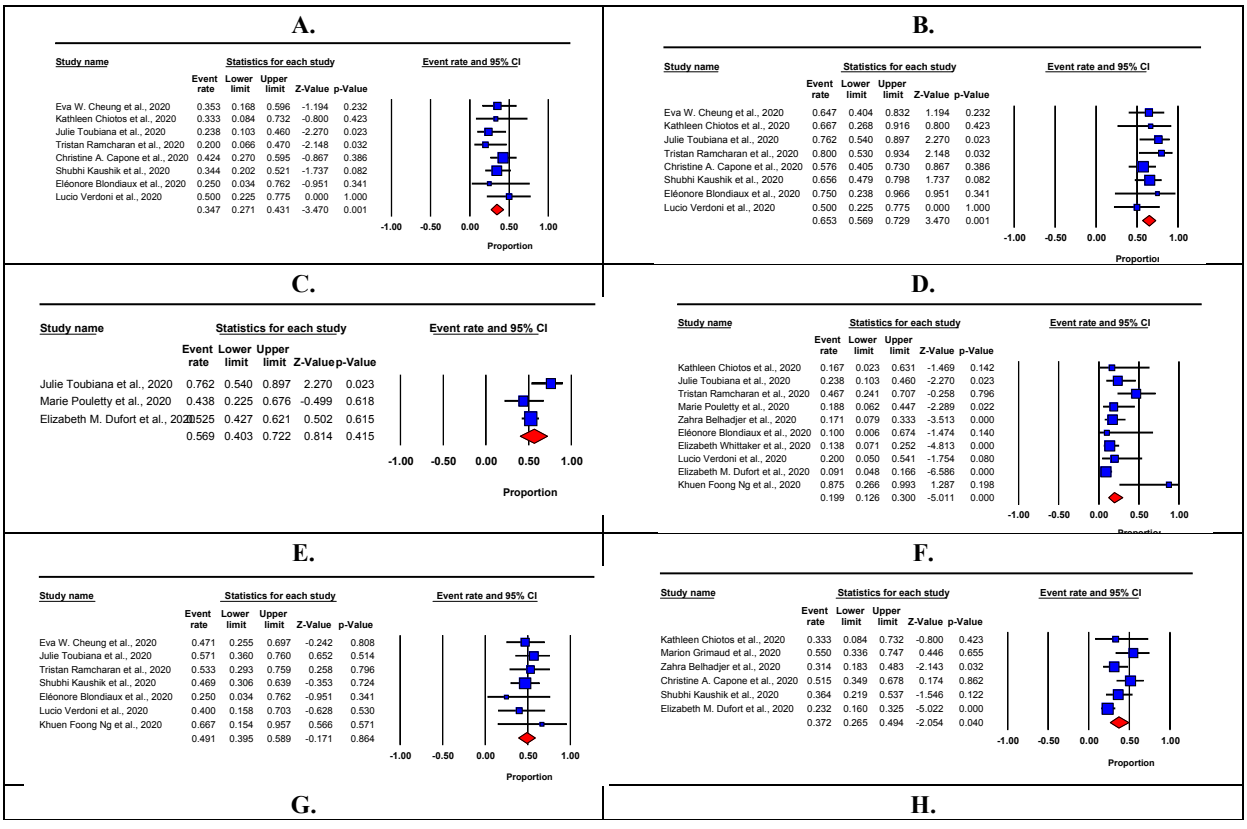
studies, which was significant (Q-value=42.62, *p<0.001*, I^2=78.88) (Table 8G).

After including 7 studies, 76% (95% CI, 68%-82.7%) of the patients were admitted to ICU. Cochran's *Q* test showed 48.9% heterogeneity among studies, which was not significant (Q-value=11.69, *p=0.069*, I^2=48.7) (Table 8H).

History of Contact with COVID-19 Patients, Chest Imaging Abnormalities, and SARS-CoV-2 Testing in COVID-19 Associated MSI-C According to Random-effects Model

After including 6 studies, 38% (95% CI, 17.2%-64.7%) of the patients had a history of contact with COVID-19 patients. Cochran's *Q* test showed 78% heterogeneity among studies, which was significant (Q-value=22.99, *p<0.001*, I^2=78) (Table 9A).

Table 8. Forest plots of cardiovascular manifestations and need for ICU admission in coronavirus disease 2019 (COVID-19) associated MSI-C; using the binary random-effects method. Blue squares represent an individual study's effect; the square's size varies to reflect a particular study's weight. The blue horizontal lines represent CI's. The red diamond represents the overall or summary. A: Normal Left ventricular function prevalence in 8 studies. B: Decreased Left ventricular function prevalence in 8 studies. C: Myocarditis prevalence in 3 studies. D: Coronary artery dilation prevalence in 10 studies. E: Pericardial effusion prevalence in 7 studies. F: Non-invasive ventilation ratio in 6 studies. G: Invasive ventilation ratio in 10 studies. H: ICU admission ratio in 7 studies



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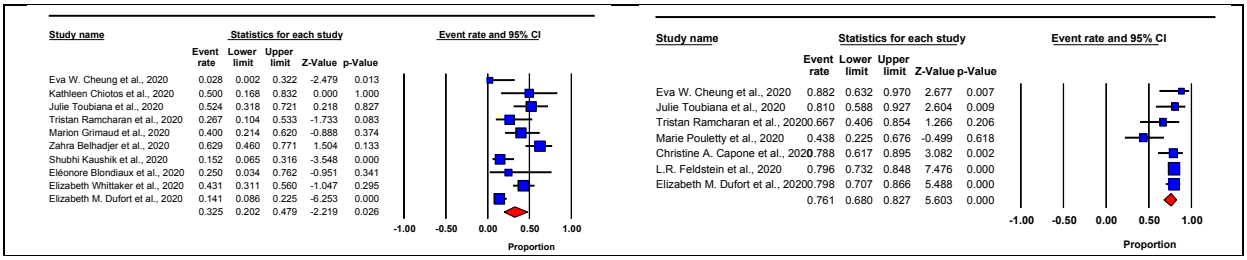


After including 8 studies, 45.9% (95% CI, 34.1%-58.2%) of the patients had abnormalities in chest radiography or computed tomography, including ground-glass opacity, interstitial abnormalities, or local patchy shadowing). Cochran's *Q* test showed 23.66% heterogeneity among studies, which was not significant (Q-value=9.2, *p=0.24*, I^2=23.66) (Table 9B).

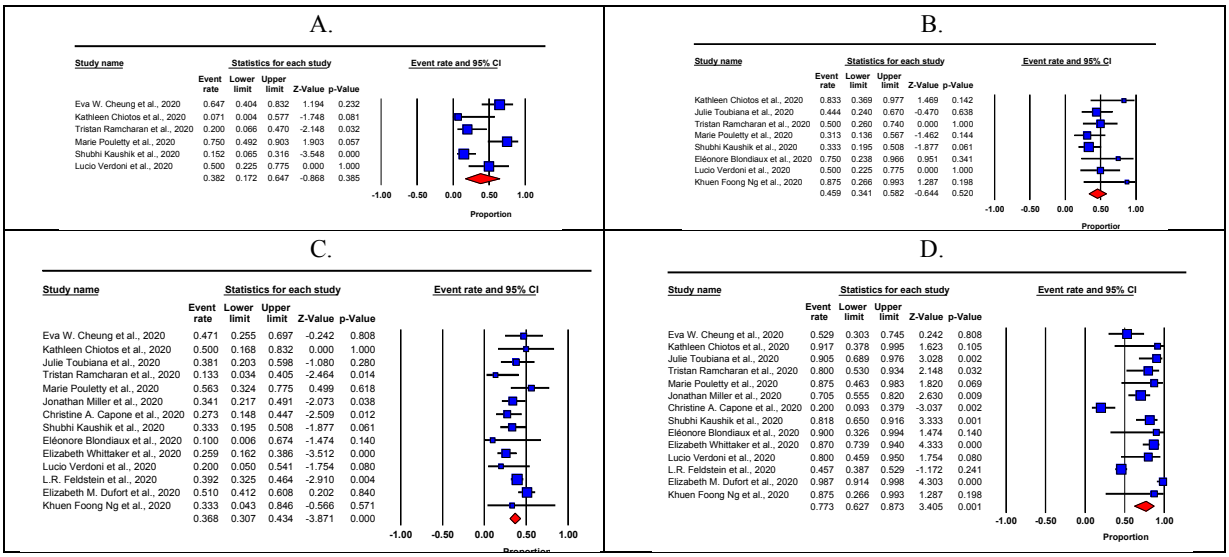
After including 14 studies, 36.8% (95% CI, 30.7%-43.4%) of the patients had positive nasopharyngeal SARS-CoV-2 RT-PCR. Cochran's *Q* test showed 40% heterogeneity among studies, which was not significant (Q-value=21.67, *p=0.061*, I^2=40) (Table 9C).

After including 14 studies, 77.3% (95% CI, 62.7%-87.3%) of the patients had positive SARS-CoV-2 serum serology. Cochran's *Q* test showed 84% heterogeneity among studies, which was significant (Q-value=82, *p<0.001*, I^2=84) (Table 9D).

Publication Bias

Publication bias was assessed using a funnel plot. It is expected that in the absence of publication bias, studies distribute symmetrically about the combined effect size (Figure 2).

Table 9. Forest plots of History of contact with coronavirus disease 2019 (COVID-19) patients, chest imaging abnormalities, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing in COVID-19 associated MSI-C; using the binary random-effects method. Blue squares represent an individual study's effect; the square's size varies to reflect a particular study's weight. The blue horizontal lines represent CI's. The red diamond represents the overall or summary.A: History of contact with COVID-19 patient prevalence in 6 studies. B: Chest radiography or computed tomography abnormalities prevalence in 8 studies. C: Positive nasopharyngeal SARS-CoV-2 RT-PCR prevalence in 14 studies. D: Positive SARS-CoV-2 serum serology prevalence in 14 studies



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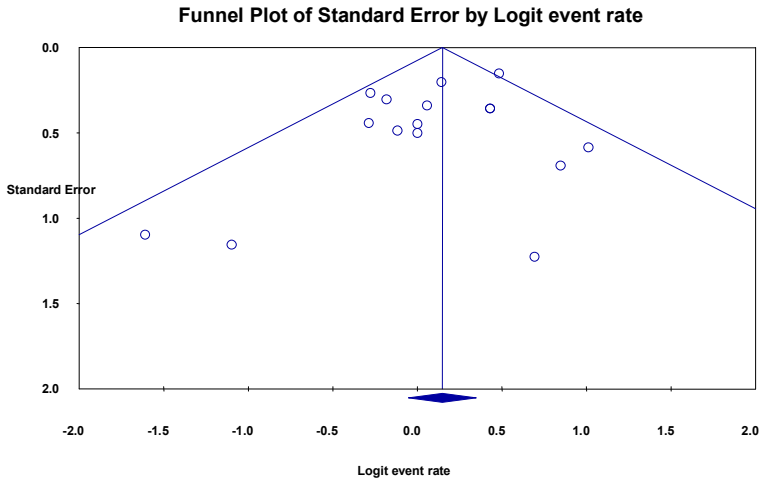

Figure 2. Funnel plot of study size (standard error) on the vertical axis by a function of effect size (logit event rate) on the horizontal axis. Studies were symmetrically distributed thus indicating the absence of publication bias

DISCUSSION

The new emerging coronavirus named SARS-CoV-2 has affected more than eleven million individuals globally until sixth July 2020 and caused more than half a million deaths between January to July 2020. The prevalence of COVID-19 was lower and clinical manifestations were milder in childhood compared to adulthood.[2] Nevertheless, after a few weeks of the peak of COVID-19 prevalence, some reports of new presentations in children emerged. These children were presented with Kawasaki like disease manifestation. Unlike the Kawasaki disease, COVID-19 infected patients who presented with Kawasaki like symptoms were older and were more likely to have respiratory, gastrointestinal, and cardiac involvement beside marked lymphopenia, thrombocytopenia, and elevated levels of serum ferritin and markers of cardiac involvement.[7] Gradually more cases were reported and raised concerns about this new presentation. Herein we aimed to analyze different presentations of this multisystem inflammatory syndrome.

This meta-analysis was based on sixteen studies, that were conducted on pediatric patients with clinical and laboratory evidence of COVID-19 associated MIS-C. Among these patients, 77% were seropositive, and 37% had a positive result of SARS-Cov-2 PCR.

The current meta-analysis revealed that MIS-C was more prevalent but not statistically significant in male children compared to females (54% and 46% respectively). This finding was similar to other reports of a slight male predominance in children with critical COVID-19 disease.[25-27] The current meta-analysis found that 34% of the patients were Hispanic and 23% were white. Spread rate and complications may be different between various ethnicities due to differences in behaviors, communications, preexisting conditions, socioeconomic factors, access to health care, and so on. Data about ethnic disparities in severe cases of COVID-19 are very limited, and to date, there was no report about the effect of ethnicity on the outcomes of COVID-19.[27,28] The analysis revealed that 28% of affected patients were overweight, and 38% had close contacts with COVID -19 patients. These parameters might be affected by ethnicity and lifestyle. On the other hand, with the worldwide spread of COVID-19, hand hygiene and staying at home were introduced as the best ways of infection prevention. This sedentary lifestyle can increase weight gain and may worsen preexisting conditions.[29,30]

Kawasaki disease is among the most prevalent vasculitis in childhood. Kawasaki disease is classically presented with fever (more than five days) and at least four clinical signs and symptoms including bilateral non-purulent conjunctivitis (80-90%), the involvement of oropharyngeal mucus membrane (80-90%), changes in peripheral extremities (80%), skin rash (more than 90%) and at least one cervical lymph node larger than 1.5 centimeters (50%). The prevalence of Kawasaki disease is higher in individuals of Asian and Pacific Island ancestry, but its incidence rate is lowest in white children. Kawasaki disease often occurs in children

younger than five years old and is more prevalent in boys compared to girls.[31-33] Similarly, a slight male predominance was found in MIS-C. Despite several reports of higher mean age of affected individuals, the current meta-analysis could not find such a predominance, because unfortunately, all studies reported age as Median and Interquartile range (IQR), which could not be meta-analyzed. Another factor that is expected to have an essential role in the pathogenicity of MIS-C is the human leukocyte antigen (HLA). To the best of our knowledge, till the time this article was prepared, no studies assessed HLA typing in COVID-19 patients.

Fever is the hallmark of Kawasaki disease and, without fever, the diagnosis of this disease is questioned. The current meta-analysis revealed that fever occurred in more than 97% of the COVID-associated MIS-C patients. It seems that fever is also one of the main criteria of COVID-19 associated MIS-C. Maculopapular or polymorphous skin rash occurred in about 60% of the patients. The frequency of this dermatologic presentation was lower than its prevalence in Kawasaki disease. The findings of the current meta-analysis revealed that conjunctivitis was less prevalent in COVID-19 associated MIS-C compared to Kawasaki disease (54% and 80% respectively). Similar findings were also found for cervical lymphadenopathy (23% in COVID-19 associated MIS-C and 50% in Kawasaki disease).[34] Among the abnormalities in peripheral extremities, including edema (26%), which was mostly in extremities, and skin desquamation (23%), Both of these presentations are more common in Kawasaki disease compared to COVID-19 associated MIS-C.[32] Based on the findings of the current meta-analysis, oropharyngeal mucous membrane involvement occurred in nearly 60% of children, which seemed to be lower than the frequency of oropharyngeal mucous membrane involvement in classical Kawasaki disease (80%).[32]

The current meta-analysis found that respiratory system signs and symptoms occurred in 39% of the patients, while respiratory system involvement in computed tomography or chest X-ray occurred in 46% of COVID-19 associated MIS-C patients. This finding was similar to Kawasaki disease, in which cough, rhinorrhea, and hoarseness frequently occur. The prevalence of these findings was approximately 35% of Kawasaki patients. However, because of COVID-19 infection, we expect a higher frequency of respiratory symptoms. It may be due to the higher prevalence of upper rather than lower airway presentations in children.[32,34,35]

The current meta-analysis found that 33% of COVID-19 affected children had some neurologic symptoms, including headache, neck stiffness, and vision changes. The common presentations of neurologic involvement in classical Kawasaki disease are irritability, which is probably due to aseptic meningitis. This presentation is also uncommon in COVID-19 infection. Although sensory deficits in the peripheral nervous system, including impairment in smell and taste senses, have been reported frequently in adult patients, these manifestations were rarely reported among children.[36] However, some reports have stated that the neurologic involvement was present in about 30% of SARS-CoV-2 affected individuals. These presentations may include headache, malaise, seizure, ischemic stroke, cerebral hemorrhage, and impaired consciousness.[37,38] The exact mechanism of neurologic involvement is unknown, but a possible hypothesis is the direct virus insult or damage secondary to hypoxemia due to lung involvement. Considering the potential neuroinvasive capability of the SARS-CoV2 virus, we can propose that it is essential to monitor COVID-19 patients for short and long-term neuropsychiatric consequences.[36]

Gastrointestinal tract involvement occurs in approximately 20-35 % (and to 61 % in some reports) of children with Kawasaki disease, but the current meta-analysis revealed that gastrointestinal abnormalities occurred in 80% of COVID-19 patients. These symptoms included abdominal pain, vomiting, and diarrhea. Several hypotheses suggest that the gastrointestinal presentation of Kawasaki disease is among risk factors for IVIG unresponsiveness and worse outcome in the coronary artery. The exact mechanism for this finding is unknown but the possible mechanisms may include delay in diagnosis and IVIG administration.[34,39]

The current meta-analysis revealed that approximately 55% of COVID-19 associated MIS-C had signs and symptoms of shock during the disease. The majority of these patients required vasopressors. Half of the patients had pericardial effusion, and 57% had myocarditis. Coronary dilation occurred in 20% of affected patients. Sixty-five percent had decreased left ventricular function, and 35% had a normal left

ventricular function.

However, patients with classical Kawasaki disease in at least one third to half of the cases had early myocarditis. This complication usually has a good prognosis and responds to IVIG administration. Most of the cardiac dysfunctions are the consequence of severe coronary artery involvement. Coronary artery aneurism occurs in about 25% of untreated patients. However, coronary artery aneurism usually develops in the disease course. Therefore, coronary artery dilation could be more prevalent if COVID-associated MIS-C patients were followed up. Recently there is much concern about Kawasaki disease shock syndrome (KDSS), which may occur in subsequent coronary artery abnormalities or decreased left ventricular function.[32] Based on the findings of a study the prevalence of KDSS was 7%.[40] The observed higher frequency of cardiogenic shock in COVID-19 associated MIS-C patients may be associated with simultaneous COVID-19 infection. Current data suggest that SARS-Cov-2 can be localized in organs other than the lungs.[41]

On the other hand, the involvement of different organs is possible as a result of medium-vessel vasculitis in Kawasaki disease. Kidney involvement was reported in multiple surveys. In one study, acute kidney injury was reported in 28% of patients, and at least half of Kawasaki patients developed renal involvement with nuclear imaging techniques.[42] On the other hand, acute kidney injury occurs frequently in COVID-19 patients and maybe associated with respiratory and cardiac involvement.[43] Our analysis revealed that 31% of COVID-19 associated MIS-C patients had acute kidney injury. Kidney injury may indicate poor prognosis in these patients.

COVID-19 associated MIS-C may explain a worsened condition and ICU admission. Among the included population, 37% needed noninvasive ventilation, while 32% needed invasive ventilation. The included papers reported 8 patients deceased during the follow-ups. Therefore, the mortality rate was 1.33%.

Acute phase reactants, peripheral blood smear, and absolute lymphocyte count, cytokine level, and other laboratory findings can be very helpful in diagnosis and determining the prognosis of COVID-19 associated MIS-C. However, due to the space limitation in writing the paper, all the collected data could not be presented in one paper. The remaining data will be discussed in another review article. Furthermore, different protocols have been suggested for therapeutic propose in COVID-19 associated MIS-C patients; however, none of these protocols have yet been validated.

Finally, According to the current meta-analysis on current evidence, we can conclude that SARS-CoV-2 infected patients that have the combination of fever and mucocutaneous involvements, similar to which we find in Kawasaki disease, and multiple organ dysfunction are probable findings in COVID-19 associated MIS-C. Gastrointestinal and cardiovascular involvement is among the most prevalent organ dysfunctions in such cases. Therefore, echocardiography should be considered in pediatric patients with evidence of SARS-CoV-2 infection, with clinical and paraclinical manifestations of multi-organ involvement. These patients are susceptible to develop cardiac complications. It is crucial to diagnose cardiac complications as soon as possible, as this may lead to an improvement in prognosis.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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