Multisystem Inflammatory Syndrome in pediatric COVID-19 patients: A meta-analysis

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Abstract

Purpose Significant numbers of children and teenagers with COVID-19 have developed a severe inflammatory condition with a Kawasaki-like disease. Some needed intensive care unit admission, and others recovered quickly. We aimed to summarize the clinical and laboratory features of patients with Kawasaki-like features diagnosed during the COVID-19 pandemic. Methods A literature search in Web of Science, PubMed, Scopus, and Science Direct up to June 30, 2020. The mean or untransformed proportion and 95%CI were estimated. Results Analysis of 15 articles (318 COVID-19 patients) revealed that the mean age was 9.10 years. Although many presented with typical Kawasaki-like features; fever (82.4%), polymorphous maculopapular exanthema (63.7%), oral mucosal changes (58.1%), conjunctival injections (56.0%), edematous extremities (40.7%), and cervical lymphadenopathy (28.5%), atypical gastrointestinal (79.4%) and neurocognitive symptoms (31.8%) were also common. They had elevated LDH, D-dimer, CRP, procalcitonin, interleukin-6, troponin I levels, and lymphopenia. Nearly 77.0% developed hypotension, and 68.1% went into shock, while 41.1% had acute kidney injury. Intensive care was needed in 73.7% of cases, 13.2% were intubated, and 37.9% required mechanical ventilation, with only one reported fatality case. Intravenous immunoglobulins and steroids were given in 87.7% and 56.9% of the patients, and anticoagulants were utilized in 67.0%. Pediatric patients were discharged after a hospital stay of, on average, 6.77 days (95%CI:4.93-8.6). Conclusion Recognizing the typical and atypical presentation of pediatric COVID-19 patients has important implications in identifying children at risk. Monitoring cardiac and renal decompensation and early interventions in patients with "multisystem inflammatory syndrome" is critical to prevent further morbidity.

1 INTRODUCTION

The coronavirus disease 2019 (COVID-19) has led to a global pandemic with significant morbidity and mortality.[1] The pediatric population appears to be affected in a much smaller number than adults, with only 1.7% of cases in the United States occurring in children younger than 18. In other European countries, the number of cases in children is less than 2%.[2-4] Currently, it is unclear whether this is due to lower infection susceptibility in children or if the asymptomatic disease is much more common in those under the age of 18.[5; 6]

Significant numbers of children and teenagers, tested positive for COVID-19 antibodies, have developed a severe inflammatory condition with many disease characteristics of Kawasaki syndrome.[7] As case reports pile up, the world is suddenly paying attention to this pediatric condition that may be related to COVID-19.[8]Kawasaki disease is a rare acute pediatric vasculitis, usually involves small to medium-sized arteries in

a wide array of organs and tissues, and can cause coronary artery aneurysms, myocardial infarction, and pericarditis.[9] It is characterized by fever, exanthema, lymphadenopathy, conjunctival injection, and changes to the mucosa and extremities. Kawasaki disease is relatively uncommon, with an incidence rate of 20.8 per 100,000 in the United States, mainly in children aged five years or younger.[10] The etiology of this syndrome remains unknown; however, antigen-driven delayed immune reaction following viral or bacterial infection in genetically susceptible individuals is the current leading hypothesis.[9] In the last two decades, the coronavirus family has been proposed to be one of the triggers of Kawasaki syndrome. Human New Haven coronavirus (HCoV-NH) was identified in the respiratory secretions of 72.7% of children with Kawasaki disease[11], and positive CoV-229E antibodies was detected by immunofluorescence assay in patients with Kawasaki disease[12], eliciting a putative link with COVID-19 disease.

Verdoni et al. described an outbreak of a Kawasaki-like disease occurring in Bergamo, Italy, at the peak of the COVID-19 pandemic.[13] As of May 21, other confirmed and suspected children of similar presentations have been reported throughout the United States.[14] This Kawasaki-like disease appears to cause a hyper-inflammatory shock state. Hypotension with a requirement for fluid resuscitation seems to be common[15]. Some patients required inotropic support. Also, patients with this syndrome appear to respond well to intravenous immunoglobulin. However, the disease course seems more severe than the typical Kawasaki's disease as adjunct anti-inflammatory treatments were necessary for several patients, with some requiring high-dose corticosteroids. The use of biologics such as infliximab has also been described.[13; 16]

Despite these findings, much remains unknown about this rare Kawasaki-like disease. Some children have needed intensive care unit (ICU), others recovered quickly. The goal of this meta-analysis was to summarize the clinical and laboratory features of patients with Kawasaki-like disease diagnosed during the COVID-19 pandemic.

2 METHODS

2.1 Search strategy

This current meta-analysis was carried out according to the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) statement.[17] Relevant literature was retrieved from Web of Science, PubMed, Scopus, and Science Direct search engines up to June 30, 2020. Our search strategy included the following terms: ("Novel coronavirus 2019", "2019 nCoV", "COVID-19", "Wuhan coronavirus," "Wuhan pneumonia," or "SARS-CoV-2") and ("Kawasaki-like disease", "Kawasaki disease", "Kawasaki syndrome", "multisystem inflammatory syndrome", "pediatric inflammatory syndrome", or "pediatric inflammatory, multisystem syndrome"). Besides, we manually screened out the relevant potential article in the references selected. The above process was performed independently by three participants.

2.2 Study selection

No time or language restriction was applied. Inclusion criteria were as follows: (1) Types of Studies: retrospective, prospective, observational, descriptive or case-control studies reporting COVID-19 patients (<18 years) with the multisystem inflammatory syndrome; (2) Subjects: diagnosed patients with COVID-19 (3) Exposure intervention: COVID-19 patients diagnosed with Real-Time polymerase chain reaction, radiological imaging, or both with at least 4 out of 5 principal features of typical Kawasaki syndrome (apart of the persistent fever at least for five days): (i) bilateral conjunctival injection, (ii) oral changes such as cracked and erythematous lips and strawberry tongue, (iii) cervical lymphadenopathy, (iv) extremity changes such as erythema or palm and sole desquamation, and (v) polymorphous rash. Patients presented with fever lasting five or more days and with 2-3 of these findings were considered as incomplete (atypical) Kawasaki disease[18]; and (4) Outcome indicator: the mean and standard deviation or median and interquartile range for COVID-19 related complications and mortality.

The following exclusion criteria were considered: (1) Case reports, reviews, editorial materials, conference abstracts, summaries of discussions, (2) Insufficient reported data information; or (3) *In vitro* or *in vivo* studies.

2.3 Data abstraction

Two investigators (RME, RM) separately conducted literature screening, data extraction, and literature quality evaluation, and any differences were resolved through a third reviewer (MHH). Information extracted from eligible articles in a predesigned form in excel, including the last name of the first author, date and year of publication, journal name, study design, country of the population, and sample size. Variables were stratified into eight categories, including demographic data, Kawasaki disease criteria, other clinical presentations, comorbidities, hospitalization, laboratory measurements, SARS-COV-2 screening, and medications.

2.4 Statistical analysis

All data analysis was performed using OpenMeta[Analyst][19] and comprehensive meta-analysis software version 3.0.[20] First, a single-arm meta-analysis for laboratory tests was performed. The mean or untransformed proportion and 95% confidence intervals (CI) were used to estimate pooled results from studies. A continuous random-effects model was applied using the DerSimonian-Laird (inverse variance) method.[21; 22] Heterogeneity was evaluated using Cochran's Q statistic and quantified by using I^2statistics, which represents an estimation of the total variation across studies beyond chance. Articles were considered to have significant heterogeneity between studies when the p-value less than 0.1 or $I^2 > 50\%$. Finally, publication bias was assessed using a funnel plot and quantified using Begg's and Mazumdar rank correlation with continuity correction and Egger's linear regression tests. Asymmetry of the collected studies' distribution by visual inspection or P-value < 0.1 indicated obvious publication bias.[23]

3 RESULTS

3.1 Literature search

The flow chart summarizing the literature search of this meta-analysis study is illustrated in Fig. 1. A total of 261 articles were recorded using five major online databases (Web of Science, PubMed, Scopus, ScienceDirect, and MedRxiv) till June 30, 2020. After inspection of the retrieved records, a total of 73 articles were removed due to duplication, and 188 records were recognized. Upon screening the title and abstract, our team excluded various articles, including case reports (n = 28), review articles (n = 37), irrelevant reports (n = 42), or editorial items (n = 63). A final of 18 records were appraised for eligibility, with 3 records were excluded for no sufficient data. Eventually, a total of 15 eligible reports were identified for the quantitative assessment of this meta-analysis, with 15 records characterized single-arm analysis.

3.2 Characteristics of the included studies

The main characteristics of the included records in this meta-analysis are demonstrated in Table 1. The articles published online from May 6 until June 30, 2020, included 5 records from France [Paris (5)], 5 records from USA [New York (4), and Pennsylvania (1)], 4 records from UK [London (2), and Birmingham (2)], and one record from Italy [Bergamo (1)]. A total of 318 children with a pediatric inflammatory, multisystem syndrome (Kawasaki-like disease) associated with SARS-COV-2 infection were registered in this meta-analysis. Nine records were retrospective studies, another two were prospective studies, while descriptive case series accounted for four studies.

3.3 Demographic characteristics of pediatric patients

Our meta-analysis included 318 COVID-19 patients presented with the multisystem inflammatory syndrome. Their mean age was 9.10 years (95% CI: 8.49-9.71), while the mean BMI was 19.34 Kg/m^2(95% CI: 17.86-20.82). The pooled prevalence of boys accounted for 50.5% across studies. Proportion of Black patients was 36.8% (95%CI: 26.3%-47.4%) higher than the White (16.4%, 95%CI: 10.7%-22.1%) and Asian cohorts (13.6%, 95%CI: 4.7%-22.6%) (Table 2A).

3.4 Clinical presentation of COVID-19 patients

Young patients underwent confirmatory tests for COVID-19 disease by either reverse transcription-polymerase chain reaction (RT-PCR) of nasopharyngeal swab (proportion = 46.5%, 95%CI: 12.9%-80.1%)

or anti-SARS-COV-2 IgG analysis (proportion = 69.6%, 95%CI: 48.9%-90.2%) (Table 2B). For the six clinical criteria of Kawasaki disease, fever (proportion = 82.4%, 95%CI: 69.8%-95.1%) and polymorphous maculopapular exanthema (proportion = 63.7%, 95%CI: 53.8%-73.5%) were the most frequent principal features, followed by changes of lips and oral cavity (proportion = 58.1%, 95%CI: 38.6%-77.6%) and bilateral non-purulent conjunctival congestion (proportion = 56.0%, 95%CI: 40.0%-71.9%). Changes of peripheral extremities (proportion = 40.7%, 95%CI: 12.9%-68.5%) and acute non-purulent cervical lymphadenopathy (proportion = 28.5%, 95%CI: 13.9%-43.1%) were the least presenting features (Table 2C). Children presented more often with gastrointestinal symptoms including abdominal pain, nausea, and diarrhea (proportion = 79.4%, 95%CI: 68.1%-90.7%) and shock (proportion = 68.1%, 95%CI: 51.9%-84.3%). Neurocognitive symptoms as headache, irritability, lethargy, or visual change were reported in 31.8% of patients (95%CI: 21.9%-41.8%), while the prevalence of respiratory symptoms as cough and dyspnea accounted for 29.6% (95%CI: 19.6%-39.6%) (Table 2D). Obesity (proportion = 26.0%, 95%CI: 7.1%-44.9%) and asthma (proportion = 14.6%, 95%CI: 6.9%-22.2%) were two comorbid conditions reported in pediatric cases presented with Kawasaki-like features (Table 2E). Abnormal Chest X-ray was observed in 45.5% (95%CI: 24.9%-66.0%), while ECG abnormalities was found in 55.3% of patients (95%CI: 45.1%-65.6%) (Table 2F). Apart of studies reporting ECG findings and asthma, there was evidence of considerable heterogeneity across studies.

3.5 Laboratory data of COVID-19 patients

Pooled summary of complete blood picture showed leukocytosis (mean = 13.20 x10^9/L, 95%CI: 10.82-15.59), lymphopenia (mean = 0.93 x10^9/L, 95%CI: 0.737-1.125), neutrophilia (mean = 12.67 x10^9/L, 95%CI: 8.56-16.76), and anemia (mean = 10.4 g/dL, 95%CI: 9.55-11.39) in positively confirmed COVID-19 children.

Elevated liver enzyme levels (ALT: mean = 46.86 U/L, 95%CI: 39.1-54.6 and AST: (mean = 52.89 U/L, 95%CI: 45.9-59.8) and hypoalbuminemia (mean = 27.15 g/L, 95%CI: 23.5-30.7) was reported across studies. There was marked elevated cardiac markers; troponin (mean = 110.71 ng/L, 95%CI: 59.08-162.3), NT-proBNP (mean = 5,648.78 pg/ml, 95%CI: 3823.17-7474.3), and LDH (mean = 637.21U/L, 95%CI: 358.7-915.7). Elevated inflammatory markers were observed; C-reactive protein (mean = 215.58 mg/L, 95%CI: 192.50-238.67), erythrocyte sedimentation rate (mean = 64.64 mm/hr, 95%CI: 54.28-74.99), procalcitonin (mean = 19.24 ng/ml, 95%CI: 8.67-29.80), ferritin (mean = 763.24 ng/ml, 95%CI: 658.86-867.63), and interleukin-6 (mean = 189.67 pg/ml, 95%CI: 145.48-233.87). there was an increased evidence for coagulopathy represented as a high blood concentration of fibrinogen (mean = 6.24 g/L, 95%CI: 4.68-7.80) and D-dimer (mean = 3.79 µg/ml, 95%CI: 2.57-5.02) (Table 2G).

3.6 Pooled analysis of COVID-19 complications

Of the affected children and teenagers, 77.0% (95%CI: 56.9%-97.0%) developed hypotension, 68.1% (95%CI: 51.9%-84.3%) went into shock, and 41.1% (15.0%-67.1%) had acute kidney injury. Intensive care was needed in 73.7% of cases (95%CI: 60.3%-87.1%), 13.2% (95%CI: 0.5%-82.1%) were intubated and 37.9% (95%CI: 28.3%-47.6%) required mechanical ventilation, with only one reported fatality case. Pediatric patients were discharged after a hospital stay of, on average, 6.77 days (95%CI: 4.93-8.6) (Table 2H).

3.7 Received medications

Intravenous immunoglobulins and steroids were given in 87.7% (95%CI: 80.8%-94.7%) and 56.9% (95%CI: 33.6%-80.2%) of the children. Anticoagulants were utilized in 67.0% (95%CI: 47.6%86.3%) of pediatric patients. Anakinra (Anti-IL-1) was prescribed in only 9.4% (95%CI: 4.6%-14.2%) (Table 2I).

4 DISCUSSION

Pediatric patients have largely been overlooked during the COVID-19 pandemic, as the largest cohort of morbidity and mortality has come in elderly adult populations.[24] More recently, the insidious connection between COVID-19 infections and a syndrome similar to Kawasaki disease has been investigated as healthcare professionals noticed outbreaks of the rare constellation of symptoms throughout the United States and the world.[25] The context of these reports is essential as officials weigh the risks of reopening schools with the pandemic ongoing, and physicians are treating pediatric patients with severe inflammatory responses. The

association of Kawasaki disease to coronaviruses is still a continuous area of research, and the COVID-19 pandemic provides a unique opportunity to investigate the connection of coronavirus infection to a pediatric inflammatory response that mimics Kawasaki disease.

The COVID-19-associated multisystem inflammatory syndrome patients tended to be much older than typical Kawasaki disease patients. A large sample of Korean Kawasaki disease patients showed a mean age of just 2.54 years compared to 9.10 in this meta-analysis.[26]This finding is especially important because children with onset of Kawasaki disease aged nine or older are at a significantly higher risk of developing coronary artery aneurysms and left ventricular abnormalities; a feared outcome is up to 25% of untreated children.[27] Older age may be one of many factors in Kawasaki-like disease that contributed to such high proportions of patients experiencing shock and hypotension, along with elevated troponin and BNP levels. Although the cardiac manifestations of Kawasaki disease typically resolve within two years, the long-term effects of an inflammatory response in Kawasaki disease are not fully known with microvascular changes and intimal thickening proposed as possible sequelae.[28]

Patients in this meta-analysis presented with many typical symptoms of Kawasaki disease, as well as several atypical ones. A previous study on Kawasaki disease risk factors for developing coronary artery aneurysms showed that having more of the typical five symptoms is a protective factor. At the same time, atypical presentations are a risk factor.[29] Although many of the patients in our analysis who developed Kawasaki-like illness related to COVID-19 had a polymorphous maculopapular exanthema, nearly half of patients lacked oral mucosal changes and conjunctival injections, and over half lacked cervical lymphadenopathy and peripheral edematous changes to extremities. Atypical gastrointestinal and neurocognitive symptoms were frequent and may have contributed to delayed recognition of the children's condition as an inflammatory disease similar to Kawasaki disease, thus delaying intravenous immunoglobulin administration. Abnormal electrocardiograms and chest X-rays were also common findings on admission for the multisystem inflammatory syndrome. The differences between this clinical picture and Kawasaki disease will likely lead to delays in treatment that could be detrimental to patients. It will be necessary for pediatric tertiary care centers to stay apprised to the evolving presentation of this inflammatory illness. One postulation for the protective association of a patient's number of symptoms and lower risk of coronary artery aneurysms is less delay in the administration of treatments like intravenous immunoglobulin. Another is that dysfunctional immune systems are less likely to produce as many classic symptoms of the disease.[29]

The massive inflammatory response to infection with COVID-19 is a significant point of focus for research, novel therapeutic developments, and vaccine research trials. Pediatric patients in this meta-analysis had markedly elevated inflammatory markers, including C-reactive protein and procalcitonin, which have been previously associated with an increased risk of coronary artery aneurysms in Kawasaki disease.[29] The pathophysiology of Kawasaki disease and its complications are driven by an intense inflammatory cell response primarily to medium-sized blood vessel walls.[30]Children who develop Kawasaki disease often have a viral illness that precipitates this immune response. About 69.6% of the patients in this meta-analysis tested positive for SARS-CoV-2 IgG antibodies, a higher number than tested positive for the nasal swab polymerase chain reaction, which suggests that a COVID-19 infection weeks earlier could have triggered the multisystem inflammatory syndrome and hemodynamic shock.

Many of the laboratory findings in this pediatric population were consistent with findings in adult patients who developed severe respiratory disease from SARS-CoV-2. Elevated lactate dehydrogenase, d-dimer levels, procalcitonin levels, troponin I level, and lymphopenia have been demonstrated as markers of worse outcomes in adult COVID-19 patients.[31] Interleukin-6 (IL-6) has been associated with the "cytokine storm", or macrophage activation syndrome-like disease thought to be a factor in the development of acute respiratory distress syndrome in adult patients.[32] IL-6 also plays a role in the pathogenesis and, more recently, targeted therapy of childhood inflammatory disorders like systemic juvenile idiopathic arthritis.[33] Similarly, children who developed multisystem inflammatory syndrome in this meta-analysis had remarkably high IL-6 levels with a mean of 189.67 pg/mL, exhibiting the role of systemic inflammation. Further research could evaluate whether immunomodulatory therapies like tocilizumab, in addition to intravenous immunoglobulin, could

be useful for pediatric patients at risk of developing progressing to the multisystem inflammatory syndrome.

One of the limitations of this meta-analysis was that the studies were conducted in the United States and Europe. East Asian countries, which historically have higher rates of Kawasaki disease, have pediatric populations that have had longer COVID-19 exposure times, and retrospective studies could be helpful to assess differences in prevalence and outcomes. This region is also known to have different phylogenetic SARS-CoV-2 genomes, which could influence the inflammatory response seen in multisystem inflammatory syndrome patients.[34]

5 CONCLUSION

The findings presented in the meta-analysis have important implications worldwide, as many countries still struggle with COVID-19, and hotspots put children at risk for infection. More research into the pathophysiology of multisystem inflammatory syndrome is needed to understand how it differs from that of Kawasaki disease. It could also begin to provide an idea of why some children experience shock and hypotension, while others have less acute complications. Also, a comparison of relative rates of coronary artery aneurysms in multisystem inflammatory syndrome *versus* Kawasaki disease would help medical decision making.

Although multisystem inflammatory syndrome still appears to be a rare occurrence in COVID-19 positive children, it has become clear that the Kawasaki-like disease requires aggressive medical management with a multidisciplinary team and close, long-term follow up. Recognizing the atypical presentation of the multisystem inflammatory syndrome, monitoring patients for cardiac and renal decompensation, and early interventions to treat the exaggerated immune response in these patients is critical to prevent further morbidity.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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Abbreviations

ALT: Alanine aminotransferase, Anti-TNF: Anti-tumor necrosis factor, AST: Aspartate aminotransferase, CK: creatine kinase, COVID-19: Coronavirus disease 2019, CRP: c-reactive protein, ESR: Erythrocyte sedimentation rate, HCoV-NH: Human New Haven coronavirus, Ig: Immunoglobulins, LDH: Lactate dehydrogenase NT-proBNP: N-terminal pro b-type natriuretic peptide, PICU: Pediatric intensive care unit, PRISMA: Preferred Reporting Items for Systematic reviews and Meta-analysis, RT-PCR: Reverse transcription-polymerase chain reaction, SARS- COV-2: Severe acute respiratory syndrome-coronavirus -2, WBCs: White blood cells count.

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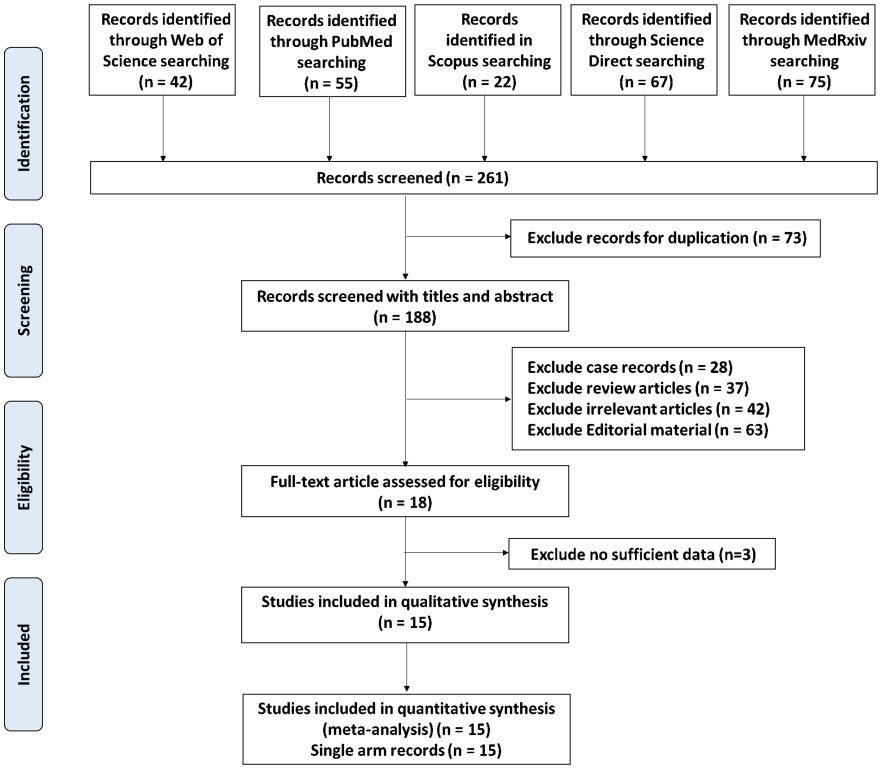
Figure legend

FIGURE 1 Flowchart for the systematic literature search.



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