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Systematic Review

Multisystem inflammatory syndrome in infant temporally associated with SARS-CoV-2 infection

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ABSTRACT

Since the end of December 2019, corona virus disease (COVID-19) has spread globally. Though the majority of COVID-19 cases in pediatric age group have not been critical, a novel disease named as multisystem inflammatory syndrome in children (MIS-C) have been emerging as the pandemic progresses. A systemic review of the literature was performed in the principle medical databases including Pubmed, Embase and Google Scholar between December 2019 and March 2021. A total of 40 articles were identified in the described database. Altogether 12 articles met the inclusion criteria and were eligible. The critical and severe case were more in infant age group, also the number of hospitalization was more in infant age group than other pediatric age groups. A number of case reports reflected that infants with COVID-19 positive may present with shock and sepsis. The mean age of MIS-C COVID-19 positive children was 1.1 year emphasizing the vulnerability of infant age group to this novel disease MIS-C. MIS-C is a new type of presentation of COVID-19 infection. Special emphasis should be given in infant age group with COVID-19 who are vulnerable to develop MIS-C.

Keywords: Multisystem inflammatory syndrome in children (MIS-C), Infant, COVID-19

INTRODUCTION

Emerging and re-emerging pathogens are global challenges for public health.[1] Coronaviruses are enveloped RNA viruses that are distributed broadly among humans, other mammals and birds and that cause respiratory, enteric, hepatic and neurologic diseases.[2] SARS-CoV-2, causing COVID-19, led to a pandemic health crisis within a short period of time. Severe COVID-19 and associated mortality has been most in elderly and patients with co-morbidities such as cardiovascular disease, diabetes mellitus and chronic lung disease. Since the outbreak, COVID-19 was generally described as asymptomatic or mild in children, causing few pediatric hospitalizations and minimal mortality.[3]

While data are available for adult patients with COVID-19, to date a number of limited reports have analysed pediatric patients infected with SARS-CoV-2. On the other hand, a significant proportion of children were reported with severe and fatal disease in contrast with COVID-19 respiratory disease. This novel disease is referred to as MIS-C.[4,5] To date, a number of scattered cases of MIS-C in infant age group have been reported. There are also some studies of MIS-C on children reflecting the severity especially in infant age group. To our knowledge, this was the first systematic review that

assesses and focuses the clinical features of MIS-C in infants with SARS-CoV-2 infection.

METHODS

Search strategy and article selection

Search was done of the literature available in the principle medical database including PubMed, Embase, Google Scholar using the subject headings terms SARS-CoV-2 or COVID-19 in infant or infection or sepsis or critical infant case and MIS-C between December 2019 and March 2021. Yet unpublished document were not included.

Eligibility criteria

Case series, case reports and cross-sectional, case-control, COHORT (either prospective or retrospective) or clinical trial studies reflecting infant age group were included. Studies of critically ill children with COVID-19 were also considered and the cases of MIS-C reported in these studies were also explored. Only articles in English were considered. Adult cases have already been described, but these were not included in this review (Figure 1).

Study selection and data collection process

First, the inclusion and exclusion criteria for this review were defined, after which one of the researchers performed the systematic search of the literature and reviewed the most relevant articles. In case of doubt, or a lack of harmonies regarding the inclusion of an article, a second reviewer was consulted to decide. A total of 40 articles were identified in the described database. After eliminating the duplicates 40 articles were screened on title and abstract of which 12 met the inclusion criteria and were eligible.

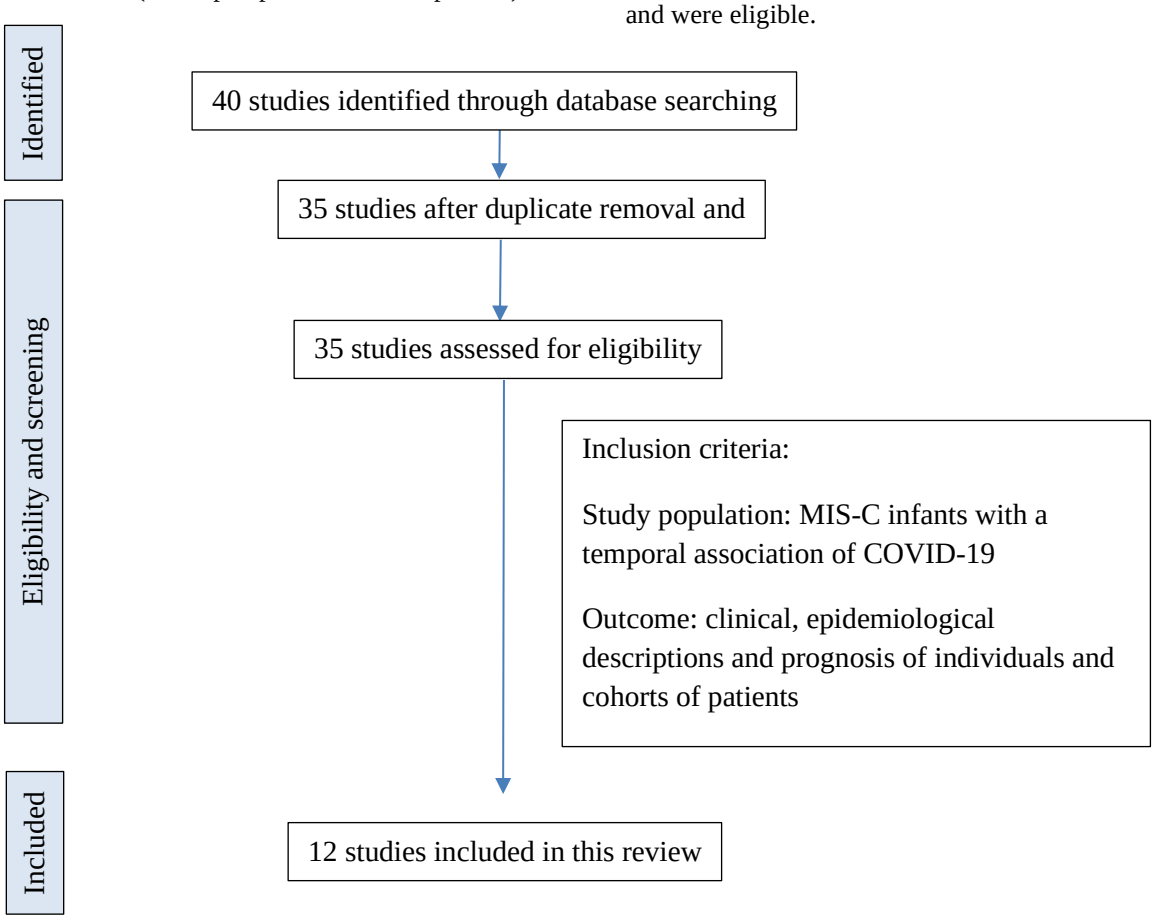

Figure 1: Systemic review of this article.

RESULTS

The pathogenesis of COVID-19 may be similar to other flu viruses but the clinical presentations are different from those usually found in those classical respiratory pathway. Riphagen et al on 24 April 2020 described a new presentation of SARS-CoV-2 in a COHORT of eight children with COVID-19 who required hospitalization in intensive care and had an unusual clinical presentation characterized by a severe hyperinflamatory state.[4-7]

The Royal college of paediatrics and child health called this new entity PIMS-TS.[8] Subsequently, the CDC and WHO called it MIS-C.[9,10] In general, both terms refer to the same entity and the MIS-C has been most frequently used.

A retrospective study was done on 2143 pediatric patients with COVID-19 based on the epidemiological characteristics and transmission dynamics of children's COVID-19 in China from 16 January 2020 to 8 February 2020. We found that the proportion of severe and critical cases was 10.6%, 7.3%, 4.2%, 4.1% and 3.0% for the age group of <1, 1-5, 6-10, 11-15 and >15 years, respectively. These results reflected that young children, particularly infants, were at risk to COVID-19 infection. On this account, the mechanisms for the difference in clinical manifestations between children and adults remained to be set on.[14]

Accounting for both under ascertainment factors yielded a severity proportion for infants that was calculated as 40/3662 or 1.1%. This more accurately estimated the desired denominator (all children infected with SARS-CoV-2).[15]

In a multicenter Italian study of SARS-CoV-2 infection in children and adolescents it was reported that among the infected children under one year of age, 52/66 were hospitalized versus 24/38, 13/24 and 21/40 among the 1 to 5 years old, 6 to 10 years old and over 10 years old, respectively. Although in this report about 40% were under 1 year of age and the majority of them were hospitalized. Of them, two children required ICU admission, one was a neonate and another was a 2 month old infant.[16] On the other hand Agdam et al observed clinical sign of sepsis in a 15 day old neonate and was COVID-19 positive.[17]

On the other hand an alarming finding was revealed in a research done by Hoang et al that revealed the evidence of MIS-C features in 11 children where the mean age was 1.1 year (N=11) in comparison to COVID-19 children (N=14) where the mean age was 7.5 year. In this study Hoang et al reviewed 131 studies across 26 countries comprising 7780 pediatric patients and showed a comparison between COVID-19 children with and without MIS-C. Clinical characteristics between COVID-19 children and MIS-C was fever 10 (71.4%) versus 10 (90.9%), cough 8 (57.1%) versus 6 (54.5%), dyspnoea 4 (28.6%) versus 8 (72.7%), vomiting 1 (7.1%) versus 5 (45.5%) 0.02 and diarrhoea 3 (21.4%) versus 5 (45.5%) 0.02 respectively. According to this study, lymphopenia was marked in MIC-children as well as increased levels of lactate dehydrogenase, CRP and D-dimer.[18] Moises et al presented their experience with a 6 month old infant who presented with fever, cyanosis and cardiogenic shock secondary to severe pulmonary hypertension and right ventricular failure. This new onset severe right ventricular failure was associated with COVID-19 on that young infant without previous history of heart disease.[19]

DISCUSSION

What was currently known was that children manifested milder symptoms and were less likely to be severe in comparison to adults. However, on 14 May 2020 the United States centers for disease control and prevention (CDC) released a health monitory report. That report focused a limelight on MIS-C associated with COVID-19.[20] This information prompted an international alert and stemmed a subset of pediatric patients who were manifesting with severe inflammation, multi-organ failure and testing positive for SARS-CoV-2.[18] Newer studies have demonstrated that the aftereffect of COVID-19 can results in a number of enormous disease burden in a number of pediatric cases like shock and multisystem inflammation temporarily associated with COVID-19, though severe illness was not commonly seen.

Of concern, many of the studies were not complete and did not include an extensive picture of the patients. Findings in this review reflected composite clinical presentation. So, COVID-19 was very dynamic and growing rapidly and we hoped for the rates, especially for MIS-C, of our outcomes to change. Despite some common features this review authenticate MIS-C was a diverse entity from Kawasaki disease or Kawasaki disease shock syndrome or COVID-19 in children. Most of the studies on pediatric patients did not focus on a specific age group, but this review told us, clinicians should remain vigilant with other age categories like infant in comparison to other age group.[7]

Dong et al conveyed a fearsome finding in which the proportion of severe and critical cases were higher in neonates when compared to the >16 year old age group (10.6% versus 3.0%). This study highlighted only disease severity and there was inadequacy of clinical findings in pediatric age groups.[14] The clinical findings like fever, cough, diarrhoea, dyspnoea, lymphopenia, increased LDH, D-dimer and CRP were the clinical features presented by MIC children but were quite different from children with COVID-19.[18] On the other hand Nguyen et al suggested MIS-C may be the post-infectious immune mediated response.[21]

CONCLUSION

Multisystem inflammatory disease is a new type of presentation of SARS-CoV-19 infection. This study highlights the necessity of giving special attention in COVID-19 positive infant age group, who may present with systemic features of shock with no co-morbidities. It should be considered as a new disease with unique symptoms, a greater variety of clinical courses and possible different pathophysiological mechanisms. Further epidemiological, immunological, clinical and genetic research is needed in infant age group is needed, together with long term follow-up studies of MIS-C patients.

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