



# Relationship between Kawasaki disease and COVID-19 for the development of MIS-C in children: a brief systematic review

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DOI: <https://doi.org/10.54448/mdnt21610>

Received: 09-12-2021; Revised: 10-12-2021; Accepted: 11-08-2021; Published: 12-15-2021; MedNEXT-id: e21610

## Introduction

The pandemic of COVID-19 affected adults more severely compared to children who presented severe and even rare clinical manifestations, besides consequences defined as indirect and direct. The indirect effects consist of educational deficits, lack of socialization, mental health impairment leading to pathologies such as depression and anxiety, increased violence, decreased vaccination coverage, increased hunger, it is also considered that these indirect effects of COVID-19 in children are greater than those caused by the direct form, such as clinical consequences and even death [1,2].

Representative of the direct form are the manifestations that could be classified as Kawasaki syndrome and/or toxic shock syndrome [3]. Kawasaki disease (KD) is an acute primary systemic vasculitis that affects mainly medium-caliber vessels and is diagnosed primarily by clinical analysis. In severe cases, KD manifests as toxic shock syndrome, which may or may not be followed by multiple organ dysfunction syndrome [4,5].

Thus, the worsening of this condition may define the syndrome was called Multisystem inflammatory syndrome in children (MIS-C), which has incidence in children between 5 and 17 years of age, with or without previous cardiac involvement and positive for SARS-Cov-2 virus with severe disease. Then, besides the gastrointestinal involvement, there are also skin lesions that are probably derived from long-lasting fever, non-productive conjunctivitis, and neuropathic symptoms, and also, there is a severe cardiovascular tissue lesion, where it can evolve with compromising of the arterial and vascular walls, especially the coronary ones, due to its close connection with the infected myocardium.

Thus, this study aimed to analyze the relationship between Kawasaki disease and COVID-19 for the development of MIS-C.

## Methods

This is a systematic literature review based on the following scientific questions: 1 - Is there a relationship between the manifestation of Kawasaki Disease and COVID-19? 2 - If there is such a relationship, can another condition arise? 3 - What are the manifestations of MIS-C? Are there other consequences? The articles selected for the study had to meet the following eligibility criteria: (1) be published in a national and international journal; (2) in the period from 2020 to 2021; (3) and be freely available in full. Articles that did not answer the scientific questions proposed by the study were excluded.

A literature search was conducted in the electronic databases BVS/LILACS, Scielo, and PubMed in the period from 2020 to 2021. The search strategy included the following descriptors: "Kawasaki Disease OR Kawasaki Syndrome", "MIS-C" and "COVID-19". In a first step to select the studies, duplicates were removed and the research team screened the titles. Next, abstracts of eligible studies were selected to perform full-text screening. The selected articles underwent peer review, and disagreements between reviewers were reviewed by the study advisor.

After full-text screening, research team members extracted data from the included studies using a data extraction form, which included information on study characteristics (title, year and country of publication), methods (study design), and scientific questions were answered through the content of the articles.

## Results and Discussion

A total of 606 articles were found,  $n = 499$  from the PubMed platform,  $n = 77$  from Scielo, and  $n=30$  from Lilacs. Of the articles that met the inclusion criteria,  $n = 34$  were found in total, of these only  $n=9$  were from Scielo,  $n = 4$  from Lilacs, and  $n = 21$  from PubMed. Children manifest a high inflammatory response that possibly causes cardiac lesions and develops Kawasaki disease more rapidly. Consequently, these different presentations when compared to adults, cause complications in some devices, such as cardiovascular, the main one being early myocarditis in 56% of patients, evolving with hemodynamic instability and developing Kawasaki Disease Shock Syndrome (KDSS). KDSS can affect up to 7 out of 10 patients with Kawasaki Disease, but when associated with COVID-19, this complication reaches 52% [5-17].

Among the first series of cases containing multisystemic inflammatory syndrome, eight patients in the age range of 4 to 17 years were reported [4]. Thus, all of them evolved to cardiogenic shock and one of the patients to coronaritis, which is characteristic of Kawasaki syndrome. There was a pediatric case of DK and COVID-19 concurrently published in April 2020. After that, similar cases to this one were published in European and American countries about multisystemic inflammatory syndrome, in which it has many clinical and laboratory aspects similar to DK [5-10], but differ in the rates of cardiac involvement, age range, and predominance of African descendant ethnicity [4,11-14].

The cases in question occurred a few days after the manifestation of COVID-19 in the patients. MIS-C has a lower frequency of respiratory symptoms consequent to hemodynamic decompensation [16,17]. However, there are three inheritance patterns in cases of children hospitalized with MIS-C, these being: shock or organ failure, persistent fever, but without features of Kawasaki Disease; second pattern that characterizes the diagnosis of DK; and the third pattern that is severe containing cardiac, gastrointestinal, and systemic dysfunction [18]. The serological test with detection of anti-IgG [16] antibodies is used to confirm the diagnosis of active viral infection in patients with Kawasaki Disease, and was applied to 44 children participating in this study, showing a reactive result in 91% of cases [19-27].

It is notable that this inflammatory cardiovascular condition occurs mainly in pediatrics in 50% of all reported cases in children under 2 years of age, and 80% of the other cases that are concentrated in ages 2 to 5 years. The association between severe respiratory viral infection corresponds between 9% and 42% of

children with Kawasaki vasculitis who were positive for this severe respiratory infection with 30 days before presenting with the symptomatology of this systemic inflammation [28,29].

## Conclusion

There is a relationship between the damage at the cellular level by the virus and the severe vascular inflammatory condition, but it is noticeable that the cases do not present patterns of occurrence, except for a symptomatology extremely similar to Kawasaki Syndrome, without the need for previous cardiac involvement. Therefore, MIS-C is responsible for the cardiac damage caused by SARS-CoV-2. Therefore, it is extremely important to differentiate the presentation of each of these pathologies, so that early and appropriate management can occur.

**Keywords:** Kawasaki disease. MIS-C. COVID-19.

## Acknowledgement

Nil.

## Funding

Not applicable.

## Data sharing statement

No additional data are available.

## Conflict of interest

The authors declare no conflict of interest.

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