Original Article

Heart Failure in Children and Adolescents with Covid-19: A Systematic Review of the Literature

Lucas Quaresma Martins,[1] *Gabriel Ribeiro de Souza,*[1] *Daniel Garcia da Gama Alves,*[1] *Kaylane Fernanda Costa de Melo,*[1] *Paula Cordeiro Aguiar de Almeida,*[1] *Ádria Rayane Lima Cascaes,*[1] *Antonio Maria Zacarias Araújo Monteiro*[2]

Universidade do Estado do Pará,[1] *Belém, PA – Brazil*
Centro Universitário do Estado do Pará,[2] *Belém, PA – Brazil*

Abstract

Background: **Cardiovascular structural/functional changes caused by COVID-19 may be related to the presence of heart failure (HF), especially in children and adolescents, as the SARS-CoV-2 virus invades cardiomyocytes, leading to cardiac dysfunction.**

Objective: **To assess the mechanism by which COVID-19 becomes a risk factor for the development of HF in children and adolescents.**

Methods: **This was a systematic literature review of articles indexed in PubMed, BVS and SciELO, following the PRISMA recommendations. DeCS/MeSH descriptors were used in the search.**

Results: **A total of 685 studies were identified: 418 in Pubmed, 264 in BVS and three in SciELO. After exclusion of 160 duplicate articles, and analysis of titles and abstracts, 14 articles were read in full, and 10 selected for the final sample. All articles were published between 2020 and 2022; there were 10 cohort studies (eight retrospective and two prospective). Six articles addressed the Multisystem Inflammatory Syndrome in Children (MIS-C), and four articles addressed the reduction in left ventricular ejection fraction in COVID-19 patients.**

Conclusions: **Most patients recovered without cardiovascular sequelae, although MIS-C may cause severe systemic failure, which led to death in some studies. More research and more comprehensive studies on this theme are warranted.**

Keywords: **Heart Failure; Child; Adolescent; COVID-19; SARS-CoV-2.**

Introduction

According to the Brazilian Society of Cardiology, heart failure (HF) is a complex clinical syndrome, in which the heart cannot contract or relax efficiently enough to meet all tissue metabolic demands, or when it does, it does exclusively with above physiological filling pressures. Therefore, HF is triggered by structural or functional changes associated with reduced cardiac output and/or increased filling pressures.[1]

These pathological changes may be associated with diseases that affect the cardiovascular system, as exampled by COVID-19, a contagious infectious disease considered a pandemic in 2020.[2] COVID-19 correlates with HF, since its etiologic agent, the SARS-CoV-2 virus, invades cardiomyocytes, causing myocardial dysfunction and other cardiovascular complications, with a mortality rate of 52%.[3,4]

Mailing Address: Lucas Quaresma Martins •
Universidade do Estado do Pará - Centro de Ciências Biológicas e da Saúde – Travessa Perebebuí, 2623. Postal Code 66087-662, Belém, PA – Brazil
E-mail: lucasquaresmamartins@gmail.com
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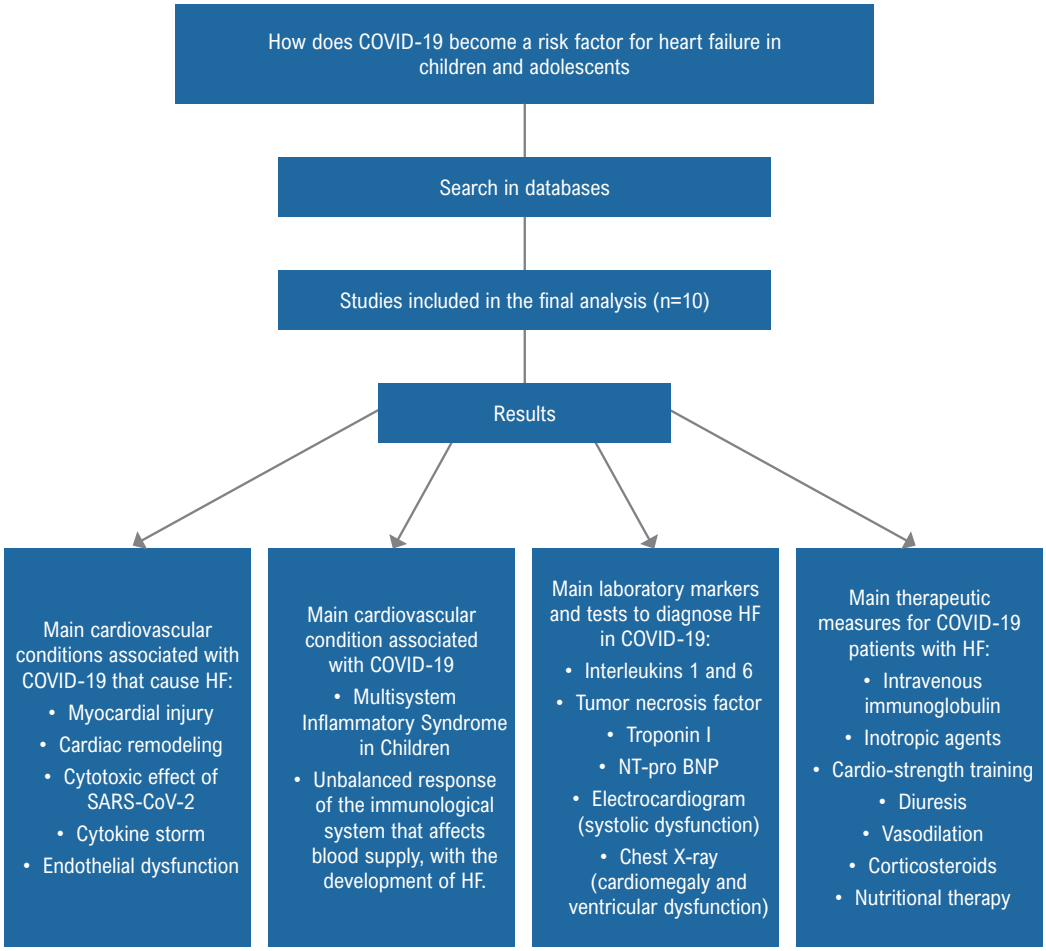
With respect to COVID-19 manifestations and outcomes by age range, the clinical course is less aggressive in children than adults or older patients, due to physiological specificities that affect disease progression. In pediatric patients, the most common symptoms are low fever, cough, rhinorrhea, and sore throat.[5] However, with advances in scientific knowledge about COVID-19, new outcomes related to cardiovascular system and HF have been reported, including Multisystem Inflammatory Syndrome in Children (MIS-C), which affects the respiratory tract of these children.[6]

Consequently, the possible negative systemic effects in children and adolescents with COVID-19 and its relationship with HF are notable. Nevertheless, studies investigating the effects of diseases, and their associations with age are scarce, which is a limiting factor for the development of effective therapeutic approaches.[7] Thus, the present study aims to assess how COVID-19 becomes a risk factor for the development of HF in children and adolescents. This study will contribute to scientific community and society in providing important knowledge about the subject.

Methods

This study was a systematic review, which aims to conduct an organized bibliographic search for the most relevant

Central Illustration: Heart Failure in Children and Adolescents with Covid-19: A Systematic Review of the Literature



ABC Heart Fail Cardiomyop. 2024; 4(2):20240001

studies on a health-related topic. In our study, the topic was developed using the PICO (Population, Intervention, Comparison/Control, and Outcome) and the search question: "How does COVID-19 become a risk factor for HF in children and adolescents?" The study followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations to minimize biases.[8] Since the study was a literature review, it did not require ethical approval and used secondary data only.

Data collection and filtering

Data collection was performed through a search on online databases including the US National Library of Medicine National Institutes of Health (PubMed), *Biblioteca Virtual em Saúde* (BVS) and Scientific Electronic Library Online (SciELO) on 12 May 2023. The following DeCS/MeSH (Descritores em Ciências da Saúde/Medical Subject Headings) descriptors were used in the search: heart failure, COVID-19, SARS-CoV-2, Coronavirus, Child, Pediatrics and Adolescent, in addition to their versions in other languages. For the search for combination of the terms, the Boolean operators AND and OR were used; hence the following search strategy was implemented: "Heart Failure" AND (Covid-19 OR SARS-COV-2 OR Coronavirus) AND (Child OR Pediatrics OR Adolescent).

Three steps were followed for the article selection: (1) search in the database for the descriptors cited, with application of filters and exclusion of duplicates in different databases; (2) selection of titles and abstracts, following the inclusion and the exclusion criteria; and (3) reading of full texts based on inclusion and exclusion criteria. During this process, three authors performed these steps and two acted as reviewers. The Zotero reference management software was used for data filtering and organization of selected data, specifying the reason and the step data were excluded. During the study period, there

was no lack of consensus among investigators on the selection of studies to compose the final sample.

Inclusion and exclusion criteria

The following inclusion criteria were used: observational, case-control, cohort studies, published in full, available in Portugues and English, that answered the research question.

The exclusion criteria were articles that did not answer the research question for not correlating HF and COVID-19 in children and adolescents, studies in which the main focus was patients with cardiovascular diseases prior to SARS-CoV-2 infection, and studies with incomplete or unavailable methods.

Data analysis

For analysis of the articles selected, the investigators made a synthesis of the studies, examining the most important aspects, based on inclusion criteria and adequacy of the theme. The results were described in a summary table, including the following items: study number, authors, year of publication, type of study, country, population, mean age of patients, time of follow-up, and main findings.

To assess the risk of bias, we used the Newcastle-Ottawa score, which evaluates the studies based on criteria related to cohort selection and comparison, and the study.[9] The Joanna Briggs Institute (JBI) critical Appraisal checklist was used to assess the quality of evidence by evaluation of studies' design, development, and analysis.[10]

Data were first organized in a spreadsheet in the Microsoft Office Excel 2016, and the studies that met the inclusion criteria of the review were selected. Then, information collected from the studies included in the final sample were categorized based on the research question. Analysis of data was made qualitatively, taking the following four steps: 1) full and detailed reading of the article; 2) data description and construction of summary chart; 3) detailed reading of the papers; and 4) analysis of the article content.

Results and Discussion

A total of 685 papers were identified in the databases – 418 in PubMed, 264 in BVS and three in SciELO). However, 160 duplicate articles were excluded, resulting in 525 articles. Titles and abstracts of the articles available in the databases were read, as well as some private articles, yielding eight articles indexed in PuMed, five indexed n BVS and one in SciELO, with a total of 14 articles, that were considered eligible after full reading. After the exclusion criteria were applied, two articles were excluded due to the lack of "Methods" section, and two for not answering the research question of the present study. Ten articles were then analyzed using the Newcastle-Ottawa and the JBI scales. Figure 1 represents the PRISMA flowchart of the article selection steps.

No article was excluded during the analysis of biases and quality of evidence using the instruments previously mentioned. Thus, 10 articles, considered relevant and scientifically reliable were included in the present systematic review. Table 1 describes the score of each manuscript according to the Newcastle-Ottawa and JBI scales.

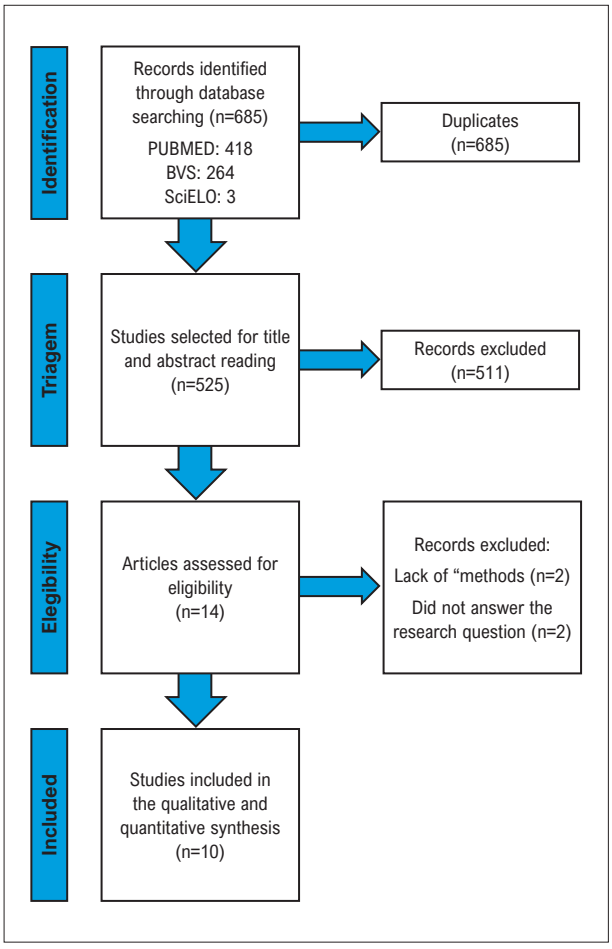


Figure 1 – *PRISMA flowchart detailing the steps for study selection; source: the authors.*

After full reading and analysis of the studies included, the main information of the articles selected (study number, authors, year of publication, type of study, country of origin, sample population, mean age of patients, time of follow-up and main results) were organized in a summary table (Table 2).

Four studies (E4-E6 ad E10) highlighted the direct association of HF with severe cases or complications of mild COVID-19, which was corroborated by Costa et al.,[21] and the physiopathology of the cardiovascular involvement linked to several factors including direct myocardial injury (E5), cardiac remodeling due to increased arterial stiffness, direct cytotoxic effect of SARS-VCoV2, cytokine storm, endothelial damage and dysfunction, hyperinflammation, increased oxygen demand, electrolyte imbalance, side effects of pharmacological treatment of COVID-19 (E6), pleural effusion and atelectasis (E4).[21]

MIS-C was the main subject in six manuscripts (E1, E2, E6-E8, E10), showing the close relationship between HF and this COVID-19 complication. MIS-C manifested within a mean of four to six weeks after infection (E3). The literature analyzed tend to attribute it to an unbalanced response of

Table 1 – Analysis of biases and quality of evidence of the studies selected using the Newcastle-Ottawa and the Joanna Briggs Institute scales

#	Newcastle-Ottawa			Q.A.	Joanna Briggs Institute											R.B.
Article	Sel.	Com.	Des.		Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	
E1	**	*	***	Fair	S	S	S	S	N	I	S	S	S	NA	S	Low
E2	***	*	***	Good	S	S	S	N	I	I	S	S	S	NA	S	Moderate
E3	***	*	***	Good	S	S	S	S	N	I	S	S	S	NA	S	Low
E4	****	*	***	Good	S	S	S	S	S	I	S	S	S	NA	S	Low
E5	***	*	***	Good	S	S	S	S	N	I	S	S	S	NA	S	Low
E6	***	*	***	Good	S	S	S	N	NA	S	S	S	S	NA	S	Low
E7	****	*	***	Good	S	S	S	S	N	I	S	S	S	NA	S	Low
E8	***	*	***	Good	S	S	S	N	N	I	S	S	S	NA	S	Moderate
E9	***	*	***	Good	S	S	S	N	N	I	S	S	S	NA	S	Moderate
E10	***	*	***	Good	S	S	S	S	N	I	S	S	S	NA	S	Low

Source: the authors. Sel.: Selection; Com.: Comparability; Out.: Outcome; Q.A.: Quality of the article; R.B.: Risk of bias. Asterisks represent the stars in the Newcastle-Ottawa scale. Good; 3 or 4 stars in selection domain, 1 or 2 stars in comparability domain and 2 or 3 stars in outcome; fair: 2 stars in selection domain, 1 or 2 stars in comparability domain and 2 or 3 stars in outcome domain. Q.1-Q.11 indicate questions 1 – 11 of the Joanna Briggs Institute Critical Appraisal Checklist; Y: yes; N: no; U: unclear; NA: not applicable; high risk of bias: <49% of questions answered with "yes"; moderate risk: 50 - 69% of questions answered with "yes" and "low" > 70% of questions with "yes".

the immunological system (E1-E3), frequently leading to myocardial injury – one of its main targets – and consequently affecting the blood supply (E1-E3, E6, E10), similarly to that reported by Vieira et al.[22] More severe MIS-C was described in older children (E2, E3, E10), leading to death in patients of two studies (E5, E10).[22]

Regarding the hospital course of patients infected by SARS-CoV-2 who developed MIS-C, according to the E1, there was an average delay of six days from the first clinical signs to manifestation of HF symptoms. This is a considerable time, particularly as compared with the two day-interval from the first general signs to hospitalization of the patient affected, described by Prata-Barbosa et al.[23] In addition, as also highlighted in the E1, direct and indirect intensive care unit (ICU) admission rates, analyzed in the review, were considerably higher than the 8% reported in the E5, among patients without diagnosis of MIS-C.[23]

MIS-C may lead to multiple organ failure, affecting mainly the cardiovascular, gastrointestinal, and nervous systems (E6, E10). Main manifestations of HF reported in the articles include cardiac injury, such as left ventricular dysfunction (E1, E2, E6, E9 and E10) and valvulitis (E3, E6 and E9) and diffuse damage, such as endothelial dysfunction (E3, E6, E8-E10). This leads to HF as pathological dilatation, commonly of coronary arteries (E10) through the myocardium and the whole body (E6).[24]

The early diagnosis of MIS-C may prevent the occurrence of cardiovascular damage – like HF – caused by the disease (E1) and is extremely useful, since its presence is an indicative of poor prognosis (E5) of COVID-19. The immediate treatment of MIS-C is important for the restoration of vital organ function.[25] Although its etiology has not been completely defined, the cytokine storm phenomenon has been frequently reported, with predominance of interleukin-1, interleukin-6 and tumor necrosis factor (E3). Biochemical markers of myocardial damage and HF (E3, E10), as well as 12-lead electrocardiogram and echocardiogram (E3) are useful for the rapid diagnosis and treatment of the disease.[25]

With respect to ventricular activity, in general, all patients had some degree of ejection fraction reduction or impairment, especially those with MIS-C. However, a left ventricular ejection fraction (LVEF) lower than 30% (i.e., reduced LVEF, characterizing an important cardiac dysfunction associated with HF) in more severe cases was reported in only two articles (E1 and E 10). Consequently, in agreement with Barberato et al.,[26] most cases of ventricular dysfunction in pediatric patients was associated with previous cardiac comorbidity.[26]

In E2, there was a prevalence of 66.7% of mild and moderate left ventricular dysfunction in patients aged older than six years, which is considerably higher than the prevalence in the whole sample (40%). This may be explained by the immaturity of the immune system of patients in younger age ranges and inborn errors of immunity triggered by SARS-CoV-2 in older children, leading to MIS-C-related hyperinflammation, as concluded by Sancho-Shimizu et al.[27]

Besides, according to E6, the ejection fraction reduction is directly correlated with a reduction in flow-mediated dilation in cardiac tests, possibly due to endothelial damage caused by hyperinflammation in MIS-C. In this regard, endothelial damage induced by SARS-CoV-2 is related to a greater number of cases of ischemia/reperfusion, which may result in chronic myocardial damage, including systolic ventricular reduction and HF.[28]

Table 2 – Articles selected for review

#	Authors	Year	Type	Country	Sample	Mean age	Follow-up	Main results
E1	Belhadjer et al.[11]	2020	Retrospective cohort study	France and Switzerland	35	10 years	One month	10 patients had FE below 30% and 25 between 30 and 50%. Recovery of left ventricular function was observed in 71% of patients, mean time of delay of two days after admission. No patient had a thrombotic or an embolic event.
E2	Campanello et al.[12]	2022	Retrospective cohort study	Italy	25	Five years	18 months	Median LVEF was 55% (IQR 50, 60), but 40% of patients had left ventricular dysfunction (LVEF < 53%). Echocardiogram at discharge showed recovery of LVEF and regression of coronary dilatation and small aneurysms
E3	Stasiak et al.[13]	2022	Retrospective cohort study	Poland	51	Seven years	17 months	Patients who developed heart failure had an ejection fraction of 66%. Although laboratory tests of all patients returned to normal after six weeks, only 13 children did not develop cardiac sequelae
E4	Wen et al.[14]	2022	Retrospective cohort study	China	1062	NA	71 months	Only 14 patients had heart failure. Patients received nutritional myocardial therapy, positive inotropic drugs, diuresis, and vasodilation treatment. Average hospital stay of the severe cases was 15 days, all were cured or improved and discharged. There was no death.
E5	Kari et al.[15]	2021	Retrospective cohort study	Saudi Arabia	88	NA	Two months	Four patients admitted to the pediatric ICU died, and one developed heart failure. More than 50% of children were discharged within seven days of hospitalization
E6	Çiftel et al.[16]	2022	Retrospective cohort study	Turkey	38	8.8 years	Seven months	20 patients had LVEF < 55%, mostly in patients with MIS-C. All patients with MIS-C have recovered. Only half of patients with severe MIS-C have recovered, and the other half developed cardiopulmonary complications like congestive HF. One patient died due to multiple-organ failure
E7	Mól et al.[17]	2021	Retrospective cohort study	Poland	66	6.5 years	Four months	One third of patients had cardiac dysfunction; 95% of children developed conjunctival hyperemia
E8	Blumfield et al.[18]	2020	Retrospective cohort study	USA	16	9.2 years	One month	10 patients had systolic myocardial dysfunction and cardiomegaly; nine patients had congestive HF or pulmonary ardiogenic edema

E9	Diniz et al.[19]	2020	Retrospective cohort study	Brazil	48	7.5 years	Three months	33 patients recovered and were discharged, eight were hospitalized in the ICU or in the ward. All deaths occurred in the MIS-C group. All patients had HF related to left ventricular dysfunction, one with severe disease
E10	Grama et al.[20]	2022	Retrospective cohort study	Romania	34	6.8 years	13 months	Five patients had LVEF < 55% and two had LVEF < 30%. Severe complications were observed in the MIS-C group, in addition to long-term like congestive HF in one patient. Half of patients with severe MIS-C did not have cardiac sequelae

Source: the authors; LVEF: left ventricular ejection fraction; ICU: intensive care unit; EF: ejection fraction; MIS-C: Multisystem Inflammatory Syndrome in Children.

Three studies (E1, E2 and E3) reported a similar mean recovery time (seven days) of ventricular function after cardiovascular impairment due to SARS-CoV-2 infection, followed by treatment, with significant improvement of LVEF and HF. This was accompanied by normalization of myocardial enzymes in most patients (E2). This result differs from that reported by Goldraich et al.[29] who found enzymatic and structural changes in adults even 56 days after acute systemic inflammation. Besides, according to E3, in COVID-19 patients with cardiac contractility abnormalities and preserved ejection fraction, manifestations of the disease remained subclinical (E3).[29]

Regarding laboratory and image findings, six articles (E1, E2, E3, E7, E8 and E9) correlate the increase in troponin I levels with cardiovascular diseases, including the direct association with myocardial injury (E2), development of HF (E1, E3, E7 and E8) and right and left ventricular dysfunction (E9). A strong relationship of increased N-terminal pro b-type natriuretic peptide (NT-proBNP) with effects on the ejection fraction has been established in four studies (E2, E3, E7 and E8) and with inflammatory markers in two (E3 and E7). These findings are in line with the study Tapias Filho et al.,[30] who demonstrated higher rates of cardiovascular diseases like MIS-C in patients with increased troponin I levels.[30]

Three studies (E3, E8 and E9) have found electrocardiographic abnormalities in a considerable number of patients, especially patients with myocardial systolic dysfunction, detected in 63% of MIS-C patients.[18] This was also demonstrated in the study by Gaspar et al.,[25] in which 83.3% of patients developed cardiac dysfunction with identifiable electrocardiographic changes. Chest imaging findings revealed a high frequency of cardiomegaly, congestive HF (E8) and left and right ventricular dysfunction.[25]

With respect to therapeutic approaches, three studies (E2, E3 and E9) highlighted the use of intravenous immunoglobulin (IVIg). This strategy was also shown to be effective in the study by Lozano-Espinosa et al.,[31] in which IVIg was administered to 98% of patients with MIS-C, who had a favorable course. In this context, according to E2, the combined use of IVIg and intravenous steroids contribute to a reduction in the risk of cardiovascular dysfunction – possibly associated with HF – as compared with the use of IVIg alone.[31]

On the other hand, in E3, some patients did not show a good response to the combined treatment, presenting high fever, high inflammatory markers, and persistent respiratory and circulatory failure. Therefore, an alternative therapy was used with cyclosporine and biological agents, which, according to Oliveira et al.,[32] act as immunosuppressants, and their combination should be made with caution due to possible adverse effects. Besides, as reported in E9, there was not a significant difference in mortality between patients treated with IVIg, corticosteroids and low molecular weight heparin.[19]

Three articles (E1, E4 and E7) reported the use of inotropic agents in patients with cardiac dysfunction, HF and cardiogenic shock. In E1, this therapeutic approach was applied to 80% of patients admitted to ICUs, which is in accordance with the study by Bistola et al.,[33] who pointed out that, despite their relatively high potential for adverse events, inotropes are indispensable in the management of acute HF in children. In E4, for patients with myocardial damage, a nutritional myocardial therapy was adopted, in addition to cardio-strength training, diuresis, vasodilation treatment combined with traditional Chinese medicine.[33]

In E9, 83.30% of patients with left ventricular dysfunction treated with IVIg and corticosteroids showed improvement of left ventricular systolic function after administration of these medications. E4 underscores that the early diagnosis of severe cases of cardiovascular dysfunction is crucial for a timely and effective intervention, aiming at treatment progression and patient recovery. Rossi Neto et al.[34] also highlighted the importance of a rapid diagnosis as the basis of acute HF treatment, correlating the diagnostic delay with worse prognosis.[34]

The findings of the present systematic review should be interpreted with caution, due to limitations of the study, including: (1) publication bias, inherent to the study design,

which directly depends on the criteria adopted in the databases selected; (2) lack of scientific evidence from studies addressing the subject proposed; most of the results presents were either secondary or indirect; and (3) the considerable heterogeneity of the studies selected, particularly regarding sample population.

Conclusions

In the present systematic review, we analyzed the relationship between COVID-19 and HF in children and adolescents in 10 published articles. The main finding was the predominance of studies describing MIS-C, a condition triggered by an exacerbated immune response of younger patients to SARS-CoV-2 infection, from which all patients recovered without cardiovascular sequelae, although some studies have reported cases of death, as shown in the Central Illustration.

Therefore, the present study contributes to the diffusion of scientific knowledge about the cardiovascular damage of COVID-19 in children and adolescents, not only among the scientific community but also in the context of public health. In addition, the present review concludes that the scientific production on COVID-19 as a causative factor of HF in children and adolescents is so far insufficient in light of the scale and relevance of the problem. In this sense, more research and more comprehensive studies on this theme are warranted.

Author Contributions

Conception and design of the research and Writing of the manuscript: Martins LQ, Souza GR, Alves DGG, Melo KFC, Almeida PCA, Cascaes ARL; Acquisition of data, Analysis and interpretation of the data and Statistical analysis: Martins LQ, Souza GR, Alves DGG, Melo KFC, Almeida PCA; Critical revision of the manuscript for content: Martins LQ, Souza GR, Alves DGG, Melo KFC, Almeida PCA, Cascaes ARL, Monteiro AMZA.

Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

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Study association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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