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RESEARCH ARTICLE

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Coronavirus disease 2019 (COVID-19): A systematic review of 133 Children that presented with Kawasaki-like multisystem inflammatory syndrome

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Abstract

Kawasaki-like disease (KLD) and multisystem inflammatory syndrome in children (MIS-C) are considered as challenges for pediatric patients under the age of 18 infected with coronavirus disease 2019 (COVID-19). A systematic search was performed on July 2, 2020, and updated on December 1, 2020, to identify studies on KLD/MIS-C associated with COVID-19. The databases of Scopus, PubMed, Web of Science, Embase, and Scholar were searched. The hospitalized children with a presentation of Kawasaki disease (KD), KLD, MIS-C, or inflammatory shock syndromes were included. A total number of 133 children in 45 studies were reviewed. A total of 74 (55.6%) cases had been admitted to pediatric intensive care units (PICUs). Also, 49 (36.8%) patients had required respiratory support, of whom 31 (23.3%) cases had required mechanical ventilation/intubation, 18 (13.5%) cases had required other oxygen therapies. In total, 79 (59.4%) cases had been discharged from hospitals, 3 (2.2%) had been readmitted, 9 (6.7%) had been hospitalized at the time of the study, and 9 (6.7%) patients had expired due to the severe heart failure, shock, brain infarction. Similar outcomes had not been reported in other patients. Approximately two-thirds of the children with KLD associated with COVID-19 had been admitted to PICUs, around one-fourth of them had required mechanical ventilation/intubation, and even some of them had been required readmissions. Therefore, physicians are strongly recommended to monitor children that present with the characteristics of KD during the pandemic as they can be the dominant manifestations in children with COVID-19.

KEYWORDS
children, COVID-19, Kawasaki Disease, multisystem inflammatory syndrome, pediatrics

Abbreviations: AHF, acute hearth failure; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CSS, cytokine storm syndrome; CT, computed tomography; ECMO, extra corporeal membrane oxygenation; ECO, echocardiography; G6PD, glucose-6-phosphate dehydrogenase; GI, gastrointestinal; HFNC, high flow nasal cannula; IL-6, interleukin 6; KD, Kawasaki disease; KLD, Kawasaki-like disease; LVSD, left ventricular systolic dysfunction; MERS, Middle East respiratory syndrome; MIS-C, multisystem inflammatory syndrome; PICU, pediatric intensive care unit; PIMS-TS, pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2; RT-PCR, reverse transcription polymerase chain reaction; SARS, severe acute respiratory syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VSD, ventricular septal defect.

1 | INTRODUCTION

Since December 2019, the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from the family Coronaviridae causing coronavirus disease 2019 (COVID-19) emerged in Wuhan, China, and then became a global health challenge. This was the third epidemic of the large family Coronaviridae, which induced SARS and the Middle East respiratory syndrome at the beginning of the present century.[1,2] The authors' knowledge of COVID-19 was thus based on two previous experiments in their early phases, that hyperinflammation caused by macrophage-activating syndrome and cytokine storm release (CSR) was involved in the pathogenesis of COVID-19.[3-6]

Initially, COVID-19 patients were identified with symptoms such as dry cough, fever, dyspnea, headache, weakness, and lethargy, which later appeared with gastrointestinal (GI), neurological, and cutaneous manifestations.[7,8] Early on, it seemed that children were not the target groups and they were less likely to be affected, so there were a small number of reports on childhood illnesses.[9,10] After a while, the surge of comparable reports of children attending medical centers increased with identical clinical characteristics of this disease in different countries during the pandemic. Signs and symptoms in these patients had something in common with Kawasaki disease (KD), KD shock syndrome, toxic shock syndrome (TSS), fever, shock, and skin rash. Also, conjunctivitis, extremity edema, and GI manifestations were observed based on the positive nasopharyngeal reverse transcription-polymerase chain reaction (RT-PCR) or antibody (viz. serological) testing for SARS-CoV-2 within 4 weeks of the onset of the symptoms.[11-13] With reference to the growing number of reports in the first half of May, the Royal College of Pediatrics and Child Health of the United Kingdom and the Centers for Disease Control and Prevention of the United States, respectively, declared an alert on this condition under the label "Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS)" and "Multisystem Inflammatory Syndrome in Children (MIS-C)."[14]

In this respect, MIS-C refers to a hyperinflammatory systemic condition that shares numerous similar features of KD such as lymphadenopathy, diarrhea, elevated inflammatory biomarkers, prolonged fever, skin rash alongside some separate specifications like older onset, the predominance of abdominal symptoms, cases with left ventricular systolic dysfunction and acute heart failure (AHF).[11,15] The present study was designed and implemented to demonstrate the relationship between severely ill cases with KD/MIS-C and COVID-19.

2 | METHODS

2.1 | Search databases and search strategies

This study was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) reporting guidelines[16] on July 2, 2020, and updated on December 1, 2020, to identify the studies on KD/MIS-C associated with COVID-19. To this end, the relevant studies were searched using the databases of Scopus, PubMed (i.e., MEDLINE), Web of Science, Embase (Elsevier), and Scholar. The following search keywords were also used: "coronavirus," "COVID-19," "coronavirus and infection," "SARS-CoV-19," "2019 novel and coronavirus," "Kawasaki," "hyperinflammatory," "inflammatory syndrome," "Kawasaki-like," and "MIS-C." The keywords list utilized in the search is provided as a Supporting Information appendix. The PRISMA flow diagram of the study selection process is also illustrated in Figure 1.

2.2 | Eligibility criteria

The pediatric patients (0–≤18 years of age) with more than 1 day of subjective or measured fever (≥100.4°F/38°C) and hospital stay, that presented with at least KD, Kawasaki-like disease (KLD), MIS-C, or inflammatory shock syndromes, with the evidence of COVID-19, and with confirmed SARS-CoV-2 infection using nasopharyngeal RT-PCR or antibody (viz. serological) testing were included in this study. Moreover, irrelevant studies, conference abstracts, and duplicates were excluded.

2.3 | Data extraction and quality assessment

Two independent and blinded reviewers extracted the data and then performed crosschecking. A third reviewer also resolved the disagreements via consensus. Accordingly, the data were extracted: first author's name, study setting, type of study, patient's age, gender, initial presentations at the time of hospital admission, type of hospital admission ward (pediatric ward and pediatric intensive care unit [PICU]), type of COVID-19 confirmation tests (RT-PCR and antibody [viz. serological] testing), mechanical ventilation and intubation, pulmonary and extra-pulmonary findings, electrocardiography reports, echocardiography reports, methods of treatment, complications, and outcomes. Additionally, a series of images from two studies included were presented [17,18] (Figures 2 and 3) through formal permissions obtained from their publishers. Regarding the quality assessment, two independent reviewers evaluated the risk of bias of the included cohort studies using the modified version of the Newcastle–Ottawa Scale,[19] and the National Institutes of Health Quality Assessment tool for case series/reports[20] (Tables S1 and S2).

3 | RESULTS

A total number of 69 studies were recognized in the initial search. After removing the duplicates and the irrelevant articles, 45 eligible studies including 6 cohort studies, 7 case series, 24 case reports, and 8 correspondences or letters to editors

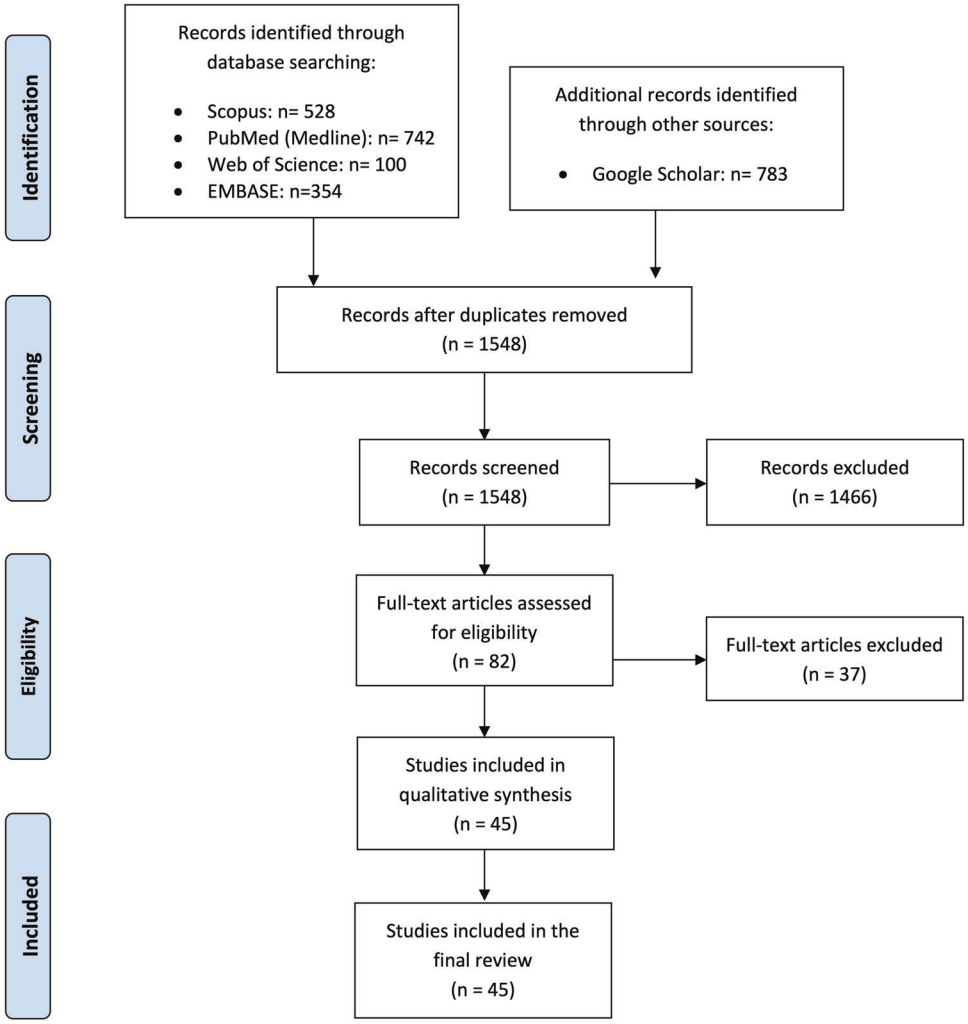

FIGURE 1 Flow diagram of the study selection process. Preferred reporting items for systematic reviews and meta-analyses (PRISMA). Adapted from Moher et al.[16] (doi.org/10.1371/journal.pmed.1000097) ©2009, under terms of Creative Commons Attribution 4.0 International License (creativecommons.org/licenses/by/4.0/legalcode)

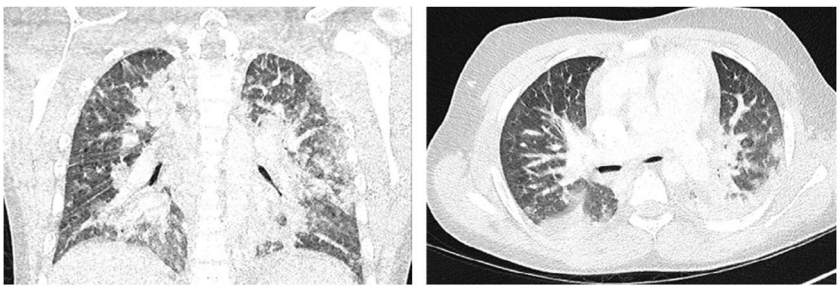

FIGURE 2 Lung window axial and coronal CT images of patient 3 that show diffuse bilateral consolidations predominantly located in the posterior aspects of the upper and inferior lobes. Images obtained from Dallan et al.[17] The Lancet Child & Adolescent Health, Vol 4(7), E21-23 July 1, 2020, and permission to use granted by Elsevier License Terms and Conditions. CT, computed tomography

related to KLD/MIS-C associated with COVID-19 were included. As a whole, 133 children with the mean age of 9 ± 4.2 (age range: 4 months to 17 years old, interquartile range: 5.5–13 years old) with 82 (61.6%) male cases, 50 (37.5%) females, and one unknown gender were reviewed (Table 1).

Moreover, the type of disease mentioned in the studies was reported, and was then classified as KD in 46 (34.6%) patients (including subtypes of atypical KD in 12 [9%] patients, incomplete KD in 18 [13.5%], classic KD in 6 [4.5%], and KD in 10 [7.5%]), MIS-C in 22 (16.5%), PIMS-TS in 25 (18.8%), and hyperinflammatory shock

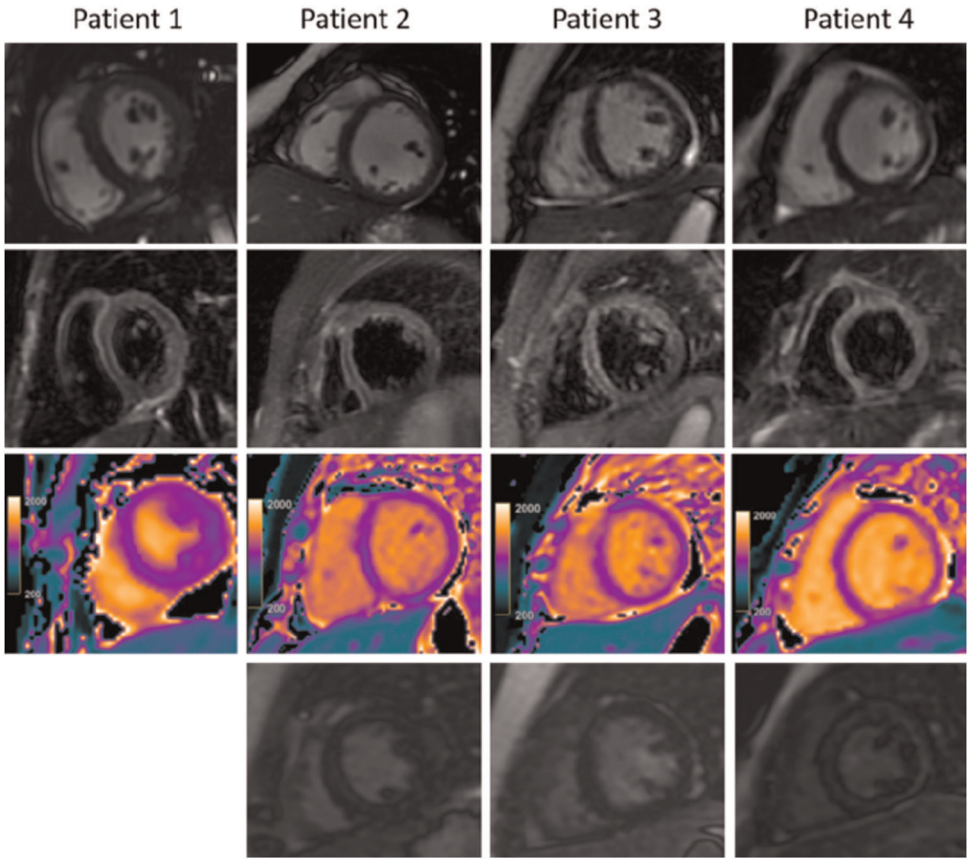

FIGURE 3 Cardiac MRI for four children with a clinical diagnosis of acute myocarditis in the setting of COVID-19-related Kawasaki-like symptoms. The top panel demonstrates minimal pericardial effusion on cine images. The second panel demonstrates increased T2-STIR signal intensity with average ratios between myocardium and muscle more than 2 in patient 2 (12-year-old male), patient 3 (11-year-old female), and patient 4 (6-year-old female). The third panel demonstrates abnormal native-T1 mapping, which was more than 1100 ms in patients 2, 3, and 4 and normal in patient 1 (8-year-old female). The bottom panel demonstrates absence of late gadolinium enhancement (LGE) in patients 2 and 3. Myocardial null times were recognized as too short in patient 4 but could not be repeated due to lack of further patient cooperation; however, a review of Look-Locker images and additional sequences revealed no LGE. Images obtained from Blondiaux et al. [18] Radiology, June 9, 2020, and permission to use granted by Ashley E. Daly, Senior Manager, Journal Rights & Communications Publications, Radiological Society of North America (RSNA). COVID-19, coronavirus disease 2019; MRI, magnetic resonance imaging

in 8 (6%) patients. Other diseases such as refractory/respiratory failure, cardiac dysfunction, and shock, hypotensive septic shock, myocarditis with heart failure, Kawasaki disease shock syndrome, and TSS were detected in 18 (13.5%) patients. Additionally, the type of disease had not been reported in 14 (10.5%) cases.

With regard to the symptoms of patients, skin rash ($n = 74$, 55.6%) was the most common one followed by conjunctivitis ($n = 65$, 48.8%), and then lip and oral cavity changes in 43 (32.3%) patients, as summarized in Table 2. Other KD clinical features such as GI symptoms ($n = 97$, 72.9%), hypotension (less than 90/50, $n = 45$, 33.8%), and pulmonary abnormalities ($n = 35$, 26.3%) were also present in these patients (Table 2). Comorbidities had been further reported in 10 (7.5%) patients, of whom one patient (No. 67) suffered from attention-deficit/hyperactivity disorder and autism, one (No. 31) had a mid-muscular ventricular septal defect, one patient (No. 69) had been affected with alopecia areata (viz. spot baldness) and hay fever. Moreover, one case (No. 71) had hypothyroidism, two patients (Nos. 30, 72, and no. 79) had mild asthma, two (Nos. 80 and 81) were suffering from obesity, one had glucose-6-phosphate dehydrogenase (G6PD) (No. 87) and one patient born with congenital adrenal hyperplasia (CAH) (No. 85).

Moreover, 122 (91.7%) patients had been confirmed to have COVID-19 infection with reference to nasopharyngeal RT-PCR or antibody (viz. serological) testing for SARS-CoV-2, of whom 14 (10.5%) cases were positive for both of them. In addition, among all patients admitted to hospitals, 74 (55.6%) cases had been admitted to PICUs. Also, 49 (36.8%) patients had required some levels of respiratory support, of whom 31 (23.3%) cases had required mechanical intubation/ventilation, 18 (13.5%) had required oxygen therapy (such as venous arterial extracorporeal membrane oxygenation [ECMO] and cases that required high flow nasal cannula [HFNC]). With regard to the outcomes, 79 (59.4%) cases had been discharged from hospitals, 3 (2.2%) had been readmitted, 9 (6.7%) had been hospitalized at the time of the study, and 9 (6.7%) patients had expired. Likewise, the outcomes had not been reported in the rest of the patients ($n = 33$).

In the initial analysis, the measured pooled mean (*SE*) for inflammatory cytokines such as C-reactive protein (CRP), erythrocyte

TABLE 1 Characteristics of children ($n = 133$) with Kawasaki-like multisystem inflammatory syndrome and COVID-19 infection

Patient no./Sex/ Age(y)	First author	Country	Type of disease (at hospital admission)	Significant findings (imaging, echocardiography)	Outcome
P1/F/10	Saeed et al.[21]	Iran	atypical KD	Patchy infiltration in chest CT, Lt. ventricle function and dilated IVC	Hospitalized
P2/F/13	Saeed et al.[21]	Iran	MIS-C	Bilateral patchy GGOs in chest CT, poor Lt. ventricle systolic function and borderline Rt. ventricle systolic function with dilated IVC	Expired
P3/F/15	Fraser et al.[22]	Canada	atypical KD	Normal echocardiography	Discharged
P4/M/16	Schnapp et al.[23]	Israel	PIMS-TS	Lt. ventricular dilatation	Hospitalized
P5/M/5	Rauf et al.[23]	India	atypical KD	Cardiomegaly with Lt. ventricular dilatation in chest X-ray, global Lt. ventricular hypokinesia with systolic dysfunction	Discharged
P6/M/5	Schupper et al.[24]	USA	Cardiogenic shock	Rt. MCA infarction, cerebral edema, diffuse contralateral subarachnoid, bilateral MCA and PCA territory infarctions, bilateral hemispheric transformation, bilateral subdural collections in brain CT	Brain death, Hospitalized
P7/M/2 m[a]	Schupper et al.[24]	USA	Refractory respiratory failure	Bilateral MCA and PCA territory infarctions with the hemorrhagic transformation. evolving hemorrhagic infarctions in bilateral occipitoparietal lobes, Lt. temporal and frontal lobes in brain MRI	Hospitalized
P8/F/11	Greene et al.[25]	USA	Incomplete KD	LV systolic function mildly decreased based on decreased shortening fraction	Discharged & readmitted
P9/M/9	Giannattasio et al.[26]	Italy	MIS-C	Two small bilateral areas of atelectasis associated to minimal pleural effusion in chest CT, Normal echocardiography	Discharged
P10/M/4 m[a]	Acharyya et al.[27]	India	atypical KD	Normal Lt. ventricular function, perivascular brightness and diffuse coronary arteries ectasia	Hospitalized
P11/F/3	Yozgat et al.[28]	Turkey	PIMS-TS	Significant increase in echogenicity of coroner vessels	Discharged
P12/F/8	Bloniaux et al.[18]	France	PIMS-TS	hypokinesis, mitral regurgitation	Discharged
P13/M/12	Bloniaux et al.[18]	France	PIMS-TS	Diffuse echo-bright appearance in myocardium, septal dyskinesia, pericardial effusion	Discharged
P14/F/11	Bloniaux et al.[18]	France	PIMS-TS	Peripheral, posterior, multilobar and bilateral distribution of a combination of GGOs and consolidations in chest CT, hypokinesis, mitral regurgitation, pericardial effusion	Discharged
P15/F/6	Bloniaux et al.[18]	France	PIMS-TS	Pericardial effusion, transient systolic dysfunction	Discharged
P16/M/5	Rivera-Figueroa et al.[29]	USA	Incomplete KD, KDSS	Enlarged cardiac silhouette in chest x-ray, a small pericardial effusion	Discharged
P17/M/16	Rosenzweig et al.[30]	USA	Acute ITP	NR	Discharged
P18/F/14	Rosenzweig et al.[30]	USA	Mixed-type AIHA	NR	Discharged

TABLE 1 (Continued)

Patient no./Sex/ Age(y)	First author	Country	Type of disease (at hospital admission)	Significant findings (imaging, echocardiography)	Outcome
P19/M10	Chiu et al.[31]	USA	atypical KD	NR, severely diminished Lt. ventricular systolic function with trace pericardial effusion	Hospitalized
P20/F/14	Chiotos et al.[11]	USA	Incomplete KD	Bilateral pulmonary infiltrates in chest CT, Rt. coronary artery dilation (Boston Z score, 3.15)	Discharged
P21/M/12	Chiotos et al.[11]	USA	MIS-C	Diffuse bilateral infiltrates in chest CT, mild LV dysfunction	Discharged
P22/F/9	Chiotos et al.[11]	USA	MIS-C	Cardiomegaly and pulmonary edema in chest X-ray, Normal echocardiography	Discharged
P23/F/5	Chiotos et al.[11]	USA	MIS-C	Peribronchial thickening with Rt. patchy infiltrates in chest X-ray, moderately diminished LV systolic function	Discharged
P24/F/5	Chiotos et al.[11]	USA	MIS-C	Significant cardiac silhouette and mild central vascular congestion in chest X-ray, LV dilation, mildly diminished LV function	Discharged
P25/F/6	Chiotos et al.[11]	USA	MIS-C	Dense bilateral airspace opacities and heart appears prominent in chest X-ray, moderate LV dilation with mildly diminished systolic shortening, developed intermittent premature ventricular contractions, bigeminy and trigeminy	Hospitalized
P26/F/16	Foong Ng et al.[32]	UK	PIMS-TS	Bilateral basal and peripheral airspace shadowing in chest x-ray, mildly impaired Lt. ventricular function, small pericardial effusion	Discharged
P27/M/17	Foong Ng et al.[32]	UK	PIMS-TS	Cardiomegaly, retrocardiac and Lt. lobe airspace opacification, Lt. pleural effusion in chest x-ray, coronary artery dilatation, RCA 4.9 mm ectasia (Z-score +3)	Discharged
P28/M/13	Foong Ng et al.[32]	UK	PIMS-TS	Collapse-consolidation in Rt. lobe in chest x-ray, mild mitral regurgitation. coronary artery dilatation, dilated RCA 4.6 mm (Z score +2.2) and LCA 4.9–5.7 mm (Z score +2.2–3.7)	Discharged
P29/M/13	Joshi et al.[33]	USA	Cardiac dysfunction & shock	Lt. basal opacity in chest X-ray, Normal echocardiography	Discharged
P30/M/6	Joshi et al.[33]	USA	Cardiac dysfunction & shock	Mild mitral regurgitation	Discharged
P31/F/13	Joshi et al.[33]	USA	Cardiac dysfunction & shock	Moderately decreased Lt. ventricular systolic function with mild mitral regurgitation, and a small pericardial effusion	Discharged
P32/M/12	Licciardi et al.[34]	Italy	PIMS-TS	Decreased systolic function, pleural effusion	NR
P33/M/7	Licciardi et al.[34]	Italy	PFAPA syndrome	Cardiomegaly and pleural effusion in chest CT, reduced systolic function	NR
P34/M/8	Verdoni et al.[35]	Italy	Incomplete KD	Regurgitation of mitral valve, pericardial effusion, aneurysm more than 4 mm	NR
P35/M/7	Verdoni et al.[35]	Italy	Incomplete KD	Normal echocardiography	NR
P36/F/3	Verdoni et al.[35]	Italy	Classic KD	Normal echocardiography	NR

(Continues)

TABLE 1 (Continued)

Patient no./Sex/ Age(y)	First author	Country	Type of disease (at hospital admission)	Significant findings (imaging, echocardiography)	Outcome
P37/F/7	Verdoni et al.[35]	Italy	Incomplete KD	Mitral valve regurgitation, pericardial effusion	NR
P38/F/7	Verdoni et al.[35]	Italy	Incomplete KD	Mitral valve regurgitation, pericardial effusion	NR
P39/M/16	Verdoni et al.[35]	Italy	Classic KD	Pericardial effusion	NR
P40/M/5	Verdoni et al.[35]	Italy	Classic KD	Normal echocardiography	NR
P41/M/9	Verdoni et al.[35]	Italy	Incomplete KD	Pneumonia in chest X-ray, mitral valve regurgitation, aneurysm more than 4 mm	NR
P42/M/5	Verdoni et al.[35]	Italy	Classic KD	Normal echocardiography	NR
P43/M/5	Verdoni et al.[35]	Italy	Classic KD	Pneumonia in chest X-ray, Normal echocardiography	NR
P44/F/12	Riollano-Cruz et al.[36]	USA	PIMS-TS	Progressive lower lobe GGOs in chest X-ray, Normal echocardiography	Discharged
P45/M/14	Riollano-Cruz et al.[36]	USA	PIMS-TS	Mild regurgitation in both the tricuspid and mitral valves, Normal Rt. Ventricular systolic function. Mildly dilated Lt. ventricle. Normal Lt. ventricular systolic function.	Discharged
P46/F/14	Riollano-Cruz et al.[36]	USA	PIMS-TS	Normal, Mildly dilated Lt. ventricle	Discharged
P47/M/5	Riollano-Cruz et al.[36]	USA	PIMS-TS	Progressive lung GGOs in chest x-ray, approximately total Rt. MCA infarction involving cortex, subcortical white matter and deep gray matter, Lt. frontal subarachnoid hemorrhage in brain CT, Severely depressed biventricular systolic function, Trivial posterior pericardial effusion	Expired
P48/M/6	Riollano-Cruz et al.[36]	USA	PIMS-TS	Normal echocardiography	Hospitalized
P49/F/11	Riollano-Cruz et al.[36]	USA	PIMS-TS	Mild peri-bronchial thickening throughout the lungs in chest X-ray, Normal echocardiography	Discharged
P50/M/17	Riollano-Cruz et al.[36]	USA	PIMS-TS	Lt. ventricle systolic function mildly depressed	Discharged
P51/F/3	Riollano-Cruz et al.[36]	USA	PIMS-TS	Normal echocardiography	Discharged
P52/M/10	Riollano-Cruz et al.[36]	USA	PIMS-TS	Small bilateral pleural effusions, ill-defined airway opacities in X-ray, Normal echocardiography	Discharged
P53/M/12	Riollano-Cruz et al.[36]	USA	PIMS-TS	Reactive airway disease, Mild proximal LMCA ectasia	Discharged
P54/M/13	Riollano-Cruz et al.[36]	USA	PIMS-TS	Progressive lung opacities in chest X-ray, mildly diffusely ecstatic Lt. main and LAD, Lt. prominent circumflex	Discharged
P55/M/5	Riollano-Cruz et al.[36]	USA	PIMS-TS	Reactive airway disease, Mildly dilated Lt. main and proximal Lt. anterior descending coronary arteries	Discharged

TABLE 1 (Continued)

Patient no./Sex/ Age(y)	First author	Country	Type of disease (at hospital admission)	Significant findings (imaging, echocardiography)	Outcome
P56/F/6	Leon et al.[37]	USA	Incomplete KD	Prominent cardiac silhouette with clear lung fields, diffuse patchy GGOs in chest X-ray, mildly decreased LV function, mild mitral valve insufficiency	Discharged & readmitted
P57/NR/14	Pain et al.[38]	USA	PIMS-TS	Typical findings of COVID-19 pneumonia in chest CT, aortic regurgitation, and progressive Lt. coronary dilatation	Discharged
P58/M/8	Oberweis et al.[39]	Luxembourg	Myocarditis with heart failure	Bilateral pneumopathies and bilateral pleural effusions in chest CT, impaired LV function, and trace mitral insufficiency as well as a small pericardial effusion	Discharged
P59/M/6	Labé et al.[40]	France	COVID-19-associated with Erythema multiforme	NR	Discharged
P60/M/3	Labé et al.[40]	France	PIMS-TS	GGOs and consolidation in the Rt. poster basal area in chest CT	NR
P61/M/4	DeBiasi et al.[41]	USA	atypical KD	NR	NR
P62/M/8	Balasubramanian et al.[42]	India	MIS-C	Rt. lobe infiltrates in chest x-ray, Normal echocardiography	Discharged
P63/M/14	Riphagen et al.[43]	UK	hyperinflammatory shock	Bilateral basal lung consolidations and diffuse nodules in chest X-ray, Rt. ventricular dysfunction, elevated Rt. ventricular systolic pressure	Expired
P64/M/8	Riphagen et al.[43]	UK	hyperinflammatory shock	Pleural effusions in chest X-ray, mild biventricular dysfunction, severely dilated coronaries	Discharged
P65/M/4	Riphagen et al.[43]	UK	hyperinflammatory shock	Pleural effusions in chest X-ray	Discharged
P66/F/13	Riphagen et al.[43]	UK	hyperinflammatory shock	Moderate to severe LV dysfunction	Discharged
P67/M/6	Riphagen et al.[43]	UK	hyperinflammatory shock	Dilated LV, AVR, peri coronary hyper echogenicity	Discharged
P68/F/6	Riphagen et al.[43]	UK	hyperinflammatory shock	Mild LV systolic impairment	Discharged
P69/M/12	Riphagen et al.[43]	UK	hyperinflammatory shock	Pleural effusions in chest X-ray, severe biventricular impairment	Discharged
P70/F/8	Riphagen et al.[43]	UK	hyperinflammatory shock	Moderate LV dysfunction	Discharged
P71/M/13	Waltuch et al.[44]	USA	atypical KD, CSS, TSS	Hazy bilateral opacities in chest X-ray, coronary artery dilatation and moderately depressed LV systolic function	NR
P72/M/10	Waltuch et al.[44]	USA	atypical KD, TSS	Peribronchial thickening with ill-defined airspace opacities in the Rt. lung in chest X-ray, mild regurgitation in both the tricuspid and mitral valves	NR
P73/M/5	Waltuch et al.[44]	USA	atypical KD, TSS	Mildly dilated proximal Lt. anterior descending coronary artery	NR
P74/F/12	Waltuch et al.[44]	USA	NR	Normal imaging	NR
P75/M/13	Bapst et al.[45]	Switzerland	MIS-C	Normal imaging	Discharged
P76/F/6 m[a]	Jones et al.[46]	USA	Classic KD	A faint opacity in the Lt. lung in chest X-ray, Normal echocardiography	Discharged

(Continues)

TABLE 1 (Continued)

Patient no./Sex/ Age(y)	First author	Country	Type of disease (at hospital admission)	Significant findings (imaging, echocardiography)	Outcome
P77/F/5	Bahrami et al.[47]	Iran	MIS-C	Normal echocardiography	Discharged
P78/F/8	Dasgupta et al.[48]	USA	PIMS-TS	Bibasilar reticulonodular opacities, enlarged cardiac silhouette with pulmonary edema and small bilateral pleural effusions, systolic and diastolic dysfunction, valvular regurgitation	NR
P79/M/12	Dallan et al.[17]	Switzerland	Septic shock	Normal imaging	Discharged
P80/M/10	Dallan et al.[17]	Switzerland	Hypotensive septic shock associated with MODS	Rt. lobe consolidation with bilateral pleural effusions	Discharged
P81/M/10	Dallan et al.[17]	Switzerland	NR	Diffuse bilateral consolidations in chest CT, Lt. anterior descending artery and Rt. coronary aneurysms, with Z scores of 4.53 and 3.30, respectively	Hospitalized
P82/M/7	Akca et al.[49]	Turkey	Incomplete KD	Bilateral diffuse GGOs, diffuse enlargement in the Lt. coronary artery (Z score of 2.0)	Expired
P83/F/10	Akca et al.[49]	Turkey	KD	Pleural effusion and GGOs	Discharged
P84/F/2	Akca et al.[49]	Turkey	Incomplete KD	Increased perivascular echogenicity in the Rt. coronary artery	NR
P85/F/2	Akca et al.[49]	Turkey	Incomplete KD	An aneurysm in the Lt. coronary artery	NR
P86/F/6	Burger et al.[50]	USA	MIS-C	Mildly decreased Lt. LV function, septal hypokinesis, and mild mitral valve insufficiency	Discharged
P87/F/13	Al Ameer et al.[51]	Saudi Arabia	atypical KD	Mild mitral regurgitation, mild pericardial effusion, and moderate depression in Lt. ventricle function	Expired
P88/M/8	Khan et al.[52]	Pakistan	atypical KD	Parenchymal opacification and pleural effusion in the Lt. lobe	Discharged & Readmitted
P89/F/9	Jackson et al.[53]	USA	MIS-C	NR	Discharged
P90/M/5	Falah et al.[54]	Pakistan	Incomplete KD	Cardiomegaly, Pericardial effusion	NR
P91/M/3	Falah et al.[54]	Pakistan	KD	GGOs and consolidation in the Rt. lung	NR
P92/M/10	Falah et al.[54]	Pakistan	Incomplete KD	Pericardial effusion	NR
P93/F/11	Falah et al.[54]	Pakistan	Incomplete KD	NR	NR
P94/F/6 m[a]	Falah et al.[54]	Pakistan	KD	Faint opacity in Lt. lobe of lung	NR
P95/M/8	Falah et al.[54]	Pakistan	KD	Rt. lobe infiltrates	NR
P96/M/4 m[a]	Falah et al.[54]	Pakistan	KD	NR	NR
P97/M/5	Falah et al.[54]	Pakistan	Incomplete KD	Cardiomegaly	NR
P98/M/11	Falah et al.[54]	Pakistan	Incomplete KD	Cardiomegaly, Pericardial effusion	NR

TABLE 1 (Continued)

Patient no./Sex/ Age(y)	First author	Country	Type of disease (at hospital admission)	Significant findings (imaging, echocardiography)	Outcome
P99/M/6	Falah et al.[54]	Pakistan	KD	Bilateral pulmonary infiltrates in the Rt. base of lung	NR
P100/M/7	Almoosa et al.[55]	Saudi Arabia	NR	Acute respiratory distress syndrome (ARDS), pericardial effusion	Expired
P101/F/7	Almoosa et al.[55]	Saudi Arabia	NR	NR	Discharged
P102/M/11	Almoosa et al.[55]	Saudi Arabia	MIS-C	NR	Discharged
P103/F/3	Almoosa et al.[55]	Saudi Arabia	MIS-C	NR	Discharged
P104/M/1	Almoosa et al.[55]	Saudi Arabia	MIS-C	NR	Discharged
P105/F/12	Almoosa et al.[55]	Saudi Arabia	MIS-C	NR	NR
P106/F/6	Almoosa et al.[55]	Saudi Arabia	MIS-C	Rt. sided pleural effusion	Discharged
P107/M/5	Almoosa et al.[55]	Saudi Arabia	MIS-C	Lt. ventricular dysfunction	Discharged
P108/M/11	Almoosa et al.[55]	Saudi Arabia	MIS-C	NR	Discharged
P109/M/5 m[a]	Raut et al.[56]	India	Incomplete KD	Mild GGOs in Rt. lung, Dilated Lt. main coronary artery (3.0 mm, Z score of 4.30) and Lt. anterior descending artery (2.37 mm, score = 3.76)	Discharged
P110/M/11	Kim et al.[57]	South Korea	MIS-C	Cardiomegaly, pleural effusion with lung parenchymal consolidation, Lt. main coronary artery dilation. Rt. coronary artery dilatation and aneurysmal changes with mild pericardial effusion	Discharged
P111/F/7 m[a]	De Farias et al.[58]	Brazil	TSS	NR	Expired
P112/M/4	De Farias et al.[58]	Brazil	TSS	NR	Expired
P113/M/11	De Farias et al.[58]	Brazil	KDSS	NR	Discharged
P114/M/4	De Farias et al.[58]	Brazil	KD	NR	Discharged
P115/M/7	De Farias et al.[58]	Brazil	KD	NR	Discharged
P116/F/2	De Farias et al.[58]	Brazil	atypical KD	NR	Discharged
P117/M/9	De Farias et al.[58]	Brazil	KDSS	NR	Discharged
P118/M/6	De Farias et al.[58]	Brazil	KDSS	NR	Discharged
P119/M/4	De Farias et al.[58]	Brazil	KDSS	NR	Discharged
P120/M/4	De Farias et al.[58]	Brazil	KD	NR	Discharged
P121/M/10	De Farias et al.[58]	Brazil	KD	NR	Discharged
P122/M/12	Shahbaznejad et al.[59]	Iran	NR	Patchy GGOs and interlobar septal thickening, mild regurgitation in both the tricuspid and mitral valves, mild diastolic dysfunction	Expired

(Continues)

TABLE 1 (Continued)

Patient no./Sex/ Age(y)	First author	Country	Type of disease (at hospital admission)	Significant findings (imaging, echocardiography)	Outcome
P123/F/5	Shahbaznejad et al.[59]	Iran	NR	Bilateral plural effusion and patchy infiltration, GGOs, mild regurgitation in tricuspid valves	Discharged
P124/M/1	Shahbaznejad et al.[59]	Iran	NR	Bilateral plural effusion, basilar patchy infiltration and reverse halo sign, mild regurgitation in both the tricuspid and mitral valves	Discharged
P125/F/10	Shahbaznejad et al.[59]	Iran	NR	Mild bilateral plural effusion, mild regurgitation in both the tricuspid and mitral valves	Discharged
P126/M/1	Shahbaznejad et al.[59]	Iran	NR	Pleural effusion, mild mitral valves regurgitation	Discharged
P127/M/6	Shahbaznejad et al.[59]	Iran	NR	Bilateral GGOs, mild regurgitation in both the tricuspid and mitral valves	Discharged
P128/F/7	Shahbaznejad et al.(75)	Iran	NR	Bilateral GGOs, moderate regurgitation in both the tricuspid and mitral valves, Dilated Rt. and Lt. ventricle, myocarditis	Discharged
P129/M/1	Shahbaznejad et al.[59]	Iran	NR	Bilateral GGOs, LAD, moderate regurgitation in mitral valve, diastolic dysfunction	Discharged
P130/M/7	Shahbaznejad et al.[59]	Iran	NR	Bilateral nodular like lesions in in lungs, Sub plural atelectasis, mild bilateral pleural effusion	Discharged
P131/F/1	Shahbaznejad et al.[59]	Iran	NR	Bilateral nonspecific opacities in inferior lobes	Discharged
P132/M/11	Cirks et al.[60]	USA	MIS-C	Bilateral patchy infiltrates, bilateral pleural effusions, prominent peri bronchial cuffing, retro cardiac atelectasis, Lt. anterior descending coronary artery aneurysm (4 mm, Boston Z score +3.3)	NR
P133/F/15	Nelson et al.[61]	USA	MIS-C	Mild dilatation of the Lt. main coronary artery	Discharged

Abbreviations: AIHA, autoimmune hemolytic anemia; CSS, cytokine storm syndrome; EF, ejection fraction; FS, fractional shortening; GGOs, Ground-glass opacities; ITP, Immune thrombocytopenic purpura; IVC: Inferior vena cava; KD, Kawasaki disease; KDSS, Kawasaki disease shock syndrome; Lt, left; LV: Left ventricular; MCA: middle cerebral artery; MIS-C, multisystem inflammatory syndrome in children; MODS, multiple organ dysfunction syndrome; NR, not reported; PCA, posterior cerebral artery; PFAPA, Periodic fever, aphthous stomatitis, pharyngitis, adenitis; PIMS-TS, pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2; TSS, toxic shock syndrome.

[a]These patients age based on months.

TABLE 2 Clinical characteristics of children (n = 133) included in the study

KD principal clinical criteria	Total *N* (%)
Complete presentation (fever for at least 4 days and ≥4 principal criteria) (23)	46 (34.5)
Cervical lymphadenopathy	19 (14.3)
Rash	74 (55.6)
Lips and oral cavity changes	43 (32.3)
Changes to extremities	25 (18.8)
Conjunctival symptoms	65 (48.8)
KD associated clinical features	
Gastrointestinal symptoms	97 (72.9)
Pulmonary symptoms or abnormalities	35 (26.3)
Malaise, fatigue, lethargy	24 (18)
Myalgia, chest and thoracic pain	12 (9)
Hypotension	45 (33.8)
Edema (facial, eyelid, periorbital)	16 (12)
Other neurological features	28 (21)

Note: Values and numbers (percentages) unless stated otherwise.
Abbreviation: KD, Kawasaki disease.

sedimentation rate (ESR), ferritin, troponin, and interleukin 6 (IL-6) concentrations in patients were 226.5 ± 12.4, 67.4 ± 4.1, 1036.6 ± 108.3, 525 ± 117.7, and 412.2 ± 82.5, respectively, in those cases that have been reported.

Coronary artery dilation and aneurysm were reported in seven patients (Nos. 20, 27, 28, 81, 82, 109, and 132); of these, only one died due to severe hypoxia and disseminated intravascular coagulation, and the rest were discharged on medication.

Accordingly, patient No. 6, a healthy 5-year-old boy presented with numerous days of fever, cough, and abdominal pain. He proceeded to cardiogenic shock and tested positive for COVID-19 antibodies, and had high IL-6 levels. He developed cardiopulmonary failure requiring ECMO. After 5 days of ECMO, pupils became fixed and dilated, and head computed tomography (CT) revealed a middle cerebral artery (MCA) infarction, cerebral edema, and diffuse contralateral subarachnoid hemorrhage. His examination disclosed blank brainstem reflexes and movement. After 3 days, brain death proved following normalization of his electrolytes.

3.1 | Patients with a death outcome

In this systematic review, a total of 9 (6.7%) patients, mostly male dominance (66.6%) expired due to a wide variety of reasons. Severe heart failure and cardiac arrest played a predominant role in the mortality of these patients (n = 6). As patients Nos. 2, 87, 100, 111, 112, and 122 expired because of refractory hypotension and cardiac arrest despite all adjuvant and complementary therapies. Patients Nos. 47 and 63 showed evidence of MCA ischemic infarction in CT of the head that might be due to heart failure and shock, which are not directly mentioned in the literature. Although the SARS-CoV-2 is known as a respiratory infection that causes respiratory symptoms, only one patient (No. 82) passed away due to severe hypoxia even with venovenous ECMO.

All dead cases came with an initial stable presentation that their condition deteriorated days (ranged 3–180 days) after hospitalization. Greater severity of the condition and a higher risk of mortality may be triggered by poor nutrition, comorbidities (that may facilitate the expansion of marked hyperinflammatory syndrome), and also cardiac dysfunction evidenced by lower cardiac output and ejection fraction. Patients Nos. 111 and 112 suffered from poor nutrition; patient No. 122 had a history of chronic renal failure, and patient No. 87 was with G6PD deficiency. All the mentioned patients were hospitalized in the PICU and required supplemental oxygenation, of which six patients had tracheal ventilation, and the rest of them were ventilated by veno-arterial ECMO (Nos. 2, 47, and 82). Although RT-PCR tests for COVID-19 were positive for all these patients, immunoglobulin G antibody against SARS-CoV-2 detected just in two of them.

Coronary artery dilation in dead patients was reported in one patient (No. 82) with a Z score of 2, and a coronary artery aneurysm was not revealed in each of them. Lung parenchyma condition was reported in six patients of the death cases, of which most appeared as diffuse patch ground-glass opacification/opacity in both lungs (Nos. 2, 47, 63, 82, and 122), and one of them (No. 100) progressed to acute respiratory distress syndrome.

4 | DISCUSSION

As with the COVID-19 pandemic and its progress, the incidence of patients admitted with KD and other related diseases and symptoms such as KLD and MIS-C has increased, so there have been several reports from different countries.[21,22] In this study, available evidence published updated globally until December 1st were systematically reviewed, and hyperinflammatory condition in children following COVID-19, threatening their lives, were reported. We found that more than half of children with KLD associated with COVID-19 had been admitted to PICUs, a quarter had required mechanical ventilation/intubation and even some of them had been required readmissions. Moreover, a 6.7% mortality rate was observed in children with KLD associated with COVID-19 that mostly due to severe heart failure, cardiac arrest, and refractory hypotension. Additionally, the male gender could be recognized as a poor prognostic factor with a fatality rate of two times higher than the female.

Despite more than half a century since the initial reports of KD, no clear cause has been thus far identified, and no specific pathology has been recognized.[23] Considering the higher number of cases with KD after the outbreak of viral respiratory diseases, the most accepted hypothesis is the strange response of the immune system to

one or more unknown pathogens in genetically predisposed patients.[24,25] The presumed causative pathogens include influenza, chlamydia pneumonia, retroviruses, the Epstein-Barr virus, and primate erythroparvovirus 1, generally referred to as parvovirus B19.[26] There are also conflicting reports about coronaviruses, while there are pieces of evidence of KD, following a novel human coronavirus (HCoV), called new haven coronavirus, alphacoronaviruses, and respiratory diseases, which have been ruled out in some studies.[27-29]

The aforementioned systematic review of the cohort studies, case series/reports, and correspondences or letters to editors also unveiled various clinical hallmarks of patients admitted to hospitals with the manifestations of KD during the COVID-19 pandemic. In 133 cases examined, COVID-19 had been confirmed in 91.7% of the cases based on the nasopharyngeal RT-PCR and antibody (viz. serological) testing, albeit the RT-PCR had been less sensitive compared with serology, which was consistent with the findings by Akca et al.[65 62] Despite a wide range, all cases had been under the age of 18, and the average age had been higher than patients with KD. In the studies reviewed, not all patients had typical KD characteristics, and even with possessing similar symptoms, several names had been mentioned for diagnoses, among which most patients that had been admitted with a diagnosis of PIMS-TS and MIS-C had been placed next in this line. Other diagnoses, including various types of KD alongside hyperinflammatory shock, hypotension, and AHF, had lower proportions.

With an overview of the gender distribution of the patients developing KD in association with COVID-19, male dominance had been apparent, which had the same order with KD alone.[30] Among the death reports in the reviewed cases, the ratio of male to female had been 2:1, so that the male gender could be recognized as a poor prognostic factor, which was consistent with mortality in adults with COVID-19, with the fatality rate of male two to three times higher than female. In adults, this effect had been hypothesized to be dependent on males with higher angiotensin-converting enzyme 2 expression, X chromosome immunological consequences, and hormonal differences[31,32]; So, ignoring the latter, the two other causes could be generalized to children.

The study results revealed that GI manifestations were also prevalent in patients exhibiting KD associated with COVID-19, with a higher incidence rate than those in both non-COVID-19 KD and children with COVID-19 alone. Other subsequent symptoms including skin rash, conjunctivitis, hypotension, lip, and oral cavity changes, and pulmonary abnormalities were not consistent with both KD patients with or without SARS-CoV-2 infection.[23,32] The particular reason for this was obscured by a probable scenario of the profile of the complex inflammatory factors along with the preceding two diseases and its discrete unfamiliar immunopathology.

More than half of the hospitalized patients had been admitted to PICUs, a quarter of them undergoing mechanical ventilation, and others receiving HFNC and ECMO. This level of dependence on respiratory support was higher than the values reported in COVID-19 patients with pulmonary involvement, both in children and adults,[33] probably due to various reasons including different types of immunopathology and hyperinflammatory state of this condition[34] indicating the necessity of conducting a multidisciplinary study on pediatric patients during the COVID-19 pandemic.

Elevated cytokine production is a prominent characteristic of severe COVID-19. Like most severe COVID-19 cases, which present an extreme increase in inflammatory cytokines, including IL-6, CRP, ESR, and ferritin,[3-6] the literature review revealed the abnormal quantity of these values. On the other hand, a high level of troponin in patients indicates cardiac tissue damage, which was one of the leading causes of death in this study.

Also, this study revealed a higher mortality rate among patients with KD associated with COVID-19, compared to each of them alone, given that nine children had died and one had proceeded to brain death.[35,36] Hyperinflammation state and augmented cytokine production in KD amidst the CSR associated with COVID-19, leading to several increased cytokines was further presumed causative in the progress of this condition that could make it more common in COVID-19; however, its inflammatory profile was different from that of COVID-19. The increased CRP and ferritin observed in the reviewed cases were supportive here. Nevertheless, the role of high troponin levels and hypotension in patients should not be missed, which could show serious cardiovascular diseases and their effects on higher mortality rates, insofar as inotropes had particular importance in the treatment of these patients following intravenous immunoglobulin and antibiotics (Table 3).

The majority of the cases examined in this study were from the US and Europe, although 27 patients were from Iran and India, and Saudi Arabia. The geographical dispersion could have diverse reasons, which were in line with the study by Akca et al.[62] At the first glance, it was not evident whether this trend was due to different coronavirus variants, genetic predisposition, or more accurate registration and care systems in those countries or not. It did not necessarily mean the absence or

TABLE 3 Treatment of children (n = 133) included in this study

Characteristics, (%) otherwise stated	Total (N = 133)
Treatment	
Intravenous immunoglobulin (2 g/kg) infusion	91 (68.4)
Intravenous immunoglobulin (2 g/kg) retreatment	5 (3.7)
Steroids (2–10 mg/kg/day)	47 (35.3)
Aspirin	45 (33.8)
Broad-spectrum antibiotics	77 (57.9)
Inotropes	55 (41.3)
Hydroxychloroquine	14 (10.5)
Anakinra	8 (6)
Tocilizumab	23 (17.3)
Remdesivir	2 (1.5)
Diphenhydramine	1 (0.7)
Favipiravir	9 (6.7)
Ritonavir	1 (0.7)
Mesenchymal stem cell treatment	1 (0.7)

scarcity of cases in other parts of the world. The vast majority of demised patients in this review had circulation problems, and they suffered from heart failure and refractory hypotension despite aggressive therapy that didn't respond to efforts. In most of them, the cytokine profile is different from whatever is generally seen in COVID-19 patients. Echocardiography of these patients mostly has various degrees of cardiac dysfunction, and in some cases, the arterial aneurysm was observed. It seems that their condition gets more critical when the cytokine storm begins to rise; while, in most of the above patients (death patients), the number of cytokines at the time of death is much higher than from the first examination. An equivocal point that needs further investigation is cytokine profile correlation with prognosis in these patients. However, we encounter a CSS in most patients who die; not all patients with high levels of inflammatory cytokines had complicated conditions. Although differences in the approach and treatment of patients can be one of the causes of this problem, due to the similarity of drug treatment and their focus on suppressing the immune system, other factors, including genetic variations, might be remarkable in this regard. One of the expired patients (No. 87) had a history of G6PD deficiency. The G6PD deficiency was introduced as a predisposing factor in the increasing incidence of COVID-19 because it plays a pivotal role in coronavirus viral gene expression and viral particle production. So, the action of this deficiency in the increase of mortality rate should also be investigated.[37]

Among the limitations of this review study, at first, incomplete datasets for numerous properties, which made it impossible to present appropriate comparisons and conclusions. Second, the duration of follow-ups was inadequate, leading to the omission of their long-term sequel. Thirdly, selection bias in the studies concerned in some countries was undeniable, as they might have been written in different languages rather than English. Considering the studies were slightly heterogeneous and their information was not comparable in some characteristics, multidisciplinary research in this field is recommended to shed light on the obscure dimensions of this condition.

5 | CONCLUSION

This systematic review established that approximately two-thirds of children with KLD associated with COVID-19 had been admitted to PICUs. Moreover, around one-fourth of them had required mechanical ventilation/intubation and even some of them had required readmissions. Therefore, pediatricians and physicians are strongly recommended to monitor children that present with fever, GI symptoms, and other characteristics of KD during the pandemic as they can be the dominant manifestations in children with COVID-19. Accordingly, irreversible complications can be prevented through early diagnosis and treatment.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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AUTHOR CONTRIBUTIONS

Pedram Keshavarz: investigation, writing—original draft, writing—review and editing, data curation. **Fereshteh Yazdanpanah**: investigation, writing—original draft, writing—review and editing, data curation. **Sara Azhdari**: writing—review and editing, data curation. **Hadiseh Kavandi**: data curation, writing—review and editing. **Parisa Nikeghbal**: investigation, data curation, writing—review and editing. **Amir Bazyar**: Investigation, data curation. **Faranak Rafiee**: investigation, data curation. **Seyed Faraz Nejati**: investigation, data curation. **Faranak Ebrahimian Sadabad**: investigation, data curation, writing—review and editing. **Nima Rezaei**: writing—review and editing, conceptualization, investigation.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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