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Systematic Review / Meta-analysis

Contributing factors to pediatric COVID-19 and MIS-C during the initial waves: A systematic review of 92 case reports

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ABSTRACT

Background: As the coronavirus disease 2019 (COVID-19) pandemic continues to sweep the world with unprecedented speed and devastation, data has shown that cases in the pediatric population have been significantly lower than in the adult population. We conducted a systematic review of case reports to identify the contributing factors of confirmed pediatric COVID-19 patients.

Methods: Using the PubMed platform, and Cochrane Central, we searched for primary studies alone. All database searches were performed between December 2019 and December 2020. We incorporated keywords including "pediatrics," "Case reports," "Cases," "Covid-19″ into all searches.

Results: A total of 92 records were included in this novel review. Of all patients, 58% were male and the mean age of the patients was 6.2 years (SD: 5.9). Contributing factors to MIS-C infections were G6PD deficiency (17.6%), Group A streptococcus co-infection (17.6%), infancy (11.8%), whereas those in COVID-19 pediatric patients included congenital (18.5%), and genetic defects (13.8%), in addition to vertical transmission or during infancy (16.9%). Data of baseline demographic characteristics and clinical sequelae of included COVID-19 pediatric and MIS-C patients is presented.

Conclusion: With schools reopening and closing, the pediatric age group is susceptible to high rates of COVID-19 community transmission. We provide insights into potential contributing factors to pediatric COVID-19 and MIS-C patients. These insights are critical to guide future guidelines on the management and potential vaccination efforts.

1. Introduction

As the coronavirus disease 2019 (COVID-19) pandemic continues to sweep the world with unprecedented speed and devastation, data has shown that cases in the pediatric population have been significantly lower than in the adult population [1]. There have been 31,174,627 confirmed cases and 962,213 deaths globally due to COVID-19 infection caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), as of September 22, 2020 [2]. As of August 2020, 7.3% of all COVID-19 cases in the United States reported to the Centers for Disease Control and Prevention (CDC) have been in children [1]. In China, only 2% of the 72,314 cases that were reported by February 11, 2020, were in people under the age of 19 [3]. The number of pediatric cases with severe disease progression requiring hospitalization has been low, and in the majority of cases, worldwide children appear to be mostly asymptomatic with mild symptoms [4,5]. Hospitalization rate and disease severity have been shown to significantly increase with age, with adults and the elderly facing worse outcomes than children [3].

Thus far, there is limited research and data available to elucidate the clinical features and risk factors for what leads to severe disease in the

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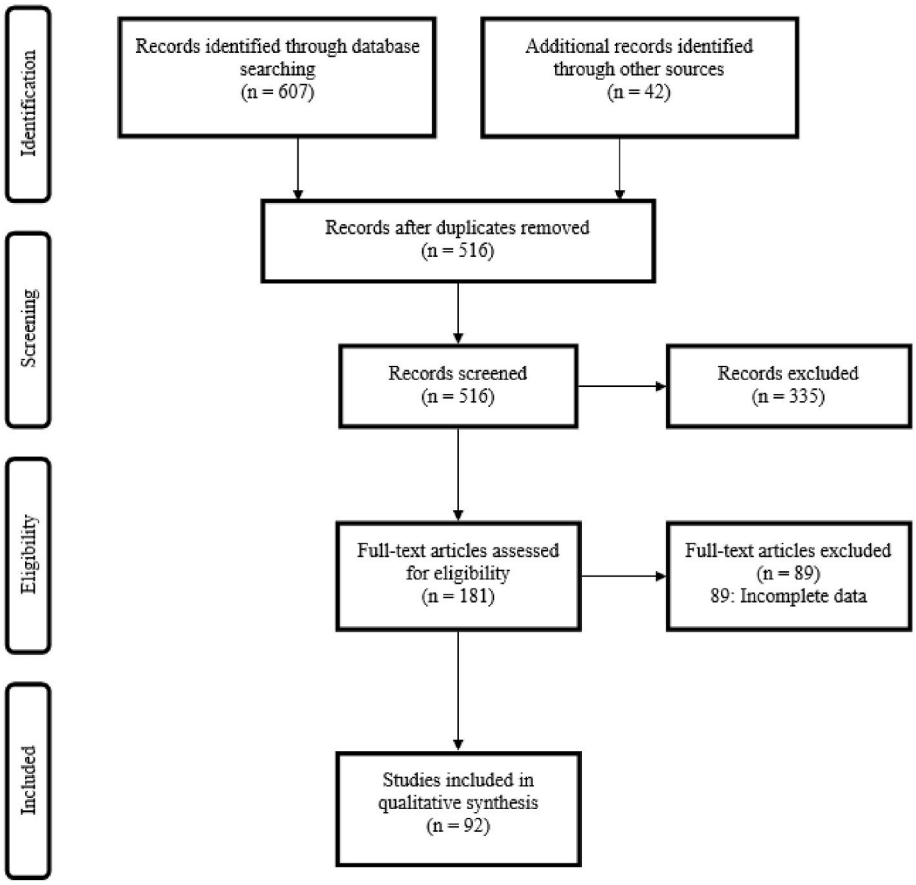

Fig. 1. Prisma flowchart.

pediatric age group. Cases involving COVID-19-associated multisystem inflammatory syndrome in children (MIS-C) have cropped up in increasing numbers, raising concern as these children require admission to intensive care units (ICUs) [5,6]. A standardized case definition and spectrum of the disease are still emerging, but entities such as the World Health Organization (WHO), Centers for Disease Control and Prevention (CDC), and Royal College of Pediatrics and Child Health (RCPCH) have developed preliminary definitions that identify the following criteria for MIS-C: inflammation with fever and elevated inflammatory markers, organ dysfunction, hypotension/shock, positive or recurrent SARS-CoV-2 status, and the exclusion of other probable diagnoses [6].

While children and adolescents make up a relatively small portion of total COVID-19 cases, the risk of unintended asymptomatic spread is concerning. As lockdown restrictions ease and communities reopen, determining the role children play in COVID-19 transmission is both important and necessary, especially in terms of potential consequences for schools resuming in-class learning and young people interacting with multigenerational contacts. Several studies have suggested that children may not be the sources of infection or the index cases in most clusters; children get infected from adults as opposed to transmitting the infection to adults [7,8]. However, multiple studies demonstrate the possibility of infection transmission via pediatric asymptomatic carriers [9–11]. Nasopharyngeal viral load of SARS-CoV-2 does not appear to differ based on age, indicating that children could be just as infectious as adults [12]. We conducted a systematic review of case reports to identify the contributing factors of confirmed pediatric COVID-19 patients.

2. Methods

A systematic review protocol was developed a priori. The approach to data synthesis is novel and deviated from standard systematic reviews in this area. Due to the importance and relevance of case reports amid the COVID-19 pandemic, our approach is case-driven and employs a more rigorous system for data presentation. This study was registered with Research Registry under the following identifier: "reviewregistry1354" [13]. AMSTAR 2 ratings were determined to be of low quality [14].

2.1. Research question

This review addressed the following research question: "What are the contributing risk factors and clinical features to severe COVID-19 disease in the pediatric age group?"

2.2. Searching the literature

Two early to mid-level researchers developed and tested the search strategy by consulting with the review team. The third researcher resolved any discrepancies while conducting a systematic review. We performed numerous search runs related to pediatric cases utilizing the same base strategy for all. Using the PubMed platform, and Cochrane Central, we searched for primary studies alone. All database searches were performed from December 2019 until December 2020. We undertook an additional search of journals including NEJM, JAMA, Lancet, and BMJ on December 31, 2020. We incorporated keywords including "pediatrics," "Case reports," "Cases," "Covid-19" into all searches. We did not apply any research design filters for case reports to ensure that pertinent data was not omitted. Studies published in 2020 were included with no language restrictions. Systematic reviews, meta-analyses, cohorts, case series, and opinion pieces were excluded; however, case reports published as letters were retained. All references that were identified in the re-run were de-duplicated against the studies identified

Table 1
Baseline demographic characteristics of included COVID-19 pediatric patients. Only RT-PCR-confirmed COVID-19 cases were included.

Author	Country	Age	Positive contact history	Mode of delivery	Complications during antepartum, intrapartum, and postpartum period	Breastfeeding status	Immunization status	Gender	Signs and symptoms at presentation	Lag time
Sisman [44]	USA	0.03 months	Mother	Spontaneous vaginal delivery	Large for gestational age, preterm gestational age, maternal class B diabetes mellitus, and maternal morbid obesity	Currently breastfeeding	NA	Female	Fever, respiratory distress associated with mild subcostal retractions, tachypnea, and hypoxia	2 days
Wang [45]	China	0.05 months	Mother	Emergency cesarean section	Meconium-stained liquor	Never breastfed	NA	Male	Asymptomatic	NA
Vivanti [30]	France	0.1 months	Mother	Emergency cesarean section	Premature; antenatal mother COVID-19 positive; postpartum admission and intubation in NICU	Formula-fed	Compliant with age	Male	Asymptomatic	NA
Bindi [46]	Italy	0.1 months	Hospital-acquired infection	NA	Intestinal perforation	NA	NA	Male	Asymptomatic	NA
Sinelli [47]	China	0.1 months	Mother	Spontaneous vaginal delivery	None	Currently breastfeeding	Compliant with age	Female	Perioral cyanosis, poor sucking, and hypoxia	1 day
Piersigili [48]	Belgium	0.23 months	Mother	Emergency cesarean section	Premature; postpartum admission in PICU, patent ductus arteriosus, surfactant therapy, and pneumothorax; perinatally mother referred for pre-eclampsia, suspected cholelithiasis, and maternal HELLP syndrome	Interrupted	NA	Female	Asymptomatic	NA
Precit [49]	USA	0.3 months	Grandmother and sibling suspected	Spontaneous vaginal delivery	None	NA	NA	Male	Nasal secretion, and labored breathing	1 day
Aghdam [50]	Iran	0.5 months	Parents	Cesarean section	NA	NA	NA	Male	Fever, lethargy, cutaneous mottling, respiratory distress, tachypnea, and tachycardia	NA
Salik [51]	China	0.5 months	Mother	Spontaneous vaginal delivery	Low birth weight; diagnosed with teratology of Fallot prenatally	NA	NA	Female	Tachypnea, worsening cyanosis, feeding intolerance, and increasing lethargy	
Wang [52]	China	0.6 months	Mother	Spontaneous vaginal delivery	None	NA	NA	Male	Fever, vomiting, and increased number of stools	2 days
Munoz [53]	USA	0.7 months	Household contact	NA	Premature	NA	NA	Male	Nasal congestion, tachypnea, fever, and reduced feeding	2 days
Needleman [54]	USA	0.8 months	Family			NA	NA	Male	Nasal congestion, rhinorrhea,	3 days

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Table 1 (*continued*)

Author	Country	Age	Positive contact history	Mode of delivery	Complications during antepartum, intrapartum, and postpartum period	Breastfeeding status	Immunization status	Gender	Signs and symptoms at presentation	Lag time
				Spontaneous vaginal delivery	Mild hypoxic-ischemic encephalopathy				episodic intermittent apnea, and perioral cyanosis,	
Canarutto [55]	Italy	1 month	Father	Spontaneous vaginal delivery	NA	Currently breastfeeding	NA	Male	Fever, rhinitis, and cough	1 day
Elbehery [56]	KSA	1.3 months	Grandparents	Spontaneous vaginal delivery	Neonatal cholelithiasis, Intrauterine growth restriction	NA	NA	Female	cough, rhinorrhea, and shortness of breathing	4 days
Dugue [57]	USA	1.4 months	Family suspected	Spontaneous vaginal delivery	None	NA	NA	Male	Cough, fever, mottled appearance, and episodes of sustained upward gaze associated with bilateral leg stiffening	1 day
Cui [58]	China	1.8 months	Parents	NA	NA	Currently breastfeeding	NA	Female	Rhinorrhea and dry cough	5 days
Robbins [59]	USA	1.9 months	NA	Spontaneous vaginal delivery	Late preterm gestational age	Currently breastfeeding	Compliant with age	Male	Fever, watery eye discharge with periorbital erythema, and soft, green stools	2 days
Fan [60]	China	3 months	Parents	NA	NA	NA	NA	Female	Fever, and diarrhea	4 days
García-Howard [61]	Spain	3 months	Mother	Spontaneous vaginal delivery	None	NA	NA	Female	Convulsions without fever	5 days
Le [62]	Vietnam	3 months	Grandmother	NA	None	Currently breastfeeding	Compliant with age	Female	Rhinorrhea, fever, and nasal congestion	4 days
Li [63]	China	3 months	Mother	NA	NA	NA	NA	Male	Non-productive cough and rhinorrhea	16 days
Loron [64]	France	3 months	Father and suspected community-acquired infection	Emergency cesarean section	Preterm, low birth weight, and mild hyaline membrane disease	NA	NA	Male	Extreme cyanosis, and recurrent apneas	11 days
Danley [65]	USA	4 months	Mother	Spontaneous vaginal delivery	Muscular ventricular septal defect	Currently breastfeeding	Compliant with age	Male	Decreased oral intake, loose stools, stuffy nose, mild cough, and diaphoresis	16 days
Moazzam [66]	Pakistan	4.8 months	NA	NA	NA	NA	Compliant with age	Male	Abdominal pain, and rectal bleeding	1 day
Rodriguez-Gonzalez [67]	Spain	6 months	NA	NA	Short bowel syndrome	NA	NA	Male	Severe respiratory distress, cyanosis, nasal congestion, cough, and fever	14 days
Heinz [68]	USA	6 months	Mother	NA	NA	NA	NA	Female	Sore throat, cough, nasal congestion, and diarrhea	1 day
Jafari [69]	Iran	6 months	Mother	Emergency cesarean section	Premature birth due to maternal hypertension; monitored in NICU for 10 days after birth	Currently breastfeeding	Compliant with age	Male	Poor feeding, dyspnea, fever, tachypnea, and hypoxia	3 days
Kam [70]	Singapore	6 months	Parents	NA	NA	NA	NA	Male	None	Unknown
Soumana [71]	Niger	8 months	Mother suspected	NA	NA	NA	NA	Male	Fever, diarrhea, and respiratory distress	NA
Qiu [72]	China	8 months		NA	Atrial and ventricular	NA	NA	Male	Fever, cough, wheezing,	7 days

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Table 1 (*continued*)

Author	Country	Age	Positive contact history	Mode of delivery	Complications during antepartum, intrapartum, and postpartum period	Breastfeeding status	Immunization status	Gender	Signs and symptoms at presentation	Lag time
			Hospital-acquired suspected		septal defects, and aortic stenosis repairs				recurrent apnea, hypoxia, mottled skin, cold fingers, petechiae, and gross hematuria	
Navaeifar [73]	Iran	1 year	Parents	NA	NA	NA	Compliant with age	Male	Fever, and rash	4 days
Sieni [74]	Italy	1.1 years	Parents, hospital-acquired infection suspected	NA	NA	NA	NA	Female	Asymptomatic	NA
Mao [75]	China	1.2 years	Mother, and grandmother	NA	None	Currently breastfeeding	Compliant with age	Male	Fever, dry cough, rhinitis, and decreased appetite	2 days
Mansour [76]	Beirut	1.3 years	Parents	Spontaneous vaginal delivery	None	NA	NA	Female	High-grade fever, hypoactivity, and severe diarrhea	6 days
Lahfaoui [77]	Morocco	1.4 years	Mother	NA	NA	Currently breastfeeding	Compliant with age	Female	Fever, tachypnea, tachycardia, mucocutaneous pallor, and fatigue	2 days
Essajee [78]	South Africa	2.6 years	None	NA	NA	NA	Compliant with age	Female	Left-sided weakness, lethargy, enlarging cervical lymphadenopathy, and decreased appetite	NA
Nikoupour [79]	Iran	3 years	NA	NA	Premature	NA	NA	Male	Weakness, malaise, anorexia, severe dry cough, tachypnea, and respiratory distress	4 days
Alsuwailem [80]	Saudi Arabia	4 years	Extended family suspected	NA	NA	NA	NA	Female	Subjective fever, progressive, severe, and generalized abdominal pain, and non-bloody, non-bilious vomiting	3 days
Diercks [81]	USA	4 years	Hospital-acquired infection suspected	NA	NA	NA	NA	Female	Asymptomatic	NA
Morand [82]	France	4.6 years	Mother	Spontaneous vaginal delivery	None	NA	NA	Female	Fever, cough, polypnea	5 days
Kihira [83]	USA	5 years	NA	NA	NA	NA	NA	Male	Fever, cough, and abdominal pain	3 days
Mercolini [84]	Italy	5 years	Family suspected	NA	NA	NA	NA	Female	Fever, and rhinorrhea	2 days
Freij [85]	USA	5 years	Parents	NA	NA	NA	NA	Female	Fever, confusion and headache	6 days
Theophanous [86]	USA	6 years	None	NA	Preterm gestational age, and failure to thrive	NA	NA	Male	Right-sided facial droop, asymmetric smile, drooling, and inability to fully close the right eye	1 day
Alloway [87]	USA	7 years	Family	NA	NA	NA	NA	Female	Abdominal pain, non-bloody non-bilious vomiting, and fever	2 days
Yildirim [88]	Turkey	7 years	NA	NA	NA	NA	NA	Female	chest pain, dyspnea and fatigue	NA
Dinkelbach [89]	Germany	7 years	NA	NA	NA	NA	NA	Male	Cough, myalgia, and fever	7 days
Chen [90]	China	7 years	Community transmission suspected	NA	NA	NA	NA	Female	Irregular fever, sore throat,	1 day

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Table 1 (*continued*)

Author	Country	Age	Positive contact history	Mode of delivery	Complications during antepartum, intrapartum, and postpartum period	Breastfeeding status	Immunization status	Gender	Signs and symptoms at presentation	Lag time
									diarrhea and mild kidney injury	
Farley [91]	USA	8 years	NA	NA	NA	NA	NA	Male	Abdomianl pain, respiratory distress, status epilepticus and non-bilious, non-bloody vomiting	1 day
Genovese [92]	Italy	8 years	Parents	NA	NA	NA	NA	Female	Papulovesicular skin eruption, and cough	6 days
Oberweis [93]	Belgium	8 years	NA	NA	NA	NA	NA	Male	Fever, coughing, weight loss, and severe fatigue	4 days
Yoo [94]	South Korea	8 years	Father	NA	NA	NA	NA	Male	Cough	3 days
Park [95]	Korea	10 years	Mother	NA	NA	NA	NA	Female	Low-grade fever, and productive cough	15 days
Tsao [96]	China	10 years	Close contact	NA	NA	NA	NA	Female	Fever, fatigue, non-productive cough, and ascending rash	21 days
Almeida [97]	Brazil	10 years	Parents	NA	NA	NA	NA	Female	Fever, cough, sore throat, and gross hematuria	1 day
El-Assaad [98]	USA	10 Years	NA	NA	NA	NA	NA	Male	Fever, fatigue, cough, diarrhea, vomiting, myalgias, and trunkal nonpruritic rash	7 days
Bhatta [99]	USA	11 Years	NA	Spontaneous vaginal delivery	None	NA	Compliant with age	Male	Isolated afebrile seizure	1 day
McAbee [100]	USA	11 years	NA	NA	NA	NA	NA	Male	Status epilepticus, generalized weakness, and fever	2 days
Barsoum [101]	Ireland	12 years	NA	NA	NA	NA	NA	Female	Low grade fever, cough, wheeze, and breathing difficulty	NA
Patel [102]	USA	12 years	None	NA	NA	NA	NA	Female	Fever, nonproductive cough, nonbloody vomitting, worsening shortness of breath, and hematuria	5 days
Klimach [103]	UK	13 years	Parents suspected	NA	NA	NA	NA	Male	Erethematous painful papules on soles of feet, axilla and distal lower extremety, fever, myalgia, and headache	1 day
Bush [104]	USA	13 years	Mother suspected	NA	Premature, 8 month stay at NICU	NA	NA	Male	Rhinitis, mild cough, fever, skin mottling, and large stool output, and low oxygen saturation	1 day
Conto-Palomino [105]	Peru	13 years	None	NA	No	NA	Incomplete	Female	Headache, vomiting, fever, altered sensations, and hemiparesis	3 days
Gagliardi [106]	USA	14 years	NA	NA	NA	NA	NA	Male	High-grade fever, pain, and swelling in the right testis	2 days
Giné [107]	Spain	14 years	Community-acquired infection	NA	NA	NA	NA	Female	Cough, thoracic pain, fever,	11 days

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Table 1 (*continued*)

Author	Country	Age	Positive contact history	Mode of delivery	Complications during antepartum, intrapartum, and postpartum period	Breastfeeding status	Immunization status	Gender	Signs and symptoms at presentation	Lag time
									anosmia, and ageusia	
Enner [108]	USA	14 Years	NA	NA	NA	NA	NA	Female	Fever, nasal congestion, myalgia, and generalized tonic-clonic seizures with perioral cyanosis	6 days
Maniaci [109]	Italy	15 years	Mother	NA	NA	NA	NA	Male	Mild fever (37.7 °C), sore throat, nasal congestion, ethematous skin lesions on the lower limbs, and asthenia	3 days
Gefen [110]	China	16 Years	NA	NA	NA	NA	NA	Male	Fever, tachycardia, myalgias, exertional dyspnea, and cola-colored urine	5 days
Lewis [111]	USA	16 Years	NA	NA	NA	NA	NA	Female	Fever, myalgia, cough, and tachypnea	6 days
Gnecchi [112]	Italy	16 years	None	NA	NA	NA	NA	Male	Fever, and intense pain in the chest radiating to the left arm	1 day
Locatelli [113]	Italy	16 years	Mother	NA	NA	NA	NA	Male	Multiple asymptomatic plaques on fingers and toe, dysgeusia, and mild diarrhea	23 days
Latimer [114]	USA	16 years	Mother suspected	NA	NA	NA	NA	Male	Fever and an episode of generalized seizure	4 days
Craver [115]	USA	17 years	Mother suspected	NA	NA	NA	NA	Male	Headache, dizziness, nausea and vomiting	2 days
Trogen [116]	USA	17 years	NA	NA	NA	NA	NA	Male	Fever, neck pain, diffuse abdominal pain, non-bloody diarrhea, and non-bloody non-bilious emesis	7 days
Marhaeni [117]	Indonesia	17 years	Father	NA	NA	NA	NA	Female	Anosmia, and ageusia	8 days

HELLP: Haemolyses, elevated liver enzymes, and low platelet count; NA: Not available; NICU: Neonatal intensive care unit; PICU: Paediatric intensive care unit.

in the first run. The manuscript was guided by the PRISMA Statement [15].

2.3. Study selection

A two-tier study selection strategy was utilized; all abstracts and titles were initially screened for potential relevance with the reference lists screened in the next phase. Screening at both levels was conducted independently by two reviewers with references screened by a discussion with the third reviewer. Agreement of the first two reviewers was required to include the study at the end of stage 2.

2.4. Data extraction and risk of bias assessment

Data were extracted into a shared spreadsheet using a template that was initially piloted using a set of 4 case reports and adjusted by the first two reviewers. Data were extracted by one of the first two reviewers and verified by the third and fourth reviewer. A total of four reviewers extracted the data and each conducted a test run to improve the presentation of extracted data in the shared spreadsheet. Data was collected baseline demographic characteristics of included COVID-19 pediatric and MIS-C patients and clinical sequelae of included COVID-19 pediatric and MIS-C patients. We reviewed each case report in-depth to make inferences whether all contributing factors to COVID-19 was included. Only confirmed cases were included in this study. Birth complications or genetic conditions may also predispose the pediatric patient to COVID-19 were tabulated. A tool was recently developed to assess the methodological quality of case reports and case series that are included in systematic reviews [16]. The tool proposes questions that were similar to the criteria during the selection of studies as only cases with confirmed COVID-19 cases with PCR testing were added with complete reporting of listed factors above. Hence, given that the questions in the tool were already accounted for and assessed for, all reviewers opted to not conduct a separate risk of bias assessment of included case studies.

Table 2
Clinical sequelae of included COVID-19 pediatric patients. Only RT-PCR-confirmed COVID-19 cases were included.

Author	Significant radiological findings	Significant laboratory findings	Treatments received	Length of hospital stay (days)	ICU admission	Mechanical ventilation	Death	Contributing factors	SARS-CoV-2 RNA in stool specimen or anal swab
Sisman [44]	CXR within limits	Elevated neutrophil counts; reduced lymphocyte counts	Symptomatic	21 days	No	No	No	In utero or intrapartum transmission; infancy	Not tested
Wang [45]	High-density nodular shadows under the pleura of the upper and lower lobe of the right lung on chest CT scan	Elevated AST, TBil, IBil, and creatinine kinase; reduced lymphocytes	Penicillin G	17 days	No	No	No	Infancy	Negative
Vivanti [30]	Unremarkable	Mildly elevated leucocytes and proteins on CSF analysis	Symptomatic	18 days	Yes	Yes	No	Premature, vertical transmission	Positive
Bindi [46]	NA	NA	Symptomatic	60 days	Yes	NA	No	Perforated Meckel's diverticulum	Not tested
Sinelli [47]	Mild bilateral ground-glass opacity on chest CT scan	Moderate hypoxia on ABGs	Ampicillin and gentamicin (discontinued after sterile cultures)	16 days	Yes	No	No	Infancy; actively breastfeeding	Not tested
Piersigili [48]	Non-specific bilateral streaky infiltrates on CXR; unremarkable abdominal U/S	Elevated CRP; and decreased leucocyte count	Symptomatic	NA	Yes	Yes	No	Congenital heart defects; prematurity	Not tested
Precit [49]	Bilateral ground-glass opacities with no focal consolidations on CXR	Elevated blood lactate; Reduced partial pressure of oxygen	Ampicillin, and gentamicin	6 days	Yes	No	No	Metapneumovirus co-infection	Detected
Aghdam [50]	CXR within limits; Patent foramen ovale on echocardiography	Within limits	Vancomycin, amikacin, and oseltamivir	6 days	Yes	No	No	Infancy, patent foramen ovale	Not tested
Salik [51]	Bilateral pulmonary granular opacities and reduced lung volumes on CXR	NA	Surgical palliation of TOF	6 days	Yes	Yes	No	Infancy; Tetralogy of Fallot	Not tested
Wang [52]	Thickened texture of the lungs and the lung field showed patchy blur on CXR	Decreased platelets	Symptomatic	14 days	No	No	No	Positive contact history	Detected
Munoz [53]	Bilateral linear opacities and partial collapse of the right upper lobe on CXR; unremarkable echocardiogram	Elevated leucocytes, CRP, procalcitonin, and pCO2; decreased blood pH, creatinine, and BUN; positive for rhinovirus on PCR	Hydroxychloroquine, azithromycin, and vasopressors, tube thoracostomy	8 days	Yes	Yes	No	Previously healthy	Not tested
Needleman [54]	EEG and brain MRI within limits	Negative respiratory viral panel PCR	Symptomatic	1 day	No	No	No	Mild hypoxic-ischemic encephalopathy; infancy	Not tested
Canarutto [55]	Within limits	Mild neutropenia, monocytosis, and reactive lymphocytes on blood smear	Symptomatic	5 Days	No	No	No	Infancy; actively breastfeeding	Not tested
Elbehery [56]	Mild prominence of cardiomediastinal contour and pulmonary vasculature on CXR;	Elevated platelet levels, creatinine, direct bilirubin, TBil, procalcitonin, LDH, ferritin, and troponin; uncompensated	Furosemide, captopril along, acetaminophen, and anti-failure drugs	28 days	Yes	No	No	Multiple ventricular septal defects; patent ductus arteriosus	Negative

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Table 2 (*continued*)

Author	Significant radiological findings	Significant laboratory findings	Treatments received	Length of hospital stay (days)	ICU admission	Mechanical ventilation	Death	Contributing factors	SARS-CoV-2 RNA in stool specimen or anal swab
		respiratory acidosis on venous blood gases							
Dugue [57]	Excess of temporal sharp transients for age, and intermittent vertex delta slowing with normal sleep-wake cycling on EEG; unremarkable MRI head	Elevated procalcitonin; decreased leucocyte count; and negative CSF profile	Symptomatic	1 day			No	Previously healthy	Positive
Cui [58]	Patchy shadows and ground-glass opacity in the right lung on chest CT scan	Elevated lymphocyte count, platelet count, $CD8^+$ T lymphocyte count, serum IgM and troponin I, and abnormal myocardial zymogram	Interferon α-1b, amoxicillin potassium clavulanate, reduced glutathione, ursodeoxycholic acid, and Lianhua-Qingwen capsule	14 days	No	No	No	Infancy; actively breastfeeding	Detected
Robbins [59]	CXR within limits	Elavated ALP, and calcium; Reduced hemoglobin	Ceftriaxone, and symptomatic	1 day	No	No	No	Infancy	Not tested
Fan [60]	Chest CT scan within limits	Elavated neutrophil counts; Reduced lymphocyte counts	Symptomatic	30 days	No	No	No	Previously healthy	Detected
García-Howard [61]	EEG, and cerebral 1.5T MRI within limits	Elavated serum ferritin	Hydroxychloroquine, and levetiracetam	10 days	No	No	No	PRRT2 frameshift mutation in mother and patient; infancy	Not tested
Le [62]	Mild enlargement of mediastinum shadow on CXR; unremarkable on echocardiography	Elevated procalcitonin, LDH, CRP, creatinine kinase, AST, ALT, and creatinine	Azithromycin	8 days	No	No	No	Previously healthy	Not tested
Li [63]	Nodules and patchy opacification bilateraly, predominantly in subpleural area on chest CT scan	Elavated WBC count and lymphocyte count, decreased neutrophil count and CRP, and elevated LDH, ALT, AST, CK-MB, myoglobin, and troponin T-hypersensitivity	Symptomatic	30 days	No	No	No	Infancy	Not tested
Loron [64]	Unremarkable CXR, ECG, echocardiogram, and cerebral U/S	Hypercapnia and elevated bicarbonates	Caffine	2 days	Yes	No	No	Preterm birth	Not tested
Danley [65]	Mild bronchiolitis on CXR	Elavated LDH	Symptomatic	4 days	Yes	No	No	Muscular ventricular septal defect; atopic dermatitis	Not tested
Moazzam [66]	Telescoping of bowel within the bowel loop in right upper quadrant of abdomen in the subhepatic region suggesting intussusception on abdominal U/S	Elavated d-dimer; Reduced hemoglobin	Broad spectrum antibiotics, and pneumatic reduction of intussuscepted bowel	3 days	No	No	No	Previously healthy	Not tested
Rodriguez-Gonzalez [67]	Irregular pleural line, B-lines and small peripheral consolidations on	Elevated ferritin, CRP, procalcitonin, d-dimer, troponin,	Milrinone, norepinephrine, heparin, tocilizumab, azithromycin,	NA	Yes	Yes	No	Short bowel syndrome; central venous catheter parentral nutirtion	Not tested

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Table 2 (*continued*)

Author	Significant radiological findings	Significant laboratory findings	Treatments received	Length of hospital stay (days)	ICU admission	Mechanical ventilation	Death	Contributing factors	SARS-CoV-2 RNA in stool specimen or anal swab
	lung U/S; sinus tachycardia, right axis deviation, and right ventricular hypertrophy on ECG; severely dilated right chambers, severe right ventricular systolic dysfunction, and supra-systemic pulmonary hypertension on echocardiography; pattern of ground glass and numerous consolidations in the posterior-basal segments of both lungs on CT angiography	NT-proBNP, and IL-6; Reduced heamoglobin, heamatocrit, PT, pH, pCO2, and HCO3	hydroxychloroquine, methylprednisolone, meropenem, vancomycin, and fluconazole						
Heinz [68]	Patchy bilateral lung opacities and a large gastric air bubble on CXR	Elavated WBC count, ALT, AST, and CRP	IVIG	30 days	Yes	Yes	No	Iatrogenic; immunosuppressed; infancy	Not tested
Jafari [69]	Ill-defined ground-glass opacities in the mid and upper zones of both lungs on CXR	Elavated CRP; reduced lymphocytes	Vancomycin, meropenem, and oseltamivir	14 days	No	No	No	Infancy; actively breastfeeding	Not tested
Kam [70]	NA	Reduced neutrophil counts	Symptomatic	18 days	No	No	No	Infancy	Detected
Soumana [71]	Features of pneumonic consolidation in the right lung on CXR	Reduced blood glucose	Ceftriaxone, and gentamycin	2 days	No	No	Yes	Malnutrition	Not tested
Qiu [72]	Increased density, profusion and thickened lung texture, small spot-like and patchy fuzzy shadow on CXR	Elavated LDH and decreased lymphocytes, white blood cells, $CD3^+$, $CD4^+$, $CD8^+$ T cells, and fibrinogen	IVIG, lopinavir/ ritonavir, and methylprednisolone	45 days	Yes	Yes	No	Previous structural heart disease; infancy	Not tested
Navaeifar [73]	Bilateral moderate pleural effusion of the lungs on CXR; Patchy infiltration, pleural effusion, ground-glass opacity, and halo sign in both lungs on chest HRCT	Elavated leucocyte counts, CRP BUN; Reduced hemoglobin, and albumin	Ceftriaxone, hydroxychloroquine, IVIG, cetrizine, meropenam and nutritional supplements	10 days	Yes	No	No	Infancy	Not tested
Sieni [74]	Bilateral reticular markings on CXR	Elevated CRP, ferritin, and LDH levels	Piperacillin/ tazobactam, teicoplanin, lopinavir/ritonavir, hydroxychloroquine, and fluconazole	18 days	No	No	No	Acute myeloid leukaemia; immunosupression	Positive
Mao [75]	Scattered ground glass opacities in the right lower lobe close to the pleura on chest CT scan	Elevated CRP, procalcitonin; and decreased leucocyte count	Recombinant human interferon α-2b, and symptomatic	23 days	No	No	No	Previously healthy	Negative
Mansour [76]	Left upper lobe consolidation and bilateral lower lobe infiltrates on CXR	Elavated leucocytes, CRP and direct bilirubin; Reduced hemoglobin	Ceftriaxone, metronidazole, and symptomatic	5 days	No	No	No	Previously healthy	Not tested
Lahfaoui [77]	Bilateral pulmonary opacities with images of ground glass,	Normocytic normochromic anemia, elevated	Symptomatic	1 day	Yes	Yes	Yes	Actively breastfeeding	Not tested

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Table 2 (*continued*)

Author	Significant radiological findings	Significant laboratory findings	Treatments received	Length of hospital stay (days)	ICU admission	Mechanical ventilation	Death	Contributing factors	SARS-CoV-2 RNA in stool specimen or anal swab
	nodular forms predominant in the upper lobes and condensation on chest CT scan	serum creatinine, CRP, AST, ALT, d-dimer, procalcitonin and serum ferritin							
Essajee [78]	Reticulonodular pattern in keeping with miliary TB on CXR; Pan-hydrocephalus, basal meningeal enhancement and infarction involving the anterior limb of the right internal capsule, lentiform nucleus and thalamus on brain CT scan; Multiple filling defects in the venous system, mainly superior sagittal sinus and the transverse sinuses on contrast-enhanced brain CT scan	Elevated leucocyte counts, CRP, INR, PT, aPT time, fibrinogen, d-dimer, and ferritin; GeneXpert MTB/RIF positive	Isoniazid, rifampicin, pyrazinamide, ethionamide, aspirin, dexamethasone, and ventriculoperitoneal shunt	NA	No	No	No	Meningeal TB co-infection	Not tested
Nikoupour [79]	White lung on CXR	Elevated AST, ALT, BUN, creatinine, glucose, CRP, LDH, and INR; decreased leucocyte count, serum albumin and PT	Vancomycin, meropenem, azithromycin, voriconazole, hydroxychloroquine, lopinavir/ritonavir, oseltamivir, and co-trimoxazole	6 days	Yes	Yes	Yes	Liver cirrhosis, immunosupressed	Not tested
Alsuwailem [80]	Bilateral peri-bronchial wall thickening indicating small airway disease on CXR; Noncompressibility and discontinuity in the appendicular wall with adjacent turbid collection indicating perforated appendicitis on abdominal U/S	Elavated leucocytes, and neutrophil counts	Ceftriaxone, metronidazole, and amoxicillin/clavulanic acid	12 days	No	No	No	Complicated appendicitis	Not tested
Diercks [81]	NA	NA	Symptomatic	0 days	No	No	No	Previously healthy	Not tested
Morand [82]	Focal alveolar condensation of the lingula and a stable mediastinal enlargement on CXR	Elavated GGT, AST, and ALT	Symptomatic	11 days	No	No	No	Immunosupression; EBV co-infection	Not tested
Kihira [83]	Coarse bronchovascular prominence and mild cardiomegaly on CXR; Ejection fraction of 30%, and no structural cardiac anomalies on echocardiography; large acute right anterior and middle cerebral artery territory infarction and subarachnoid hemorrhage in the	Elevated d-dimer	Heparin, epinephrin, and sugammadex	NA	Yes	Yes	Yes	Previously healthy	Not tested

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Table 2 (*continued*)

Author	Significant radiological findings	Significant laboratory findings	Treatments received	Length of hospital stay (days)	ICU admission	Mechanical ventilation	Death	Contributing factors	SARS-CoV-2 RNA in stool specimen or anal swab
	left hemisphere on head CT scan								
Mercolini [84]	Marked bilateral opacification on CXR;	Elevated CRP, LDH, and IL-6	Ceftriaxone, azithromycin, and methylprednisolone	NA	Yes	No	Yes	Mucolipidosis type II; growth retardation; neurological impairment; hypertrophic cardiomyopathy	Not tested
Freij [85]	Enlargement of the lateral, third, and fourth ventricles on head CT scan; extensive progression of meningoencephalitis to her cerebellum and corpus callosum, with leptomeningeal enhancement on brain MRI; bibasilar opacities on CXR; Appearance consistent with severe encephalopathy on EEG	Elevated serum leucocyte count, platelet, d-dimer, and LDH; decreased serum sodium; Positive for TB on CSF and brain biopsy; negative for viral pathogen on CSF	Hydroxychloroquine, azithromycin, dexamethasone, remdesivir, external ventricular drain, craniectomy, and laminectomy	26 days	No	No	Yes	SIADH; meningioencephalitis	Not tested
Theophanous [86]	NA	Elavated leucocyte counts;	Acyclovir, and prednisolone	NA	No	No	No	Chromosome 17 and 19 deletions; submucosal cleft palate, surgically repaired atrial and ventricular septal defects; agammaglobulinemia with hyper IgM, hypospadias, asthma, and moderate obstructive sleep apnea	Not tested
Alloway [87]	Not assessed	Elevated lipase, platelet, LDH, and IL-6	Ketorolac, acetaminophen, ceftriaxone, and metronidazole	2 days	No	No	No	Acute pancreatitis	Not tested
Yildirim [88]	Infiltrations on the right middle and lower pulmonary zones and massive cardiomegaly on CXR; Sinus tachycardia and tall and wide P waves, suggesting bi-atrial dilatation on ECG; Restrictive cardiomyopathy, mitral and tricuspid insufficiency and left ventricular dysfunction with ejection fraction of 40% on Echocardiography	Elavated leuocyte counts, neutrophil counts, blood urea, d-dimer, and troponin	Milrinone, dopamine, and furosemide infusion	3 days	Yes	Yes	Yes	Restrictive cardiomyopathy; chronic lung disease	Not tested
Dinkelbach [89]	Bilateral diffuse ground-glass opacities and consolidation on CT chest;	Elevated CRP, creatinine, glomerular filtration rate, procalcitonin, and IL-6; decreased leucocyte count	Piperacillin/ tazobactam, atenolol, prednisolone, and remdisivir	NA	Yes	Yes	No	Folliculin interacting protien 1 deficiency; asthma; Wolff-Parkinson-White syndome; non-obstructive hypertrophic	Not tested

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Table 2 (*continued*)

Author	Significant radiological findings	Significant laboratory findings	Treatments received	Length of hospital stay (days)	ICU admission	Mechanical ventilation	Death	Contributing factors	SARS-CoV-2 RNA in stool specimen or anal swab
								cardiomyopathy; microcephaly	
Chen [90]	Patchy consolidation and ground-glass opacities distributed in the bronchial bundles or subpleural areas of both lungs on chest CT scan	Elavated leucocytes, neutrophils and CRP; decreased BUN	Lopinavir/ritonavir	5 days	No	No	No	Suspected community transmission	Detected
Farley [91]	Bilateral infiltrates on CXR; Diffuse cerebral dysfunction of non-specific etiolog on EEG; Brain CT scan with contrast within limits	Elavated neutrophil counts; Reduced lymphocyte counts	Amoxicillin, lorazepam, hydroxychloroquine, ceftriaxone, methylprednisolone, and supplements	2 days	Yes	No	No	Attention deficit hyperactivity disorder; motor tics; non-febrile seizures	Not tested
Genovese [92]	Not assessed	Reduced platelet counts	Symptomatic	7 days	No	No	No	Previously healthy	Not tested
Oberweis [93]	Normal cardiac anatomy with impaired left ventricular function, trace mitral insufficiency, andsmall pericardial effusion on echocardiography; discrete ST elevation in V3 consistent with pericarditis on ECG; biventricular systolic dysfunction and diffuse edema on cardiac magnetic resonance imaging; bilateral pneumopathies of the inferior lobes, and bilateral pleural effusions without glass-ground opacities on CXR	Elevated CRP, IL-6, urea, AST, ALT, BNP, troponin T, ferritin, and d-dimer; decreased leucocyte count, and platelets	Enoxaparin, dobutamine, milrinone, tocilizumab, and IVIG	10 days	Yes	No	No	Previously healthy	Positive
Yoo [94]	Non-specific ground glassopacity nodule in the subpleural area of the left lower lobe on chest CT scan	Unremarkable	Symptomatic, and antiviral	17 days	No	No	No	Previously healthy	Not tested
Park [95]	Patchy nodular consolidations with peripheral ground glass opacities in subpleural areas of the right lower lobe in axial and sagittal views on chest CT scan	Within limits	Symptomatic	15 days	No	No	No	Previously healthy	Detected
Tsao [96]	Not assessed	Elavated ANA; Reduced leucocyte counts and platelet counts	Acetaminophen, diphenhydramine, and IVIG	2 days	No	No	No	Rhinovirus/ enterovirus co-infection	Not tested
Almeida [97]	Renal U/S within limits	Normally shaped red blood cells on urinalysis	Symptomatic	21 days	No	No	No	Previously healthy	Not tested
El-Assaad [98]	Coarsened interstitial lung markings, and hazy retrocardiac opacification on CXR; sinus tachycardia, and normal PR length	Elevated leucocyte count, troponin, NTpBNP, CRP, ferritin, and d-dimer; positive	Epinephrine, norepinephrine, immunoglobulin, anakinra, methylprednisolone,	12 days	No	No	No	Pityriasis lichenoides chronica; atrioventricular block	Not tested

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Table 2 (*continued*)

Author	Significant radiological findings	Significant laboratory findings	Treatments received	Length of hospital stay (days)	ICU admission	Mechanical ventilation	Death	Contributing factors	SARS-CoV-2 RNA in stool specimen or anal swab
	on ECG; normal left ventricular size, severe left ventricular systolic dysfunction on echocardiography	parvovirus IgG, Epstein-barr virus IgG, and cytomegalovirus IgG on respiratory pathogen PCR	remdesivir, and heparin						
Bhatta [99]	CXR and brain CT scan within limits	Within limits	Lorazepam, and levetireacetam	2 days	No	No	No	Previously healthy	Not tested
McAbee [100]	Frontal intermittent delta activity on EEG; Brain CT scan within normal limits	Moderately elavated red cells, mildly elavated white cells and neutrophils, along with protein and glucose within limits on CSF analysis	Anticonvulsants	6 days	No	No	No	Previously healthy	Not tested
Barsoum [101]	Tiny patches of opacities on CXR	NA	Inhaled salbutamol, and budesonide/ formoterol	2 days	No	No	No	Asthma	Not tested
Patel [102]	Bilateral diffuse airspace opacities and small pleural effusion on CXR	Elavated CRP, procalcitonin, ferritin; Reduced platelet counts, and lymphocyte counts	IVIG, steroids, inhaled nitric oxide azithromycin, hydroxychloroquine, tocilizumab, and remdesivir	24 days	Yes	Yes	No	Previously healthy	Not tested
Klimach [103]	Not assessed	Elevated CRP,	Symptomatic	5 days	No	No	No	Previously healthy	Not tested
Bush [104]	Sinus tachycardia on ECG; unremarkable CXR	Elevated CRP, leucocyte count, and serum creatinine	Symptomatic	4 days	No	No	No	Renal transplant recipient; immunosuppressed; posterior reversible encephalopathy syndrome	Not tested
Conto-Palomino [105]	Diffuse brain edema on brain tomography	Elevated neutrophil count, CRP, d-dimer, and serum glucose; CSF study was consistent with a viral infection; Negative CSF bacterial growth	Hydroxychloroquine, ceftriaxone, acyclovir, azithromycin, mannitol, haloperiodol, metamizole, and dexamethasone	3 days	No	No	Yes	Previously healthy	Not tested
Gagliardi [106]	CXR within limits; Swelling of the right testis with inhomogeneous pattern and increased flow signal at color Doppler, and inflammation of the epididymis with reactive hydrocele indicating orchiepididymitis on scrotal U/S	Elevated leucocyte counts, CRP, and IL-6; Reduced lymphocyte counts	Broad-spectrum antibiotics	8 days	No	No	No	Previously healthy	Not tested
Giné [107]	Right pneumothorax and left infiltrations in CXR; 2 bullae right upper lobe apex along with diffuse ground-glass infiltrations and with regions of consolidation in chest CT	Unremarkable	Surgical intervention for persistant air leak	7 days	Yes	No	No	Asthma; persistant air leak	Not tested

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Table 2 (*continued*)

Author	Significant radiological findings	Significant laboratory findings	Treatments received	Length of hospital stay (days)	ICU admission	Mechanical ventilation	Death	Contributing factors	SARS-CoV-2 RNA in stool specimen or anal swab
Enner [108]	Bilateral infiltrates on CXR; seizure correlate arising from right posterior temporal region on EEG	Elevated d-dimer, LDH, ferritin, CRP, and ESR	Levetiracetam, caffeine, lacosamide, and remdesivir	16 days	No	Yes	No	Previously healthy	Not tested
Maniaci [109]	NA	Elavated leucoyctes, and lymphocyte counts	Azithromycin, and symptomatic	21 days	No	No	No	Positive contact history	Not tested
Gefen [110]	Kidney U/S with doppler and abdominal U/S within limits	Elavated leucocytes, AST, ALT, random urine protein-to-creatinine ratio; Very elavated serum creatinine kinase; Slightly reduced platelet counts	Amlodipine, and symptomatic	12 days	No	No	No	Autism spectrum disorder; attention deficit hyperactivity disorder; morbid obesity; obstructive sleep apnea; eczema	Not tested
Lewis [111]	Multifocal bilateral patchy opacities on CXR	Elacated AST, ALT, ferritin, CRP, d-dimer, fibrinogen, and procalcitonin; Reduced lymphocyte counts	Hydroxychloroquine, azithromycin, remdesivir, steroids, and anakinra	21 days	Yes	Yes	No	Obesity	Not tested
Gnecchi [112]	CXR within limits; Inferolateral ST-segment elevation on ECG; Hypokinesia of the inferior and inferolateral segments of the left ventricle, with a preserved ejection fraction of 52% on transthoracic echocardiography; Acute myocarditis on MRI T2-weighted short-tau inversion recovery sequences	Elavated leucocyte and neutrophil counts, high-sensitivity cardiac troponin I, creatine phosphokinase, CRP, and LDH; Reduced lymphocyte counts	Hydroxychloroquine, and antiviral therapy	12 days	No	No	No	Previously healthy	Not tested
Locatelli [113]	Unremarkable	Unremarkable	NA	NA	No	No	No	Previously healthy	Not tested
Latimer [114]	Bilateral hazy opacities on CXR	Elacated troponin-I, lactate, leucoyte counts, neutrophil counts, BUN, creatinine, BNP, ALT, AST, TBil, PT time, INA, aPT time, vWF activity, LDH, ferritin, and CK; Reduced platelets, and VWFCP activity	Hydroxychloroquine, intravenous crystalloid fluids, epinephrine infusion, and stress-dose hydrocortisone	46 days	Yes	Yes	No	Chromosome 18q deletion; epilepsy	Not tested
Craver [115]	NA	NA	NA	NA	No	No	Yes	Eosinophilic myocarditis	Not tested
Trogen [116]	Sinus tachycardia, and T-wave inversion on ECG; low lung volumes, and mild, hazy ground glass opacities at the lower lobes bilaterally on	Elevated CRP, ferritin, d-dimer, BNP, creatinine and troponin I; decreased serum sodium; negative blood cultures,	Enoxaparin, acetominophen, and apixaban	5 days	Yes	No	No	Obesity; spondylolysis, mild asthma	Not tested

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Table 2 (*continued*)

Author	Significant radiological findings	Significant laboratory findings	Treatments received	Length of hospital stay (days)	ICU admission	Mechanical ventilation	Death	Contributing factors	SARS-CoV-2 RNA in stool specimen or anal swab
	CXR; mildly depressed ejection fraction on echocardiography; normal size left ventricle with mildly decreased systolic function, normal right ventricular size with mildly diminished systolic function, and an area of hypokinesia on cardiac magnetic resonance imaging;	respiratory pathogen PCR profile, and gastrointestinal pathogen PCR profile							
Marhaeni [117]	Unremarkable	Elevated CRP, ferritin, and transferrin saturation; decreased leucocyte count, and heamoglobin	Azithromycin, osetalmivir, blood transfusion, and deferiprone	NA	No	No	No	Beta-thalassemia	Not tested

ABG: Arterial blood gases; ALT: Alanine aminotransferase; ANA: Antinuclear antibody; aPT: Partial thromboplastin time; AST: Aspartate aminotransferase; BNP: Brain natriuretic peptide; BUN: Blood urea nitrogen; CRP: C-reactive protein; CSF: Cerebrospinal fluid; CT: Computed tomography; CXR: Chest X-ray; ECG: Electrocardiography; EEG: Electroencephalography; ESR: Erythrocyte sedimentation rate; GGT: Gamma-glutamyl transferase; HRCT: High resolution computed tomography; IBil: Indirect bilirubin; IL: Interleukin; INR: International normalized ratio; IVIG: Intravenous immunoglobulin; LDH: Lactate dehydrogenase; MRI: Magnetic resonance imaging; NA: Not available; PCR: Polymerase chain reaction; PRRT2: Proline-rich transmembrane protein 2; PT: Prothrombin time; RBC: Red blood cell; SIADH: Syndrome of inappropriate antidiuretic hormone secretion; TB: Tuberculosis; TBil: Total bilirubin; U/S: Ultrasound; VWFCP: von Willebrand factor cleaving protease; WBC: White blood cell.

2.5. Presenting the evidence

All patient demographics and related variables were presented descriptively. The case report data were grouped individually using the first author and related variables. Given that we could not find any review that presented data in a case-by-case format, we structured our review to close these gaps. The country of origin and the age in months in addition to the mode of delivery were presented to highlight any missing areas in current literature. The radiological and laboratory findings were diverse given the widespread nature of included studies.

3. Results

The search yielded 649 records. After removing 133 duplicates, 516 records were reviewed by abstract and title. After initial screening, only 181 records met the pre-defined inclusion criteria and underwent full-text evaluation. Studies were eliminated due to inconsistencies in data and were omitted post-in-depth evaluation. A total of 92 records were included in this novel review (Fig. 1). Of all patients, 58% were male and the mean age of the patients was 6.2 years (SD: 5.9).

3.1. Baseline demographic characteristics of included COVID-19 pediatric patients

Table 1 summarizes the findings of 75 COVID-19 confirmed patients who did not meet the criteria for MIS-C. The majority of the cases were reported from the United States (33.3%), China (16%), and Italy (10.6%). Among the 75 patients, 39 (52%) had a confirmed positive contact history. Seven of the 13 (53.9%) patients in the neonate age group had mothers who were COVID-19 positive. The mode of delivery as stated in 21 patients, where 15 (71.4%) were delivered via spontaneous vaginal delivery, and 6 (28.6%) through emergency caesarian section. Of 62 patients, the mean (SD) lag time was 4.9 (0.6) days (Table 1).

3.2. Clinical sequelae of included COVID-19 pediatric patients

The clinical sequelae are enlisted in Table 2. Among 65 patients, the mean (SD) length of hospital stay was 12.6 (1.5) days. ICU admission was noted in 28 (38.7%) patients. Mechanical ventilation was required for 16 (21.3%) patients. Death was documented in nine (12%) of the 75 included patients. Contributing factors included 18.5% congenital defects (n = 12), genetic (n = 9), vertical transmission or during infancy (n = 11), infective etiology (n = 4), asthma (n = 3), gastrointestinal (n = 3), obesity (n = 2), malnutrition (n = 1), other causes (n = 4), and previously healthy (n = 26). SARS-CoV-2 RNA in stool specimen or anal swab was tested in only 14 of the 75 patients, with detection in 11 (14.6%) patients (Table 2).

3.3. Baseline demographic characteristics of included MIS-C patients

The findings of 17 COVID-19 MIS-C patients along with their case definitions are summarized in Table 3. The mean (SD) age of included MIS-C patients was 8 (5.3) years. Of all included patients, 17.6% had positive contact history. Notably, 64.7% of MIS-C patients were male. The mean (SD) value for a lag time was 5.5 (1.3) days (Table 3) (see Table 4).

3.4. Clinical sequelae of included MIS-C patients

Eight of 17 MIS-C patients had a mean (SD) length of hospital stay of 8.9 (4.2) days. Of all, 52.9% of patients were admitted to the ICU. Only 29.4% required mechanical ventilation/ECMO. Death was reported in only one MIS-C patient (5.9%). Notably, the following was documented

Table 3
Baseline demographic characteristics of included MIS-C patients. No data was available for the mode of delivery, antepartum, intrapartum, and postpartum complications, breastfeeding status, and immunization status. Case definitions: MIS-C associated with COVID-19 (WHO) [5]; MIS-C associated with COVID-19 (US CDC) [17]; PIMS-TS (RCPCH) [134]; Complete Kawasaki disease (AHA) [135]; Incomplete Kawasaki disease (AHA) [135].

Case Definitions	First author	Country	Age	Positive contact history	Gender	Signs and symptoms at presentation	Lag time
MIS-C Associated with COVID-19 (WHO), and Complete Kawasaki Disease (AHA)	Loo [118]	Hong Kong	4 months	NA	Male	Fever, bilateral conjunctivitis, congested throat with bright red tongue and lips, diffuse maculopapular rash over the face, trunk, limbs, and swelling with erythema over bilateral hands and feet	5 days
MIS-C Associated with COVID-19 (WHO), and Incomplete Kawasaki Disease (AHA)	Raut [119]	India	5 months	Parents	Male	Fever, irritability, upper extremities, and trunkal maculopapular rash, and conjunctivitis	5 days
Complete Kawasaki Disease (AHA)	Jones [120]	USA	6 months	None	Female	Fever, refusal to eat, maculopapular rash, and bulbar conjunctival injection without exudate, and upper extremity erythema and edema	5 days
MIS-C Associated with COVID-19 (WHO), MIS-C associated with COVID-19 (US CDC), and Incomplete Kawasaki Disease (AHA)	Loo [118]	Hong Kong	6 months	NA	Male	Fever, left cervical lymphadenopathy with abscess formation, faint maculopapular rash over trunk sparing the extremities	6 days
MIS-C Associated with COVID-19 (WHO), MIS-C associated with COVID-19 (US CDC), and Incomplete Kawasaki Disease (AHA)	Rivera-figueroa [121]	USA	5 years	None	Male	Fever, rash, swelling of the palms and soles, conjunctivitis, decreased appetite, diarrhea, dysuria, and abdominal pain	8 days
MIS-C Associated with COVID-19 (WHO), MIS-C associated with COVID-19 (US CDC), and Incomplete Kawasaki Disease (AHA)	Leon [122]	USA	6 years	NA	Female	Fever, sore throat, conjunctivitis, rash, edema of the hands and feet, and reduced appetite	6 days
MIS-C Associated with COVID-19 (WHO), MIS-C associated with COVID-19 (US CDC), and Incomplete Kawasaki Disease (AHA)	Cazzaniga [123]	Italy	6 years	Family suspected	Male	Fever, sore throat, asthenia, vomiting, diarrhea, labial and conjunctival hyperemia, and erythematous rash in the back and hands	5 days
MIS-C Associated with COVID-19 (WHO), and PIMS-TS (RCPCH)	Klocperk [124]	Czech Republic	8 years	NA	Female	Fever, headache, abdominal pain, vomiting, diarrhea, and diffuse itchy maculopapular rash	5 days
MIS-C Associated with COVID-19 (WHO), MIS-C associated with COVID-19 (US CDC), and Complete Kawasaki Disease (AHA)	Balasubramanian [125]	India	8 years	NA	Male	Fever, cough, sore throat, generalized non-pruritic erythematous skin rash, non-purulent bulbar conjunctivitis, cracked lips, strawberry tongue, edema of limbs, tender hepatomegaly, and abdominal distention	4 days
MIS-C Associated with COVID-19 (WHO), MIS-C associated with COVID-19 (US CDC), and Incomplete Kawasaki Disease (AHA)	Wacker [126]	USA	10 years	NA	Male	Fever, gastrointestinal symptoms, and hypotensive shock	7 days
MIS-C associated with COVID-19 (WHO), and MIS-C associated with COVID-19 (US CDC)	Nguyen [127]	USA	10 years	Yes	Female	Fever, abdominal pain, erythematous rash on the chest, right upper back, and arms, occasional emesis, diarrhea, and sore throat	8 days
MIS-C associated with COVID-19 (WHO), and MIS-C associated with COVID-19 (US CDC)	Greene [128]	USA	11 years	NA	Female	Fever, sore throat, malaise, poor appetite, generalized abdominal pain, leg pain, and an itchy rash starting on the palms that quickly spread to the trunk and back	4 days
MIS-C Associated with COVID-19 (WHO), and MIS-C associated with COVID-19 (US CDC)	Bapst [129]	Switzerland	13 years	Parents suspected	Male	Fever, abdominal and thoracic pain, odynophagia, non-purulent conjunctivitis, and a new skin eruption compatible with target lesions of erythema multiforme	7 days
MIS-C associated with COVID-19 (WHO), MIS-C associated with COVID-19 (US CDC), and Incomplete Kawasaki Disease (AHA)	Al Ameer [130]	Saudi Arabia	13 years	Mother	Female	Fever, sore throat, malaise, abdominal pain, diarrhea, reduced oral intake, skin rash, bilateral non-suppurative conjunctivitis, and erythematous, cracked lips, and extremity edema	5 days
MIS-C Associated with COVID-19 (WHO), MIS-C associated with COVID-19 (US CDC), and Incomplete Kawasaki Disease (AHA)	Dolinger [131]	USA	14 years	NA	Male	Fever, and abdominal pain	5 days
MIS-C Associated with COVID-19 (WHO), MIS-C associated with COVID-19 (US CDC), and Incomplete Kawasaki Disease (AHA)	Vari [132]	USA	14 years	None	Male	Fever, fatigue, abdominal pain, diarrhea, and truncal rash	4 days
MIS-C Associated with COVID-19 (WHO), MIS-C associated with	Regev [133]	Israel	16 years	Mother	Male	Fever, abdominal pain, fatigue, and sore throat	NA

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Table 3 (*continued*)

Case Definitions	First author	Country	Age	Positive contact history	Gender	Signs and symptoms at presentation	Lag time
COVID-19 (US CDC), and Incomplete Kawasaki Disease (AHA)							

AHA: American heart association; CDC: Centers for disease control and prevention; KD: Kawasaki disease; MIS-C: Multisystem inflammatory syndrome in children; PIMS-TS: Paediatric inflammatory multisystem syndrome temporally associated with COVID-19; WHO: World health organization.

as contributing factors; G6PD deficiency (17.6%), Group A streptococcus co-infection (17.6%), infancy (11.8%), Rhinovirus/Enterovirus co-infection (11.8%), Overweight (5.9%), Juvenile idiopathic arthritis (5.9%), perianal Crohn's disease (5.9%), with 23.5% being previously healthy.

4. Discussion

To our best understanding, this is the first systematic review of case reports about contributing factors to pediatric patients during the COVID-19 pandemic. The reasons for decreased prevalence and severity of COVID-19 infection in children as compared to adults are unclear; most cases in children have shown either a milder disease course than in adults or an asymptomatic course [3,17–21]. In one nationwide pediatric study in China, more than 90% of patients had an asymptomatic, mild, or moderate case [21]. Pediatric patients had lower numbers of symptoms such as pneumonia, fever, cough, and dyspnea as compared to adults [8]. Several possible explanations have been proposed for such findings. The milder symptoms could be due to a less intense immune response in children, as COVID-19 is thought to cause the bulk of its damage through a strong inflammatory response and surge in cytokines, as occurs in adults [22]. There may be a difference in ACE-2 receptor expression (the receptor for SARS-CoV-2) in the body between children and adults, and there may be a lower binding ability of ACE-2 in children [21]. It has been suggested that there may be some viral interference occurring in the respiratory tract of children and competition for the ACE-2 receptor, which could lead to decreased viral load and decreased manifestations of disease [3]. Regardless of disease severity, there is a concern for the covert spread of infection due to asymptomatic carriers, and several studies have shown that pediatric carriers could transmit the disease to adults [3,11,21]. There may also be underreporting and under-testing due to the mildness of symptoms, and this could be undervaluing the true pediatric burden of COVID-19. This is an important consideration due to the implications for public health policy and guidelines in reopening schools and recreational activities.

Although disease severity appears to be decreased in the pediatric age group, there is still a risk of children developing severe COVID-19 disease and experiencing complications. Similar to adults, children who have severe COVID-19 infection can experience respiratory failure, shock, acute renal failure, coagulopathy, and multi-organ dysfunction [17]. Current evidence shows that risk factors for severe disease include underlying medical complexities e.g. congenital anomalies, and developmental delays, congenital heart disease, asthma, immunocompromised states, cystic fibrosis, and obesity, as well as genetic, neurologic, and metabolic conditions [17,19]. A cross-sectional study in North America found that 40 out of 48 children (83%) admitted to PICUs due to COVID-19 had an underlying medical condition [19]. In one systematic review of COVID-19-positive children below the age of 18, 22% had some type of comorbidity or underlying medical condition, with chronic pulmonary conditions including asthma as the most common condition (45%), followed by congenital heart disease (23%), immune suppression (12%), and hematological or oncological conditions (6%) [23]. In the U.S., hospitalization rates were higher for children of Hispanic or Latino and black descent, which may be attributed to higher rates of underlying conditions in these demographics [17]. Similarly, a CDC report found that Hispanic children had the highest rates of hospitalization, and Hispanic children along with black children had a higher prevalence of underlying conditions [18]. Also, obesity tends to be more common in these populations, and several studies have shown that obesity is a common underlying condition for children with COVID-19 [17,18].

Some children develop multisystem inflammatory syndrome (MIS-C) following a confirmed or suspected COVID-19 infection [20]. Symptoms can include persistent fever, lesions, skin rash, abdominal pain, vomiting, diarrhea, with progression to multiorgan dysfunction (including myocarditis and acute renal failure) and shock [17]. MIS-C is similar to Kawasaki disease, a vasculitis that involves systemic inflammation and cardiac manifestations [18,24]. Studies have shown that MIS-C may occur even in the setting of negative SARS-CoV-2 tests, as in a case series that described Kawasaki-like clinical symptoms related to COVID-19 and acute myocarditis findings in four pediatric patients [24]. Another cohort study showed that patients who were determined to have MIS-C met clinical diagnostic criteria for COVID-19 and had evidence of community contact with COVID-19 infection [25]. The CDC reports that Hispanic and black patients have made up the majority of MIS-C cases, with obesity as the most common pre-existing underlying condition [18,26]. Currently, the recommended treatment for MIS-C is supportive, antiviral, and anti-inflammatory therapies [6,18].

4.1. Transmission dynamics in children

Several factors must be considered in looking at vertical and horizontal transmission in the pediatric population. Existing evidence to definitively support the vertical transmission from pregnant mothers to neonates is controversial and needs further investigation. Several studies have shown that there are no clinical findings of COVID-19 infection present in neonates with affected mothers [27]. On the other hand, a cohort study in China with 33 neonates born to affected mothers found three neonates who had SARS-CoV-2-positive nasopharyngeal and anal swabs as well as pneumonia findings on chest x-ray [28]. Intrauterine transmission is also supported by a study of 6 infants born to infected mothers in which 5 infants were found to have elevated serum IgG virus-specific antibodies - IgG is the only antibody type that significantly crosses the placenta from mother to fetus [29]. More importantly, two infants were found to also have increased IgM serum concentrations, which are not typically transferred cross-placentally, suggesting that it may have been produced by the neonates in response to the virus has crossed the placenta [29]. A case study involving an infected pregnant mother who delivered a neonate with SARS-CoV-2-positive nasopharyngeal and anal swabs, as well as clinical manifestations, showed that there was SARS-CoV-2 viral load present in the placenta and the amniotic fluid, confirming transplacental transmission in this case [30]. It is important to note that the viral load was much higher in the placenta than in the amniotic fluid or maternal blood; a possible mechanism of infection could be due to the highly expressed angiotensin-converting enzyme 2 (ACE2) receptors in placental tissue, as ACE-2 is the receptor for SARS-CoV-2 [30]. It has been determined that in addition to being highly expressed in placental tissue, ACE2 is also expressed in fetal heart, lung, and liver tissues; ACE-2 expression increases in liver hepatocytes and fibroblasts from the first to the second trimester of

Table 4
Clinical sequelae of included MIS-C patients. Only one case reported the SARS-CoV-2 RNA in stool which was negative.

Significant radiological findings	Significant laboratory findings	Treatments received	Length of hospital stay (days)	ICU admission	Mechanical ventilation/ ECMO	Death	Contributing factors
Dilated left coronary artery and right coronary artery on echocardiography	Elevated ESR, and CRP	IVIG, and dipyridamole	NA	NA	NA	No	G6PD deficiency
Mild opacity in right middle lung zone on CXR; Left anterior descending artery with increase perivascular brightness with lack of tapering on echocardiography	Elevated CRP, ESR, ferritin, leucocyte count, and NT-proBNP; Reduced hemoglobin, serum albumin, and sodium	IVIG, aspirin, and azithromycin	NA	No	No	No	Infancy
Faint opacity in the left midlung zone on CXR; Echocardiography within limits	Elevated CRP, and ESR; Reduced serum sodium, and albumin	IVIG, and ASA	NA	No	No	No	Infancy
4 cm × 1.5 cm × 1.6 cm abscess over the left lower jugular region. CXR normal on chest CT scan; 4 mm pericardial effusion with increased echogenicity over both coronary arteries and a small proximal left coronary artery aneurysm on echocardiography	Elevated ESR, CRP; Reduced hemoglobin, serum sodium, albumin, leucocyte counts, neutrophil counts	Piperacillin/tazobactam, cloxacillin G-CSF, IVIG, and dipyridamole	NA	NA	NA	No	G6PD deficiency; methicillin-sensitive Staphylococcus aureus co-infection
Enlarged cardiac silhouette on CXR; Small global pericardial effusion on echocardiogram	Elevated leucocyte counts, ESR, CRP, procalcitonin, ferritin, ALT, and troponin; Reduced hemoglobin, platelet counts, serum sodium, and albumin	IVIG	6 days	Yes	No	No	Group A streptococcus co-infection
Diffuse patchy pulmonary opacities on CXR; Mildly decreased LV function, and MV insufficiency on echocardiography	Elevated CRP, LDH, ferritin, troponin, d-dimer, fibrinogen, serum potassium, creatinine, BUN lactate dehydrogenase, and leucocyte counts; Reduced serum sodium	Vancomycin, clindamycin, and ceftriaxone, dopamine, IVIG, and aspirin	7 days	Yes	Yes	No	Group A streptococcus co-infection
Minimal pericardial effusion, and mild mitral insufficiency on echocardiography; Accentuated broncho vascular markings in bilateral peri-hilar and paracardiac region on CXR; Pulmonary infiltrates at the right base and minimal pericardial effusion on lung ultrasound; Ileocolic meteorism with multiple small diffuse air-fluid levels on abdominal x-ray; Fluid in the pelvis and right iliac fossa, and spleen size at the upper limits on abdominal CT scan	Elevated CRP, ferritin, procalcitonin, fibrinogen, AST, ALT, and GGT; Reduced serum sodium, and albumin	IVIG, amoxicillin/clavulanic acid, cefotaxime, hydroxychloroquine, aspirin, and enema	NA	No	No	No	Rhinovirus and Enterovirus co-infection
Mild signs of hypoventilation in the retrocardiac region with no infiltration or consolidation on CXR; Paralytic ileus with appendicitis on abdominal ultrasound	Elevated CRP, procalcitonin, ferritin, soluble IL-2 receptor, d-dimer, urea, creatinine, AST, troponin, and proNT-BNP	Methylprednisolone, IVIG, and prophylactic nadroparin	15 days	No	No	No	Previous history of juvenile idiopathic arthritis
Right upper and middle lobe infiltrates on CXR; Echocardiogram within limits	Elevated leucocyte counts, neutrophil counts, CRP, ESR, and ferritin; Reduced serum sodium; 2+ proteinuria	Tocilizumab, IVIG, meropenem, vancomycin, and clindamycin	14 days	Yes	Yes	No	Rhinovirus/ Enterovirus co-infection
Left anterior descending and right coronary artery long segmental dilatations, and 40% ejection fraction on echocardiography; Cardiac	Elevated inflammatory markers, BNP, and troponin T	IVIG, corticosteroids, and anakinra	NA	Yes	No	No	Overweight

(*continued on next page*)

Table 4 (*continued*)

Significant radiological findings	Significant laboratory findings	Treatments received	Length of hospital stay (days)	ICU admission	Mechanical ventilation/ ECMO	Death	Contributing factors
magnetic resonance imaging (MRI) within limits							
Perihilar peribronchiolar thickening without consolidation on CXR	Elevated CRP, ESR, ferritin, d-dimer, AST, ALT, BNP, PT/INR, fibrinogen, and troponin I; Reduced lymphocyte count	Vancomycin, ceftriaxone, and enoxaparin	4 days	Yes	No	No	Previously healthy
CXR within limits; LV systolic function mildly decreased based on decreased shortening fraction on echocardiogram; S1Q3T3 on ECG	Elevated CRP, d-dimer, ferritin, LDH, procalcitonin, leucocyte counts, PT/INR, fibrinogen, troponin, BNP, BUN, and creatinine; Reduced lymphocyte counts	Milrinone, norepinephrine, furosemide, ceftaroline, clindamycin, piperacillin-tazobactam, enoxaparin, vitamin K, tocilizumab, convalescent plasma, remdesivir, steroids, and IVIG	NA	Yes	No	No	Previously healthy
Bibasal pneumonia on chest CT scan; Multiple peritoneal lymph nodes on abdominal CT scan	Elevated CRP, procalcitonin, and troponin; Reduced leucoyte counts, and platelet counts	Ceftriaxone	7 days	No	No	No	Previously healthy
Mesenteric lymphadenitis on abdominal ultrasound; Bilateral patchy lung infiltrates with mild-to-moderate bilateral effusion on CXR; Mild mitral regurgitation, mild pericardial effusion, and moderate depression in left ventricle function with ejection fraction 32% on echocardiography	Elevated ESR, ferritin, troponin, leucocyte counts, LDH, PT/INR, and AST; Reduced serum sodium, potassium, and albumin	Favipiravir, clindamycin, penicillin G, tocilizumab, low-molecular-weight heparin, milrinone, epinephrine, norepinephrine, and continuous renal replacement therapy	6 days	Yes	Yes	Yes	G6PD deficiency
CXR within limits; 28 cm of ileitis, a 2.3 cm perianal abscess and fistula on MR enterography; Mediastinal lymphadenopathy, and hepatosplenomegaly on CT chest. Abdomen, and pelvis	Elevated CRP, ESR, IL-6, IL-8, TNF-α, d-dimer, ferritin, FEU, ALT, AST, ALP; Reduced serum albumin	Piperacillin/tazobactam, ciprofloxacin, metronidazole, hydroxychloroquine, azithromycin, enoxaparin, and infliximab	NA	NA	NA	No	Small bowel, perianal Crohn's disease
Mild cardiomegaly and pulmonary edema on CXR; Severely decreased biventricular systolic function with left ventricular fractional shortening of 19.9%, mild to moderate tricuspid and mitral regurgitation, and trivial dilation of the left coronary artery on echocardiogram; Thickening of the distal ileum and diffuse lymphadenopathy on CT scan;	Elevated CRP, ESR, BNP, and troponin I; decreased lymphocyte count	Ceftriaxone, penicillin G, phenylepinephrine, epinephrine, diuretics, milrinone, IVIG, and aspirin	12 days	Yes	Yes	No	Group A streptococcus co-infection, constipation, and eczema
Mildly reduced systolic left ventricular function with ejection fraction 50% and mild mitral regurgitation on echocardiography	Elevated CRP, PT/INR, d-dimer, troponin-I, and pro-BNP; Reduced platelet counts, and hemoglobin	IVIG and high-dose aspirin, and methylprednisolone	NA	Yes	Yes	No	Previously healthy

ASA: Acetylsalicylic acid; AST: Aspartate aminotransferase; BNP: Brain natriuretic protein; BUN: Blood urea nitrogen; CRP: C-reactive protein; CT: Computed tomography; CXR: Chest X-ray; ECMO: Extracorporeal membrane oxygenation; EF: Ejection fraction; ESR: Erythrocyte sedimentation rate; G6PD: Glucose-6-phosphate dehydrogenase; G-CSF: Granulocyte colony-stimulating factor; GI: Gastrointestinal; IL: Interleukin; INR: International normalized ratio; IVIG: Intravenous immunoglobulin; LV: Left ventricle; MCA: Middle cerebral artery; MR: Mitral regurgitation; NK: Natural killer; PEG: Percutaneous endoscopic gastrostomy; PT: Prothrombin time; WBC: White blood cell.

pregnancy, suggesting that the liver may be a vulnerable organ for SARS-CoV-2 infection in neonates [31]. Another case study suggested probable congenital infection in a neonate with positive nasopharyngeal swabs who also had elevated liver enzymes [32]. It is important to consider that there are many limitations with determining intrauterine or intrapartum transmission from mother to fetus or neonate, including sensitivity and specificity of diagnostic tests, sample collections and detecting contamination, the timing of infection about pregnancy trimester, and inconsistencies in testing maternal blood, amniotic fluid, and cord blood [33]. To address this, a classification system has been proposed to categorize cases as confirmed, probable, possible, unlikely, and not infected, based on case definitions for maternal infection during pregnancy, congenital infections in live and stillborn neonates, and neonatal infections acquired intrapartum and postpartum [33].

4.2. Role of fecal shedding in COVID-19

The question of the fecal-oral route providing an alternate means of transmission in COVID-19 has been raised with varying studies and evidence [1–5]. Viral shedding of SARS-CoV-2 in feces was observed in 40.5% of infected patients [34]. Data suggests a prolonged duration of viral shedding can occur; one study found that respiratory samples stayed positive for an average of 16.7 days after first symptom onset while fecal samples stayed positive for an average of 27.9 days, an average of 11.2 days longer [35]. Another study found that 64.29% of positive patients remained positive in fecal swabs 6–10 days after nasopharyngeal swabs had turned negative [36]. In a study with 10 pediatric SARS-CoV-2 patients, eight had persistently positive rectal swabs after nasopharyngeal swabs were negative, and two remained positive up to 13 days post-discharge [37]. Possibly, viral load in feces could impact horizontal transmission particularly via spontaneous vaginal deliveries, and comprehensive studies are necessary to investigate this [38].

5. Recommendations

A consideration under the umbrella of transmission routes and risk is breastfeeding; currently, both the WHO and CDC state that it is unlikely that COVID-19 can be transmitted through breast milk based on current evidence, and recommend taking the usual precautions against transmission such as handwashing and wearing a face mask while feeding [39,40]. Breastfeeding is a very important part of early childhood nutrition and development as well as maternal health, and at present, it is best for known or suspected COVID-19-positive mothers to continue breastfeeding with careful contact precautions to prevent droplet transmission [41].

The role of pediatric patients in transmitting COVID-19 must not be overlooked. Evidence suggests that even if the majority of cases are asymptomatic, children may still be spreading the infection to adults and through the community [3,11,21]. In one retrospective study in the United States that traced three outbreaks at childcare facilities, 12 COVID-19-positive children were found to have transmitted to 12 out of 46 (26%) contacts outside of the facilities (confirmed or suspected cases) [42]; all of these children had mild or no symptoms. To help mitigate such spread, masks are recommended in anyone over the age of 2, but those who are too young to wear masks may still spread the disease as well; in one case, an infant of 8 months was found to have transmitted the virus to both parents [42]. Secondary transmission from infected children to both household and non-household contacts could not be ruled out in several outbreaks in childcare programs that reopened in Rhode Island in June 2020 [43]. Established guidelines such as wearing masks, frequent handwashing, surface disinfection, and social distancing must be observed amongst the pediatric population and those who come into contact with children to decrease transmission [42,43]. Timely investigation of potential cases and efficient contact tracing also play a crucial role in mitigation [42,43].

6. Conclusion

The understanding of COVID-19 is continually evolving with children appearing to be less frequently affected than adults. However, pediatric COVID-19 patients have been observed to present with severe disease sequelae known as MIS-C. As the pandemic evolves, the risk factors for COVID-19 and MIS-C in pediatric patients are not entirely established. It is also important to identify pediatric patients at risk of critical disease as has been established in the adult age group. With schools having reopened, the pediatric age groups may be susceptible to community transmission of COVID-19. Finally, a coordinated effort to establish informed decisions about disease susceptibility and severity in the pediatric age group is required.

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Registration of research studies

Name of the registry: Research Registry.
Unique Identifying number or registration ID: reviewregistry1354.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.104227.

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