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...
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 (months) | 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         | 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         | Mother                   | Emergency cesarean section | Meconium-stained liquor | Never breastfed | NA                  | Male   | Asymptomatic                      | NA       |
| Vivanti [30] | France  | 0.1          | 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          | Hospital-acquired infection Mother | Spontaneous vaginal delivery | None | Currently breastfeeding | NA                  | Male   | Asymptomatic                      | NA       |
| Sinelli [47] | China   | 0.1          | 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 | Periportal cyanosis, poor sucking, and hypoxia | 1 day    |
| Piersigili [48] | Belgium  | 0.23         | Mother                   | Emergency cesarean section | None | Currently breastfeeding | NA                  | Male   | Asymptomatic                      | NA       |
| Precit [49]  | USA     | 0.3          | Grandmother and sibling suspected Parents | Spontaneous vaginal delivery | None | Currently breastfeeding | NA                  | Male   | Nasal secretion, and labored breathing | 1 day    |
| Aghdam [50]  | Iran    | 0.5          | Parents                 | Cesarean section | NA                  | NA                  | NA                  | Male   | Fever, lethargy, cutaneous mottling, respiratory distress, tachypnea, and tachycardia Tachypnea, worsening cyanosis, feeding intolerance, and increasing lethargy | NA       |
| Salik [51]   | China   | 0.5          | Mother                   | Spontaneous vaginal delivery | Low birth weight; diagnosed with teratology of Fallot prenatally | NA                  | NA                  | Female |                                  |          |
| Wang [52]    | China   | 0.6          | Mother                   | Spontaneous vaginal delivery | None | NA                  | NA                  | Male   | Fever, vomiting, and increased number of stools Nasal congestion, tachypnea, fever, and reduced feeding | 2 days   |
| Munoz [53]   | USA     | 0.7          | Household contact | Spontaneous vaginal delivery | Premature | NA                  | NA                  | Male   | Nasal congestion, rhinorrhea, | 2 days   |
| Needleman [54] | USA     | 0.8          | Family                   | NA                  | NA                  | NA                  | Male   | Nasal congestion, rhinorrhea, | 3 days   |

(continued on next page)
| 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 |
|-----------------|---------|----------|--------------------------|------------------|---------------------------------------------------------------------|----------------------|--------------------|--------|----------------------------------|-----------|
| Canarutto [55]  | Italy   | 1 month  | Father                   | Spontaneous vaginal delivery | Mild hypoxia-ischemic encephalopathy                               | NA                   | Currently breastfeeding | NA     | Male                             | 1 day     |
| Elbehery [56]   | KSA     | 1.3 months | Grandparents             | Spontaneous vaginal delivery | Neonatal cholelithiasis, intrauterine growth restriction           | NA                   | NA                 | Female | cough, rhinorhea, 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                 | Spontaneous vaginal delivery | NA                                                                 | NA                   | Currently breastfeeding | NA     | Female                           | 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                 | Spontaneous vaginal delivery | None                                                               | NA                   | NA                 | Female | Convulsions without fever           | 5 days    |
| García-Howard [61] | Spain | 3 months  | Mother                  | Spontaneous vaginal delivery | None                                                               | NA                   | NA                 | Female | Rhinorhea, fever, and nasal congestion | 4 days    |
| Le [62]         | Vietnam | 3 months  | Grandmother             | Spontaneous vaginal delivery | None                                                               | Currently breastfeeding | Compliant with age | Male   | Non-productive cough and rhinorhea | 16 days   |
| Li [63]         | China   | 3 months  | Mother                  | Emergency cesarean section | Preterm, low birth weight, and mild hyaline membrane disease disease | NA                   | NA                 | Male   | Extreme cyanosis, and recurrent apneas | 11 days   |
| Loron [64]      | France  | 3 months  | Father and suspected community-acquired infection | Emergency cesarean section | Muscular ventricular septal defect                                | Currently breastfeeding | Compliant with age | Male   | Decreased oral intake, loose stools, stuffy nose, mild cough, and diaphoresis | 16 days   |
| Danley [65]     | USA     | 4 months  | Mother                  | Spontaneous vaginal delivery | NA                                                                 | NA                   | NA                 | Male   | Abdominal pain, and rectal bleeding | 1 day     |
| Moazzam [66]    | Pakistan | 4.8 months | NA                      | NA                | NA                                                                 | NA                   | NA                 | Male   | Severe respiratory distress, cyanosis, nasal congestion, cough, and fever | 14 days   |
| Rodriguez-Gonzalez [67] | Spain | 6 months  | NA                      | NA                | Short bowel syndrome                                               | NA                   | NA                 | Male   | Poor feeding, dyspnea, fever, tachypnea, and hypoxia | 3 days    |
| Heinz [68]      | USA     | 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   | Sore throat, cough, nasal congestion, and diarrhea | 1 day     |
| Jafari [69]     | Iran    | 6 months  | Mother                  | Emergency cesarean section | Currently breastfeeding                                             | Compliant with age   | Male   | 3 days                            |           |
| Kam [70]        | Singapore | 6 months  | Parents                 | Spontaneous vaginal delivery | NA                                                                 | NA                   | NA                 | Male   | None                             | Unknown   |
| Soumana [71]    | Niger   | 8 months  | Mother suspected        | Spontaneous vaginal delivery | NA                                                                 | NA                   | NA                 | Male   | Fever, diarrea, and respiratory distress | NA        |
| Qiu [72]        | China   | 8 months  | NA                      | Atrial and ventricular | NA                                                                 | NA                   | NA                 | Male   | Fever, cough, wheezing, | 7 days    |

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| 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 |
|--------------|------------------|---------|--------------------------|------------------|---------------------------------------------------------------------|----------------------|-------------------|--------|-------------------------------------|----------|
| Navaeifar    | Iran             | 1 year  | Parents                  | NA               | Hospital-acquired suspected septal defects, and aortic stenosis repairs | NA                   | Compliant with age | Male   | Fever, and rash                      | 4 days   |
| Sieni        | Italy            | 1.1 years | Parents, hospital-acquired infection suspected | NA               | None                                                                | NA                   | NA                | Female | NA                                  | NA       |
| Mao          | 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      | Beirut           | 1.3 years | Parents                  | Spontaneous vaginal delivery | None                                                                | NA                   | NA                | Female | Fever, tachypnea, tachycardia, mucocutaneous pallor, and fatigue | 6 days   |
| Lahfaoui     | Morocco          | 1.4 years | Mother                  | NA               | None                                                                | Currently breastfeeding | Compliant with age | Female | NA                                  | 2 days   |
| Essajee      | South Africa     | 2.6 years | None                    | NA               | None                                                                | NA                   | NA                | Female | Left-sided weakness, lethargy, enlarging cervical lymphadenopathy, and decreased appetite | NA       |
| Nikoupour    | Iran             | 3 years  | NA                      | Premature        | None                                                                | NA                   | NA                | Male   | Weakness, malaise, severe dry cough, tachypnea, and respiratory distress | 4 days   |
| Alsuwailem   | Saudi Arabia     | 4 years  | Extended family suspected | NA               | None                                                                | NA                   | NA                | Female | Subjective fever, progressive, severe, and generalized abdominal pain, and non-bloody, non-bilious vomiting | 3 days   |
| Diercks      | USA              | 4 years  | Hospital-acquired infection suspected | Mother | Spontaneous vaginal delivery | None                                                                | NA                   | NA                | Female | Asymptomatic                        | NA       |
| Morand       | France           | 4.6 years | Mother                  | NA               | NA                                                                  | NA                   | NA                | Female | Fever, cough, polynepra               | 5 days   |
| Kihira       | USA              | 5 years  | NA                      | NA               | NA                                                                  | NA                   | NA                | Male   | Fever, cough, and abdominal pain     | 3 days   |
| Mercolini     | Italy            | 5 years  | Family suspected         | Parents          | NA                                                                  | NA                   | NA                | Female | Fever, and rhinorhea                 | 2 days   |
| Freij        | USA              | 5 years  | Family suspected         | Parents          | NA                                                                  | NA                   | NA                | Female | Fever, confusion and headache        | 6 days   |
| Theophanous   | USA              | 6 years  | None                    | NA               | None                                                                | 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      | USA              | 7 years  | Family                  | NA               | NA                                                                  | NA                   | NA                | Female | Abdominal pain, non-bloody non-bilious vomiting, and fever | 2 days   |
| Yildirim      | Turkey           | 7 years  | NA                      | NA               | NA                                                                  | NA                   | NA                | Female | Chest pain, dyspnea and fatigue      | NA       |
| Dinkelbach    | Germany          | 7 years  | NA                      | NA               | NA                                                                  | NA                   | NA                | Male   | Cough, myalgia, and fever            | 7 days   |
| Chen          | China            | 7 years  | Community transmission suspected | NA               | NA                                                                  | NA                   | NA                | Female | Irregular fever, sore throat         | 1 day    |

(continued on next page)
| 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  |
|-------------------|------------|----------|--------------------------|------------------|---------------------------------------------------------------------|---------------------|--------------------|--------|-------------------------------------|-----------|
| Farley [91]       | USA        | 8 years  | NA                       | NA               | NA                                                                  | NA                  | NA                 | Male   | Abdominal 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]         | South 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, diarrhea, vomiting, myalgia, and trunkal nonpruritic rash | 1 day     |
| El-Assaad [98]    | USA        | 10 years | NA                       | Spontaneous vaginal delivery | None | NA                                                                  | Compliant with age | Male   | Isolated afibrile seizure | 1 day     |
| Bhatta [99]       | USA        | 11 Years | NA                       | Spontaneous vaginal delivery | None | NA                                                                  | Compliant with age | Male   | Status epilepticus, generalized weakness, and fever | 2 days    |
| McAbee [100]      | USA        | 11 years | NA                       | NA               | NA                                                                  | NA                  | NA                 | Male   | Low grade fever, cough, wheeze, and breathing difficulty | NA        |
| Barsoum [101]     | Ireland    | 12 years | NA                       | NA               | NA                                                                  | NA                  | NA                 | Female | Fever, nonproductive cough, nonbloody vomiting, worsening shortness of breath, and hematuria | 5 days    |
| Patel [102]       | USA        | 12 years | None                     | NA               | NA                                                                  | NA                  | NA                 | Female | Erythematous painful papules on soles of feet, axilla and distal lower extremity, fever, myalgia, and headache | 1 day     |
| Klimach [103]     | UK         | 13 years | Parents suspected        | NA               | NA                                                                  | NA                  | NA                 | Male   | Rhinitis, mild cough, fever, skin mottling, and large stool output, and low oxygen saturation | 1 day     |
| Bush [104]        | USA        | 13 years | Mother suspected         | Premature, 8 month stay at NICU | NA | NA                                                                  | NA                  | Male   | Headache, vomiting, fever, altered sensations, and hemiparesis | 3 days    |
| Conto-Palomino [105] | Peru      | 13 years | None                     | NA               | No                                                                  | NA                  | Incomplete         | Female | High-grade fever, pain, and swelling in the right testis | 2 days    |
| Gagliardi [106]   | USA        | 14 years | NA                       | NA               | NA                                                                  | NA                  | NA                 | Male   | Cough, thoracic pain, fever, | 11 days   |
| Giné [107]        | Spain      | 14 years | Community-acquired infection | NA            | NA                                                                  | NA                  | NA                 | Female | (continued on next page) | 11 days   |
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 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 |
|--------------|---------|----------|--------------------------|------------------|---------------------------------------------------------------------|----------------------|---------------------|--------|------------------------------------|----------|
| Emmer [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, ethematosus skin lesions on the lower limbs, and asthenia | 3 days   |
| Gefen [110]  | China   | 16 Years | NA                       | NA               | NA                                                                  | NA                   | NA                  | Male   | Fever, tachycardia, myalgia, 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   |
| Gnechi [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.
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, procalditonin, 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 cardiomediatals and pulmonary vasculature on CXR; | Elevated platelet levels, creatinine, direct bilirubin, TBil, procalditonin, 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                                      |

(continued on next page)
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 |
|-----------------|----------------------------------|--------------------------------|---------------------|-----------------------------|--------------|------------------------|-------|----------------------|-----------------------------------------------|
| Dugue [57]      | Excess of temporal sharp transients for age, and intermittent vertex delta slowing with normal sleep-wake cycling on EEG; unremarkable MRI head | Respiratory acidosis on venous blood gases; Elevated procalcitonin; decreased leukocyte count; and negative CSF profile | Symptomatic | 1 day | No | 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 |
| Robbins [59]    | CXR within limits                | Elevated ALP, and calcium; Reduced lymphocyte counts | Ceftriaxone, and symptomatic | 1 day | No | No | No | Infancy |
| Fan [60]        | Chest CT scan within limits      | Elevated neutrophil counts; Reduced lymphocyte counts | Symptomatic | 30 days | No | No | No | Previously healthy |
| García-Howard [61] | EEG, and cerebral 1.5T MRI within limits | Elevated serum ferritin | Hydroxychloroquine, and levetiracetam | 10 days | No | No | No | PRRT2 frameshift mutation in mother and patient; infancy |
| 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 |
| Li [63]         | Nodules and patchy opacification bilateraly, predominantly in subpleural area on chest CT scan | Elevated 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 |
| Loron [64]      | Unremarkable CXR, EEG, echocardiogram, and cerebral U/S | Elevated d-dimer; Reduced hemoglobin | Caffeine | 2 days | Yes | No | No | Preterm birth |
| Danley [65]     | Mild bronchiolitis on CXR         | Elavated LDH | Symptomatic | 4 days | Yes | No | No | Muscular ventricular septal defect; atopic dermatitis |
| 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 | Elevated d-dimer; Reduced hemoglobin | Broad spectrum antibiotics, and pneumatic reduction of intussuscepted bowel | 3 days | No | No | No | Preterm birth |
| 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 parenteral nutrition | Not tested |
|                 |                                  |                                  |                     |                            |              |                        |       |                      | (continued on next page) |
| 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 |
|------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------|--------------|------------------------|-------|-------------------------------------------------------------------------------------|---------------------------------------------|
| Heinz [68] | Patchy bilateral lung opacities and a large gastric air bubble on CXR                           | NT-proBNP, and IL-6; Reduced hemoglobin, hematocrit, FT, pH, pCO2, and HCO3                   | hydroxychloroquine, methylprednisolone, meropenem, vancomycin, and fluconazole      | 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             | Elevated 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 CT angiography                         | 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 | Elevated 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, cetirizine, 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; immunosuppression                              | 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                                  |
| 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 |
|-----------------|----------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------|---------------|------------------------|-------|---------------------------------------------------------------------------------------|-----------------------------------------------|
| Essajee [78]    | nodular forms predominant in the upper lobes and condensation on chest CT scan                    | serum creatinine, CRP, AST, ALT, d-dimer, procalcitonin and serum ferritin                      | Isoniazid, rifampicin, pyrazinamide, aspirin, dexamethasone, and ventriculoperitoneal shunt | NA                             | No            | No                     | No    | Meningeal TB co-infection                                                            | Not tested                                    |
| Nikoupour [79]  | 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 | NA                                                                                   | No                             | Yes           | No                     | No    | Liver cirrhosis, immunosuppressed                                                      | Not tested                                    |
| Alsuwailem [80] | White lung on CXR                                                                                   | Elevated AST, ALT, BUN, creatinine, glucose, CRP, LDH, and INR; decreased leucocyte count, serum albumin and PT | Ceftriaxone, metronidazole, and amoxicillin/clavulanic acid                         | 12 days                        | No            | No                     | No    | Complicated appendicitis                                                            | Not tested                                    |
| Diercks [81]    | Bilateral peribronchial 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 | Elevated leucocytes, and neutrophil counts                                                      | Vancomycin, meropenem, azithromycin, voriconazole, hydroxychloroquine, lopinavir/ritonavir, oseltamivir, and cotrimoxazole | 6 days                        | Yes           | Yes                    | Yes   | Previously healthy; Immunosuppression; EBV co-infection                                | Not tested                                    |
| Morand [82]     | NA                                                                                                | Focal alveolar condensation of the lingula and a stable mediastinal enlargement on CXR          | Symptomatic GGT, AST, and ALT                                                        | 0 days                         | No            | No                     | No    | Previously healthy                                                               | 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                                    |
| 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 |
|-----------------|-----------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-------------------------------|---------------|------------------------|-------|-------------------------------------------------------------------------------------|-----------------------------------------------|
| Mercolini [84]  | left hemisphere on head CT scan 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 SIADH; meningioencephalitis | Not tested                                |
| Freij [85]      | Enlargement of the lateral, third, and fourth ventricles on head CT scan; extensive progression of meningioencephalitis to her cerebellum and corpus callosum, with leptomeningeal enhancement on brain MRI; bilateral 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   |                                                                                  | Not tested                                |
| Theophanous [86] | NA                                                                                                 | Elevated 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, hypoplasia, asthma, and moderate obstructive sleep apnoa | 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 | Elevated leucocyte 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 protein 1 deficiency; asthma; Wolff-Parkinson-White syndrome; non-obstructive hypertrophic | Not tested                                |

(continued on next page)
| 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 |
|----------------|---------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|-------------------------------------|--------------------------------|----------------|------------------------|-------|--------------------------------------------------------------------------------------|-----------------------------------------------|
| Chen [90]      | Patchy consolidation and ground-glass opacities distributed in the bronchial bundles or subpleural areas of both lungs on chest CT scan | Elevated leucocytes, neutrophils and CRP; decreased BUN                                         | Lopinavir/ritonavir                 | 5                               | No             | No                     | No    | cardiomyopathy; microcephaly                                                           | Detected                                      |
| Farley [91]    | Bilateral infiltrates on CXR; Diffuse cerebral dysfunction of non-specific etiology on EEG; Brain CT scan with contrast within limits | Elevated neutrophil counts; Reduced lymphocyte counts                                           | Amoxicillin, lorazepam, hydroxychloroquine, ceftriaxone, methylprednisolone, and supplements | 2                               | Yes            | No                     | No    | Attention deficit hyperactivity disorder; motor tics; non-febrile seizures          | Not tested                                    |
| Genovese [92]  | Normal cardiac anatomy with impaired left ventricular function, trace mitral insufficiency, and small 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 | Reduced platelet counts                                                                      | Symptomatic                         | 7                               | No             | No                     | No    | Previously healthy                                                                | Not tested                                    |
| Oberwets [93]  | Non-specific ground glass opacity nodule in the subpleural area of the left lower lobe on chest CT scan | Unremarkable                                                                                  | Symptomatic, and antiviral           | 17                              | No             | No                     | No    | Previously healthy                                                                | Not tested                                    |
| Yoo [94]       | 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 | 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                              | Yes            | No                     | No    | Previously healthy                                                                 | Positive                                      |
| Park [95]      | Not assessed                                                                                     | Acetaminophen, diphenhydramine, and IVIG                                                       | Symptomatic                         | 2                               | No             | No                     | No    | Rhinovirus/enterovirus co-infection                                                  | Not tested                                    |
| Tsao [96]      | Renal U/S within limits                                                                          | Elevated ANA; Reduced leucocyte counts and platelet counts                                    | Acetaminophen, diphenhydramine, and IVIG | 2                               | No             | No                     | No    | Rhinovirus/enterovirus co-infection                                                  | Not tested                                    |
| Almeida [97]   | Coarsened interstitial lung markings, and hazy retrocardiac opacification on CXR; sinus tachycardia, and normal PR length | Normally shaped red blood cells on urinalysis                                                 | Symptomatic                         | 21                              | 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, NT-proBNP, CRP, ferritin, and d-dimer; positive            | Epinephrine, norepinephrine, immunoglobulin, anakinra, methylprednisolone,             | 12                              | No             | No                     | No    | Pityriasis lichenoides chronica; atrioventricular block                             | Not tested                                    |

(continued on next page)
| 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 |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|-----------------------------|---------------|-------------------------------|-------|-------------------------------------------------------------------------------------|-----------------------------------------------|
| Bhatta [99]     | 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                                                                                                                                      | Lorazepam, and levetiracetam                                  | 2 days                       | No                         | No                           | No                | Previously healthy                                                                 | Not tested                                   |
| McAbee [100]    | CXR and brain CT scan within limits                                                                                                                                                                                                      | Frontal intermittent delta activity on EEG; Brain CT scan within normal limits                                                                                                                                                   | Anticonvulsants                                               | 6 days                       | No                         | No                           | No                | Previously healthy                                                                 | Not tested                                   |
| Barseoun [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                                                                                                                                                                 | Elevated 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                                                                                                                                                                                                                             | Not assessed                                                                                                                                                                                                                  | 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                                   |
| Gagliardi [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, haloperidol, 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 persistent air leak                  | 7 days                       | Yes                        | No                           | No                | Asthma; persistent air leak                                                         | Not tested                                   |
| 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                                                                     | Elevated leucocytes, 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 elevated 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                           | Elavated 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                                 |
| Gnecci [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 Unremarkable | 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] | NA                                                                     | Unremarkable                     | NA                                                       | NA                            | No            | No                     | No    | Previously healthy                                        | Not tested                                 |
| Latimer [114] | Bilateral hazy opacities on CXR                                       | Elavated troponin-I, lactate, leucocyte counts, neutrophil counts, BUN, creatinine, BNP, ALT, AST, TRB, PT time, INR, aPT time, vWF activity, LDH, ferritin, and Ck; Reduced platelets, and VWFCP activity NA | 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, acetaminophen, and apixaban                      | 5 days                       | Yes           | No                     | No    | Eosinophilic myocarditis                                  | Not tested                                 |

(continued on next page)
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 |
|-----------------|---------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|---------------------|-------------------------------|---------------|------------------------|-------|----------------------|---------------------------------------------|
| Marhaeni [117]  | 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; Unremarkable | Respiratory pathogen PCR profile, and gastrointestinal pathogen PCR profile                         | Azithromycin, oseltamivir, 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 caesarean 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 absence 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, diarhea, 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), MIS-C associated with COVID-19 (US CDC), and Complete Kawasaki Disease (AHA) | Kloepperk [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 distension | 5 days |
| MIS-C Associated with COVID-19 (WHO), MIS-C associated with COVID-19 (US CDC), and Complete 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), and Incomplete Kawasaki Disease (AHA) | Nguyen [127] | USA | 10 years | Yes | Female | Fever, abdominal pain, erythematous rash on the chest, right upper back, and arms, occasional emesis, diarhea, 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) | Bapat [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) | Vare [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 COVID-19 (US CDC), and Incomplete Kawasaki Disease (AHA) | Regev [133] | Israel | 16 years | Mother | Male | Fever, abdominal pain, fatigue, and sore throat | NA |

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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 pregnancy, suggesting a possible role in vertical transmission.

| 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.
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, procalcitomin, 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 dilations, and 40% ejection fraction on echocardiography; Cardiac | Elevated inflammatory markers, BNP, and troponin T | IVIG, corticosteroids, and anakinra | NA | Yes | No | No | Overweight |

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detecting contamination, the timing of infection about pregnancy sensitivity and specificity of diagnostic tests, sample collections and consider that there are many limitations with determining intrauterine probable congenital infection in a neonate with positive nasopharyngeal 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 mography; CXR: Chest X-ray; ECMO: Extracorporeal membrane oxygenation; EF: Ejection fraction; ESR: Erythrocyte sedimentation rate; G6PD: Glucose-6-phosphate dehydrogenase; ASA: Acetylsalicylic acid; AST: Aspartate aminotransferase; BNP: Brain natriuretic protein; BUN: Blood urea nitrogen; CRP: C-reactive protein; CT: Computed tomography; MRI: Magnetic resonance imaging; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; 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; BWC: White blood cell.

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 | 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 |
| Peribilar peribronchial thickening without consolidation on CXR | Elevated CRP, d-dimer, ferritin, LDH, procalcitonin, leucocyte counts, PT/INR, fibrinogen, troponin, BNP, BUN, and creatinine; Reduced lymphocyte counts | Milirinone, norepinephrine, furosemide, cefaroline, clindamycin, piperacillin-tazobactam, enoxaparin, vitamin K, tocilizumab, convalescent plasma, remdesivir, steroids, and IVIG | NA | Yes | No | No | Previously healthy |
| CXR within limits; LV systolic function mildly decreased based on decreased shortening fraction on echocardiogram; S1Q3T3 on EKG | Elevated CRP, procalcitonin, and troponin; Reduced leucocyte counts, and platelet counts | Ceftriaxone | 7 days | No | No | No | Previously healthy |
| Bibasal pneumonia on chest CT scan; Multiple peritoneal lymph nodes on abdominal CT scan | Elevated CRP, procalcitonin, and troponin; Reduced leucocyte counts, and platelet counts | Favipiravir, clindamycin, penicillin G, tocolza, low-molecular-weight heparin, milrinone, epinephrine, norepinephrine, and continuous renal replacement therapy | 6 days | Yes | Yes | Yes | G6PD deficiency |
| 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 ≤2% on echocardiography 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 ESR, ferritin, troponin, leucocyte counts, LDH, PT/INR, and AST; Reduced serum sodium, potassium, and albumin | Ceftriaxone, penicillin G, phenylephrine, epinephrine, diuretics, milrinone, IVIG, and aspirin | 12 days | Yes | Yes | 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, 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 |
| Mildly reduced systolic left ventricular function with ejection fraction 50% and mild mitral regurgitation on echocardiography | Elevated CRP, ESR, BNP, and troponin I; decreased lymphocyte count | Ceftriaxone | 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.
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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Consent
No patients were involved in the conduction of this research.

Registration of research studies
Name of the registry: Research Registry. Unique Identifying number or registration ID: reviewregistry1354. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-the-registry?registry=osystematicreviewsmeta-analyses registryos ystematicreviewsmeta-analysesdetails/627402ca9fd2a001f6ebd6e/

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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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