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Pediatric COVID-19: Systematic review of the literature

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A B S T R A C T

Objectives: There is limited data regarding the demographics and clinical features of SARS-CoV-2 infection in children. This information is especially important as pneumonia is the single leading cause of death in children worldwide. This Systematic Review aims to elucidate a better understanding of the global impact of COVID-19 on the pediatric population.

Methods: A systematic review of the literature was performed in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to gain insight into pediatric COVID-19 epidemiology. Specifically, Pubmed and Google Scholar databases were searched to identify any relevant article with a focus on *Pediatric Covid 19, Pediatric Covid-19, Pediatric SARS-COV-2*, and *Pediatric Coronavirus 19*. References within the included articles were reviewed. All articles that met criteria where analyzed for demographics, clinical, laboratory, radiographic, treatment and outcomes data.

Results: Ten studies including two case series and 8 retrospective chart reviews, altogether describing a total of 2914 pediatric patients with COVID-19 were included in this systematic review. Of the patients whose data was available, 56% were male, the age range was 1 day to 17 years, 79% were reported to have no comorbidities, and of the 21% with comorbidities, the most common were asthma, immunosupression, and cardiovascular disease. Of pediatric patients that were tested and positive for an infection with SARS-CoV-2, patients were asymptomatic, 14.9% of the time. Patients presented with cough (48%), fever (47%) and sore throat/pharyngitis (28.6%), more commonly than with upper respiratory symptoms/rhinorrhea/sneezing/nasal congestion (13.7%), vomiting/nausea (7.8%) and diarrhea (10.1%). Median lab values including those for WBC, lymphocyte count and CRP, were within the reference ranges with the exception of procalcitonin levels, which were slightly elevated in children with COVID-19 (median procalcitonin levels ranged from 0.07 to 0.5 ng/mL. Computed tomography (CT) results suggest that unilateral CT imaging findings are present 36% of cases while 64% of pediatric patients with COVID-19 had bilateral findings. Of the studies with age specific hospitalization data available, 27.0% of patients hospitalized were infants under 1 year of age. Various treatment regimens including interferon, antivirals, and hydroxychloroquine therapies have been trialed on the pediatric population but there are currently no studies showing efficacy of one regimen over the other. The mortality rate of children that were hospitalized with COVID-19 was 0.18%.

Conclusion: In contrast to adults, most infected children appear to have a milder course and have better outcomes overall. Additional care may be needed for children with comorbidities and younger children. This review also suggests that unilateral CT chest imaging findings were seen in 36.4% pediatric COVID-19 patients. This is particularly concerning as the work-up of pediatric patients with cough may warrant a bronchoscopy to evaluate for airway foreign bodies. Extra precautions need to be taken with personal protective equipment for these cases, as aerosolizing procedures may be a method of viral transmission.

Level of evidence: 4 (Systematic Review).

Abbreviations: WHO, World Health Organization; 2019-nCoV, 2019 novel coronavirus; COVID-19, 2019 novel coronavirus disease; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CDC, Center for Disease Control; RT-PCR, reverse-transcriptase polymerase chain reaction assay; n/a, data not available; CT, computed tomography; CXR, Chest X-Ray; WBC, white blood count; CRP, C-reactive protein; Hg, hemoglobin; CKMB, Creatine Kinase-MB; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; PICU, Pediatric Intensive Care Unit; IRB, Institutional Review Board

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1. Introduction

An outbreak of unusual respiratory disease causing severe cases of pneumonia initially in Wuhan, China was caused by a novel enveloped RNA coronavirus. The World Health Organization (WHO) named the virus, the 2019 novel coronavirus (2019-nCoV) on January 7, 2020 [1]. Soon after, the virus rapidly spread throughout the world. On February 11, 2020, WHO named the illness associated with 2019-nCoV the 2019 novel coronavirus disease (COVID-19) [2]. The International Committee on Taxonomy of Viruses later renamed the 2019-nCoV virus to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3].

In the United States, 22% of the population is made up of children aged < 18 years. In comparison, the Center for Disease Control (CDC) COVID-19 Response Team has reported that 1.7% (2572/149,082) of the COVID-19 cases reported as of April 2, 2020, for which the age was known, occurred in pediatric patients aged < 18 years [4]. The CDC COVID-19 Response Team has estimated that 20% of all pediatric patients whose hospitalization status was known, were hospitalized, compared to 33% among all adults aged 18–64 years [4].

Coronaviruses (including 229E, OC43, NL63 and KHU1) are prevalent and cause a significant percentage of all common colds in immunocompetent adults and children [5]. The 2019 novel coronavirus, SARS-CoV-2, can be transmitted directly from person to person by respiratory droplets and potentially uses the ACE2 receptor to infect humans. SARS-CoV-2 has a more variable clinical course than the common cold [5].

Many of those who died of the SARS-CoV-2 have had underlying health conditions such as hypertension, diabetes or cardiovascular disease that may have compromised their immune systems. SARS-CoV-2 is more likely to infect elderly men [5,6]. In contrast, the virus is thought to have a milder effect on the pediatric population. A case series of a total four infants born to mothers with COVID-10, Chen et al. [7] in which none of three infants tested were positive for the virus nor developed clinical symptoms of disease, suggests a low likelihood of vertical transmission of the virus. Yet, there is limited data regarding the demographics and clinical features of SARS-CoV-2 in children [8]. This is especially important as pneumonia is the single leading cause of death in children worldwide [9]. This Systematic Review was performed to gain a better understanding of the global impact of Covid-19 on the pediatric population. The Northwell Health Institutional Review Board (IRB) granted this study IRB exemption.

2. Methods

A systematic literature search was performed in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [10] guidelines to increase comprehensiveness and transparency of reporting. Published studies were found using a thorough search strategy of the Pubmed and Google Scholar databases on April 10, 2020, with no language or regional restrictions. The following search terms were used: *Pediatric Covid 19, Pediatric Covid-19, Pediatric SARS-COV-2,* and *Pediatric Coronavirus 19*. References within the included articles were reviewed and the corresponding abstracts and full articles were accessed if relevant. Studies citing the included articles were searched for using Pubmed and Google Scholar databases and their corresponding abstracts and full articles also accessed if relevant. No restriction was placed on the date of publication. The literature search was originally performed in April 10, 2020 when this project first took shape and was repeated in April 16, 2020 prior to submission of the manuscript for accuracy.

Eligibility for inclusion in the review was a specific focus of COVID-19 on the pediatric population. Studies that had no data, those with data on adults, those with repeat data points due to updates, and those without data specific to patients with positive COVID-19 testing were excluded. Children were defined as being < 18 years old. Only cases with confirmed COVID-19 positive testing were included. Commentaries and editorials were excluded. Isolated case reports and repeat case series from the same region were excluded in an attempt to avoid duplicate data from large retrospective chart reviews.

A large retrospective chart review of 728 COVID-19 positive pediatric patients by Dong et al. [2] was rejected as the case data was mixed with the demographics of 1407 suspect cases without confirmatory COVID-19 positive testing. Of note, in this study, most cases were mild and one child died [2]. The data from Calvo et al. [11], was rejected as a more recent update on the demographics of COVID-19 was included [12] and this article likely included duplicate data. For similar reasons the results of Sun et al. [6], Yu et al. [13] and Xia et al. [14] were rejected. These were case series from Wuhan Children's Hospital that likely replicated data from the larger Lu et al. [8] retrospective chart review of 171 children treated at Wuhan Children's Hospital. Likewise, the results of Wei et al. [15] was rejected as the data was likely repeated from Children's Hospitals in other Chinese provinces included in studies by Cai et al. [16] and Qiu et al. [17]. Finally, the data from a series of infants born to COVID-19 positive mothers, Chen et al. was also rejected as all the infants that were tested were negative for the disease [7].

Asymptomatic was defined as "without any clinical symptoms and signs or imaging findings or disease, whereas the 2019-nCoV/SARS-CoV-2 testing result was positive". Cases were defined as confirmed COVID-19 positive if they met any one of the following criteria:

1. Nasal, nasopharyngeal, oropharyngeal swab, nasotracheal, or blood samples tested positive for 2019-nCoV/SARS-CoV-2 nucleic acid by using real-time reverse-transcriptase polymerase chain reaction assay (RT-PCR).
2. Genetic sequencing of respiratory tract or blood samples was highly homologous with 2019-nCoV/SARS-CoV-2.
3. Reports to government agencies (Center for Disease Control) indicating a positive case.

The information that was extracted were as follows: study data (author, year, level of evidence, geographic area, study age group, study design); demographics data (including age and gender, comorbidities); clinical data (presenting signs and symptoms, exposure history and coinfection data); laboratory data [white blood count (WBC), lymphocytes, hemoglobin (Hg), platelets, C-reactive protein (CRP), Creatine Kinase-MB (CK-MB), D-Dimer, procalcitonin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea, creatinine, lactate dehydrogenase (LDH), and SARS-CoV-2 testing results (aerodigestive tract, serum, urine, and fecal)], radiographic data [chest x-ray (CXR) and computed tomography (CT) scan results]; treatment data (hospitalization, pediatric intensive care unit (PICU) admission, oxygen therapy, antibiotic, antiviral and other medication regimen] and outcomes data (mortality, length of admission, repeat SARS-CoV-2 testing results).

Due to the qualitative, summative nature of this review and significant variations in study design and reporting, a meta-analysis and statistical calculations were not performed.

3. Results

3.1. Review of the literature

A search of 202 articles was performed. 10 papers were identified that were relevant to the research topic and met inclusion criteria. A PRISMA flow diagram detailing the systematic search is presented (Fig. 1). The results focused on demographics, clinical data, laboratory data, radiographic data, treatment data and outcomes data. The results of the 10 studies are summarized in Tables 1–6 ([4,8,12,16–22]). The 10 studies selected represent retrospective chart reviews and case series published in 2020 with data collection between Jan to April 2020. Data came from regions throughout the world including distinct regions of China, United States, Iran, and Spain.

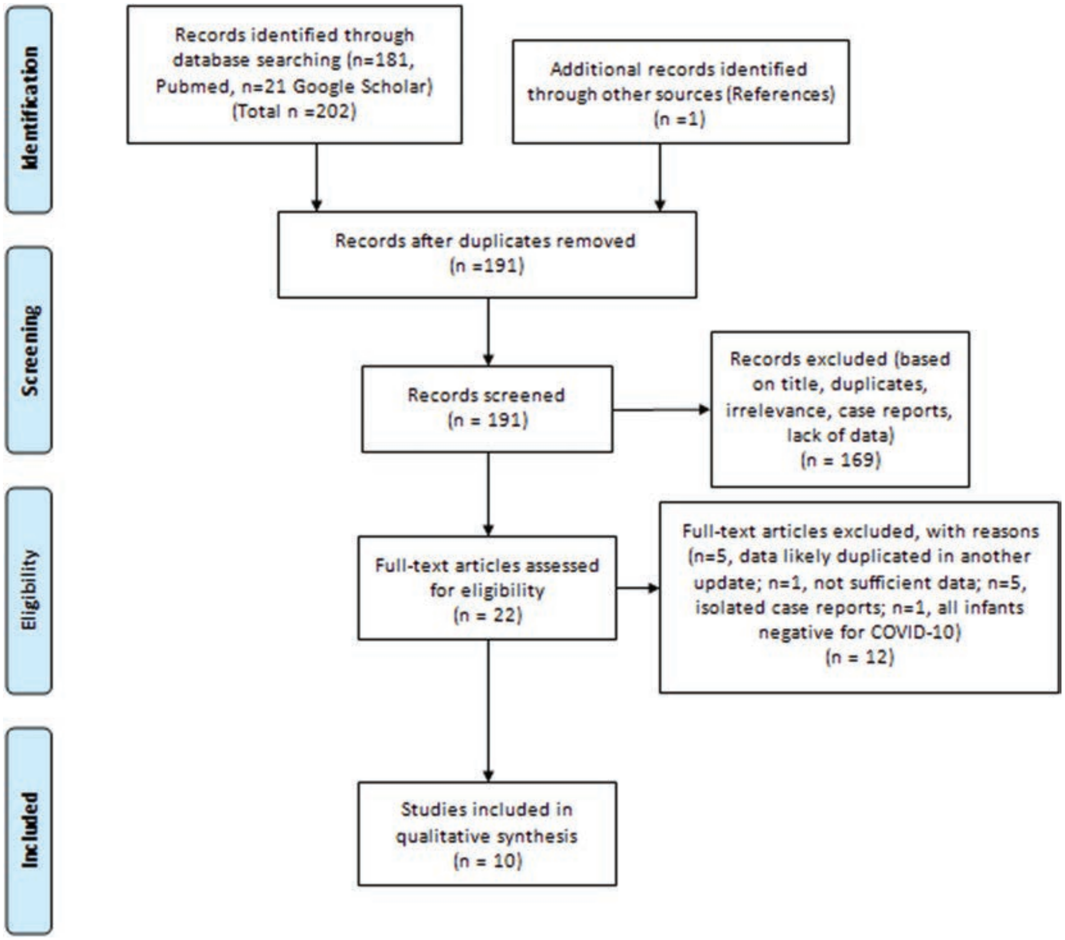

Fig. 1. Pediatric COVID-19 search strategy using PRISMA flowchart [10].

3.2. Demographics data

There were an overall of 2914 pediatric patients that tested positive for COVID-19, and were analyzed in the 10 studies included in the systematic review (Table 1). Gender was reported in all studies but data was missing for 82 individuals [4]. Of the 2832 cases with gender data available, the percentage of males ranged from 33% to 100% with an overall mean percentage of males of 56.4% (n = 1598). Patients' median age varied across studies from 1 to 11 years. Of the studies with reported means, patients' mean age varied across studies from 6.2 to 11 years, with a composite mean age of 7.9 years (n = 74, age range 1 day- 17 years).

Only two studies had "negative" COVID-19 testing data available. The retrospective chart review by Lu et al. [8] describes that of the 1391 pediatric patients that were tested for COVID-19 at Wuhan Children's Hospital, 171 patients tested positive. The retrospective chart review by Tagarro et al. [12], describes that of 365 pediatric patients tested for COVID-19 in Madrid, 41 patients tested positive. Additionally, the CDC COVID-19 Response Team describes 2572 pediatric patients tested positive for COVID-19 between Feb 12- Apr 2, 2020, but only 2470 patients have gender data available [4].

3.3. Clinical data

Across the studies, data about the incidence of comorbidities was available for 444 children, and of these, 349 were reported to have no comorbidities (78.6%, with individual study percentages ranging from 50% to 100%) and 95 out of 444 children had comorbidities (21.4%, with individual study percentages ranging from 8.7% to 50%) Of the 95 children reported to have comorbidities, only 84 children had specific data available (Table 2). Of these 84 children, 40 had asthma, 11 had immunosupression and 28 had cardiovascular disease. One patient with cardiovascular disease also had malnutrition and suspicion for an underlying metabolic disorder. Five patients out of the 84 patients with data available had "other comorbidities" but the comorbidities were not listed.

Information about COVID-19 presenting signs and symptoms in children was available for 633 cases (Table 3). Of these, 51 out of the 342 cases with data available were asymptomatic (14.9%, with individual study percentages ranging from 0% to 53.3%), 296 out of 633 patients had fever (46.8%, with individual study percentages ranging from 26.8% to 100%), 285 out of 592 patients had cough (48.1%, with individual study percentages ranging from 11.1% to 100%), 91 out of 578 had shortness of breath, respiratory distress, or tachypnea (15.7%, with individual study percentages ranging from 0% to 50%), 86 out of 629 had upper respiratory symptoms, rhinorrhea, sneezing or nasal congestion (13.7%, with individual study percentages ranging from 6.5% to 40%), 161 out of 563 had sore throat or pharyngitis (28.6%, with individual study percentages ranging from 8.3% to 46.2%), 47 out of 605 had vomiting/nausea (7.8%, with individual study percentages ranging from 0% to 10.7%), 19 out of 316 had abdominal pain (6%, with individual study percentages ranging from 3% to 8%), 62 out of 614 had diarrhea (10.1%, with individual study percentages ranging from 0% to 22.2%), 87 out of 358 had headaches (24.3%, with

Table 1
Demographics: summary of articles identified in the systematic literature review.

Article [reference]	Level of evidence Study type Study age range Study period	Study country Region Study period	COVID-19 + Patients n =	Male n = (%)	Female n = (%)	Mean age (years)	Median age (years)	Age range
Cai et al. (2020) [16]	4 Case Series ages 0–18 years Jan 11–Feb 3, 2020	**China** Anhui and Shandong Provinces Jan 11–Feb 3, 2020	10	4 (40%)	6 (60%)	6.2	6.5	3 months to 10.9 years
CDC Coronavirus Update (2020) [4]	4 Retrospective Chart Review ages 0–18 years Feb 12–Apr 2, 2020	**United States** 50 states, District of Columbia, 4 US territories Feb 12–Apr 2, 2020	2470	1408 (57%)[a]	1062 (43%)[a]	n/a	11	0 years to 17 years
Eghbali et al. (2020) [18]	4 Retrospective Chart Review ages 0–16 years n/a (prior to Apr 10, 2020)	**Iran** Tehran n/a (prior to Apr 10, 2020)	4	4 (100%)	0 (0%)	11	11	8 years to 13 years
Feng et al. (2020) [19]	4 Retrospective Chart Review ages 0–18 years Jan 16–Feb 6, 2020	**China** Shenzhen and Guangdong Provinces Jan 16–Feb 6, 2020	15	5 (33%)	10 (67%)	7.4	7	4 years to 14 years
Lu et al. (2020) [8]	4 Retrospective Chart Review ages 0–16 years Jan 28–Feb 26, 2020	**China** Wuhan Children's Hospital, Hubei Province Jan 28–Feb 26, 2020	171	104 (61%)	67 (39%)	n/a	6.7	1 day to 15 years
Qiu et al. (2020) [17]	4 Retrospective Chart Review aged 0–16 years Jan 17–Mar 1, 2020	**China** Zhejiang Province Jan 17–Mar 1, 2020	36	23 (64%)	13 (36%)	8.3	n/a	1 year to 16 years
Shen et al. (2020) [20]	4 Retrospective Chart Review Ages 0–16 years Jan 8–Feb 19, 2020	**China** Changsha and Hunan Provinces Jan 8–Feb 19, 2020	9	3 (33%)	6 (67%)	7.6	8	1 year to 12 years
Tagarro et al. (2020) [12]	4 Retrospective Chart Review ages 0–17 years Mar 2–Mar 16, 2020	**Spain** Madrid Mar 2–Mar 16, 2020	41	18 (44%)	23 (56%)	n/a	3	9 days to 15 years
Wang et al. (2020) [21]	4 Retrospective Chart Review ages 0–18 years Jan 25–Feb 21, 2020	**China** Shaanxi, Gansu, Ningxia, Hebei, Henan, and Shandong Provinces Jan 25–Feb 21, 2020	31	15 (37%)	16 (52%)	n/a	7	3 months to 17 years
Zheng et al. (2020) [22]	4 Retrospective Chart Review, ages 0–14 years Feb 1–Feb 10, 2020	**China** Wuhan urban and peri-urban area Public Hospitals, Hubei Province Feb 1–Feb 10, 2020	25	14 (67%)	11 (44%)	n/a	3	3 months to 14 years
Overall systematic review data	4 Systematic Review aged 0–18 years Jan 11–Apr 2, 2020	**China, US, Iran, Spain** Jan to April 2020	2812	1598 (57%)	1214 (43%)	7.9		1 day to 17 years

n/a, data not available.
[a] Gender data missing from 82 individuals.

Table 2
Comorbidities: summary of articles identified in the systematic literature review.

Article [reference]	No comorbidities (n =)	Comorbidities (n =)	Asthma (n =)	Immunosuppression (n =)	Cardiovascular disease (n =)
Cai et al. (2020) [16]	n/a	n/a	n/a	n/a	n/a
CDC update 2020 [4]	265	80	40	10	25
Eghbali et al. (2020) [18]	2	2	0	1	1
Feng et al. (2020) [19]	n/a	n/a	n/a	n/a	n/a
Lu et al. (2020) [8]	n/a	n/a	n/a	n/a	n/a
Qiu et al. (2020) [17]	n/a	n/a	n/a	n/a	n/a
Shen et al. (2020) [20]	n/a	n/a	n/a	n/a	n/a
Tagarro et al. (2020) [12]	30	11	n/a	n/a	n/a
Wang et al. (2020) [21]	31	0	0	0	0
Zheng et al. (2020) [22]	21	2	0	0	2
Overall systematic review data	349	95	40	11	28

n/a, data not available.

Table 3
Presentation: summary of articles identified in the systematic literature review.

Article [reference]	Presentation data available (n =)	Asymptomatic (n =)	Fever (n =)	Cough (n =)	Shortness of breath Respiratory distress Tachypnea (n =)	URI symptoms Nasal congestion Rhinorrhea Sneezing (n =)	Sore throat Pharyngitis (n =)	Vomiting Nausea (n =)	Abdominal pain (n =)	Diarrhea (n =)	Headache (n =)	Fatigue (n =)	Myalgia (n =)	Pneumonia Bronchiolitis Clinical diagnosis (n =)
Cai et al. (2020) [16]	10	0	8	6	0	4	4	0	n/a	0	n/a	n/a	n/a	5
CDC Update (2020) [4]	291	n/a	163	158	13	21	71	31	17	37	81	n/a	66	n/a
Eghbali et al. (2020) [18]	4	0	4	4	2	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	2
Feng et al. (2020) [19]	15	8	5	1	n/a	1		n/a	n/a	n/a	n/a	n/a	n/a	n/a
Lu et al. (2020) [8]	171	27	55	83	72	33	79	11	n/a	15	n/a	13	n/a	111
Qiu et al. (2020) [17]	36	10	13	7	1	7	3	1	n/a	1	3	n/a	n/a	19
Shen et al. (2020) [20]	9	2	4	1	n/a	2	1	n/a	n/a	2	n/a	n/a	n/a	n/a
Tagarro et al. (2020) [12]	41	0	11	n/a	1	14	n/a	1	n/a	1	n/a	n/a	n/a	13
Wang et al. (2020) [21]	31	4	20	14	n/a	2	3	1	n/a	3	3	3	n/a	4
Zheng et al. (2020) [22]	25	0	13	11	2	2	n/a	2	2	3	n/a	n/a	n/a	17
Overall systematic review data		51	296	285	91	86	161	47	19	62	87	16	66	171

n/a, data not available.

individual study percentages ranging from 8.3% to 27.8%), 16 out of 202 had fatigue (7.9%, with individual study percentages ranging from 2.5% to 9.7%), and 66 out of 291 had myalgia (22.7%, with individual study percentages ranging from 10.4% to 22.7%). No studies reported data points on the presence or absence of pediatric anosmia or dysgeusia. Of the studies that reported a final clinical diagnosis, 171 cases out of 318 were given the clinical diagnosis of a pneumonia or bronchiolitis (53.8%, with individual study percentages ranging from 12.9% to 68.0%).

Across the studies, information about coinfections was only available in 3 studies. Cai et al. reviewed a series of 10 COVID-19 positive pediatric patients, all of whom tested negative for influenza A and influenza B [16]. In the chart review of 41 COVID-19 positive children by Tagarro et al., 2 children tested positive for influenza B [12]. Finally, in the chart review of 25 COVID-19 positive children by Zheng et al., 2 children tested positive for influenza B, 3 children tested positive for Mycoplasma pneumonia, and 1 child tested positive for *Enterobacter aerogenes* [22].

Of the studies that included exposure data on all patients, 289 out of 338 cases had known exposure with a COVID-19 positive person or lived in/traveled to a concerning area (85.5%, with individual study percentages ranging from 39% to 100%), while 49 out of 338 have no known exposure risk factors and transmission was likely from community spread (14.5%, with individual study percentages ranging from 0% to 61.0%). Only 2 studies ([16,20]) reported data regarding the median interval from exposure to symptom onset. Of these 19 patients the median interval days from exposure to symptom onset ranged from 7 to 7.5 days.

3.4. Laboratory data

Information about median laboratory values was available from various studies. All median lab values including those for WBC, lymphocyte count, Hg, CRP, CK-MB, D-Dimer, AST, ALT, urea, creatinine, and LDH levels were within the reference ranges based on each study (Table 4) for which the data was available, with the exception of procalcitonin levels. The median procalcitonin levels ranged from 0.07 to 0.5 ng/mL. Notably, in the retrospective chart review by Lu et al. [8], the median procalcitonin was slightly elevated 0.5 ng/mL (reference range of 0.46 ng/mL). In this review, 105 out of 164 (64%) patients had procalcitonin levels ranging from 0.5 to 0.8 ng/ml. The median WBC ranged from 6 to 7.35×10^9/L. A total of 58 out of 184 patients (31.5%) with data available had a low WBC of $< 5.5 \times 10^9$/L. The median lymphocyte count ranged from 2.2 to 2.9×10^9/L. A total of 20 out of 220 patients (9.1%) with data available had a lymphopenia (lymphocyte count of $< 1.2 \times 10^9$/L).

One study, Cai et al. [16], was the only one to report on data from patients regarding SARS-CoV-2 detection in fecal and urine samples with time. Fecal testing was positive for SARS-CoV-2 RNA detection in 5 out of 6 patients that were tested and remained positive for 18 to 30 days after symptom onset. These patients are still under "close follow-up" due to the positive results. Six out of 6 patients with urine and serum testing were negative for virus detection within 2–3 days of symptom onset.

3.5. Radiologic data

Of the studies that included CXR imaging data on COVID-19 positive cases, 6 patients out of 14 that got CXRs had normal results (42.9%) and 8 out of 14 had abnormal findings (57.1%) (Table 5). Unilateral findings were seen in 5 out of the 8 patients with abnormal CXR imaging (62.5%). These findings included "unilateral patchy infiltrates" in 4 patients and a lung "opacification" in one patient. Bilateral findings of subpleural ground glass opacities were seen in 3 out of the 8 patients with abnormal CXR imaging (37.5%).

Of the studies that included complete CT imaging data (normal and

Table 4
Laboratory data: summary of articles identified in the systematic literature review.

Article [reference]	LABS (median) (reference values) data available (n =)	WBC ($4–10 \times 10^9$/L)	WBC < 5.5×10^9/L (n =)	Lymphocyte count ($1.1–3.2 \times 10^9$ cells/L)	Lymphocyte count < $1.2x10^9$L (n =)	Hg (mg/dL)	CRP (< 8 to < 25 mg/L) (n =)	Procalcitonin (< 0.46–0.5 ng/mL)	CK-MB (< 18–25 U/L)	D Dimer	ALT (< 40 U/L)	AS (<
Cai et al. (2020) [16]	10	7.35	n/a	n/a	n/a	n/a	7.5	0.07	23	0.45 μg/nl	18.5	27
CDC Update (2020) [4]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/
Eghbali et al. (2020) [18]	4	6	2	n/a	2	11.6	n/a	n/a	n/a	n/a	n/a	n/
Feng et al. (2020) [19]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/
Lu et al. (2020) [8]	171	6.8	45	2.9	6	12.6	4	0.5[a]	n/a	1.2 (mg/LFEU)[b]	15	30
Qiu et al. (2020) [17]	36	6.1	7	2.4	11	n/a	5	0.24	19	0.29 μg/nl	21	30
Shen et al. (2020) [20]	9	6.06	9	2.65	1	n/a	1.78	n/a	n/a	n/a	15.66	28
Tagarro et al. (2020) [12]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/
Wang et al. (2020) [21]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/
Zheng et al. (2020) [22]	25	6.5	n/a	2.19	n/a	n/a	14.5	n/a	n/a	n/a	12	n/

n/a, data not available; WBC, white blood count; CRP, C-reactive protein; Hg, hemoglobin; CKMB, Creatine Kinase-MB; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase.
[a] Data from 164 patients out of the 171 included in the study.
[b] Data from 149 patients out of 171 included in the study.

Table 5
Imaging: summary of articles identified in the systematic literature review.

Article [reference]	Radiologic data available (n)	CXR normal (n =)	CXR abnormal (n =)	CT normal (n =)	CT abnormal (n =)
Cai et al. (2020) [16]	10	6	4	n/a	n/a
CDC Update (2020) [4]	n/a	n/a	n/a	n/a	n/a
Eghbali et al. (2020) [18]	4	0	4	0	4
Feng et al. (2020) [19]	15	n/a	n/a	6	9
Lu et al. (2020) [8]	111	n/a	n/a	n/a	111[a]
Qiu et al. (2020) [17]	n/a	n/a	n/a	n/a	19[a]
Shen et al. (2020) [20]	9	n/a	n/a	7	2
Tagarro et al. (2020) [12]	n/a	n/a	n/a	n/a	n/a
Wang et al. (2020) [21]	30	n/a	n/a	16	14
Zheng et al. (2020) [22]	24	n/a	n/a	8	16
Overall systematic review data	Overall (n =)	6	8	37	45

n/a, data not available; CXR, Chest X Ray; CT, Computed Tomography.
[a] Study missing data of normal imaging, results not included in overall percentages.

abnormal results) on COVID-19 positive cases, 37 patients out of 82 that got CT chest scans had normal results (45.1%) and 45 out of 82 had abnormal findings (54.9%) (Table 5). Of these 45 patients with abnormal imaging, 3 had "bilateral subpleural ground glass opacities," 1 had an "opacification," 9 had "ground glass opacities," 2 had "unilateral ground glass opacities," 9 had "patchy ground glass shadows and nodules," 5 unilateral had "patchy shadows or lung consolidation" and 11 had "bilateral patchy shadows or lung consolidations." These results do not include the Lu et al. study [8] as the data was incomplete (total number of patients sent for radiographs and number of patients with normal findings were not listed) however, in this study, of the 111 patients with abnormal CT imaging, (56 patients had "ground-glass opacities" (50.5%), 32 patients had "local patchy shadowing" (28.8%), 21 patients had "bilateral patchy shadowing" (18.9%) and 2 patients had "interstitial abnormalities (1.8%). These results also do not include the Qiu et al. [17] study as the data was incomplete (total number of patients sent for radiographs and number of patients with normal findings were not listed) however, this study found that 19 out of the 19 patients with abnormal CT imaging findings had "ground glass abnormalities." Of note, this study included results of CT imaging of COVID-19 positive patients that were "asymptomatic," with the reason for imaging listed as being for "diagnostic" purposes. Finally, of the studies with abnormal CT results specifically describing imaging laterality, unilateral CT imaging findings were seen in 8 out of 22 patients (36.4%) and 14 out of 22 patients had bilateral findings (63.6%).

3.6. Treatment data

Across the studies, all but 2 were chart reviews of patients that were already hospitalized. The retrospective chart review by Tagarro et al. [12] and the CDC COVID-19 Response Team [4] describe patients that were tested but not necessarily admitted to be hospitalized. 172 out of 786 patients that tested positive in these 2 studies (21.9%, percentages ranging from 19.7% to 60.1%) were hospitalized. Of the studies with age specific hospitalization data available (Table 6), 172 out of 786 patients were children < 1 years old (27.0%, with individual study percentages ranging from 0 to 40.1%).

Of the studies with PICU admission data, 26 out of 382 hospitalized patients (6.8%) received PICU level care. Of these 26 patients, data regarding comorbidities was not available for 19 patients. Of 7 children in the PICU that had data available, all 7 had comorbidities (2 were immunosuppressed, 3 had cardiovascular disease, 1 had hydronephrosis and 1 had intussusception). Of the studies with PICU age data, 6 out of 19 PICU patients (31.6%) were < 1 year of age.

Across the studies, data about oxygenation regimen was variable. Some studies report not needing any oxygen for patients while other studies report the use of nasal cannula, high flow nasal cannula, and non-rebreather face masks. Of the studies with intubation data available, 7 out of 327 (2.1%) of hospitalized children with COVID-19 needed intubation.

Across the studies, information about medication regimen was available for 105 patients. Lopinavir-ritonavir was the most common medication used. Eghbali et al. [18] reported the use of azithromycin (1 out of 4 patients) and hydroxychloroquine (3 out of 4 patients and oseltamivir (3 out of 4 patients). Qiu et al. [17] reported the use of interferon alpha aerosolization twice a day in 36 out of 36 patients and lopinavir-ritonavir syrup twice a day in 14 out of 36 patients. Wang et al. [21] reported the use of "antibiotics" in 6 out of 31 patients, while 2 out of 31 patients received IV gamma globulin, and 29 out of 31 received antivirals (10 interferon alone, 19 received interferon in combination with 2 or more antivirals (ribavirin, abidor, oseltamivir or lopinavir/ritonavir). Shen et al. [20], reported that 9 out of 9 patients received antivirals (lopinavir/ritonavir twice a day) and 1 out of 9 received meprednisone and immunoglobulin for febrile convulsion. Zheng et al. [22] reported 13 out of 25 patients trialed "antibiotics,", 12 out of 25 received interferon arbidol, oseltamivir, or lopinavir/litonavir (alone or in combination) and 2 intubated patients received systemic corticosteroids and IV immunoglobulin.

3.7. Outcomes data

Across 7 studies for which the information about mortality outcomes was available, there were a total of 5 pediatric mortalities out of 2843 COVID-19 positive cases (0.18%). The causes of death were to be determined. One mortality occurred in an 11 year old male with aplastic anemia and a low WBC of 1.1×10^9/L. Another mortality occurred in a 10 month old child with intussusception and multiorgan failure. The data for the other 3 mortalities was not available.

Of the studies with hospital discharge data, 209 out of 292 patients were discharged (72.6%) and 81 out of 292 patients were still inpatient (27.7%) at the time of study publication. The average length of stay was only available for 38 patients and the average length of stay ranged from 6.5 to 14 days (composite mean length of stay was 13.6 days). Of the 16 patients with repeat COVID-19 testing that was negative prior to discharge, the median days after illness onset to negative COVID-19 testing ranged from 12 to 14 days.

4. Discussion

This article is a comprehensive systematic review on COVID-19

Table 6
Clinical course: summary of articles identified in the systematic literature review.

Article [reference]	Hospitalization (n =)	Age < 1 year hospitalized (n =)	PICU level care (n =)	Age < 1 year PICU level care (n =)	NO oxygen (n =)	Respiratory support	Nasal cannula (n =)	High flow nasal cannula (n =)	Nonrebreather face mask (n =)	Intubation/mechanical ventilation (n =)
Cai et al. (2020) [16]	10	2	0	0	10	0	0	0	0	0
CDC Update (2020) [4]	147[a]	59	15	5	n/a	n/a	n/a	n/a	n/a	n/a
Eghbali et al. (2020) [18]	4	0	2	0	1	2	1	n/a	n/a	1
Feng et al. (2020) [19]	15	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Lu et al. (2020) [8]	171	31	3	n/a	n/a	n/a	n/a	n/a	n/a	3
Qiu et al. (2020) [17]	36	n/a	n/a	n/a	n/a	n/a	6	0	0	0
Shen et al. (2020) [20]	9	0	0	0	0	9	9	0	0	0
Tagarro et al. (2020) [12]	25	n/a	4	n/a	n/a	4	n/a	1	2	1
Wang et al. (2020) [21]	31	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	0
Zheng et al. (2020) [22]	25	n/a	2	1	n/a	n/a	n/a	n/a	n/a	2

n/a, data not available.
[a] 147 out of 745 children with hospitalization status known.

disease in children. The preliminary clinical findings suggest that children with COVID-19 usually had a mild presentation, with common symptoms being cough and fever. It is unclear why most children with COVID-19 have less severe disease than adults it is speculated that children often experience respiratory infections and may have higher levels of antibody against the virus than adults or that their developing immune systems may respond to pathogens differently than adult immune systems [2].

It is important to note that while 21.9% of children that were tested and were positive for SARS-CoV-2 were hospitalized, testing was not universal and presumably more patients that were feeling unwell were being tested compared to screening the general population. Of the studies with age specific hospitalization data available, 27.0% of patients hospitalized were infants under 1 year of age. Many patients that required PICU level care were under 1 year of age (31.6%) or had significant underlying medical conditions.

Procalcitonin elevation was seen, across several patients with COVID-19, which was important to note as it was not common for adults to have elevated procalcitonin levels [14]. The significance of this finding is unclear. It is important to note that while children with COVID-19 could be coinfected with other viruses such as influenza B and other bacteria such as *Enterobacter aerogenes*, they also have had procalcitonin elevation without a bacterial superinfection.

Of the studies with abnormal CT results specifically describing imaging laterality, unilateral CT imaging findings were seen in 36.4% Ground glass opacities were commonly seen in CT imaging. Unilateral imaging findings are a particular concern in pediatric patients with cough and may warrant a bronchoscopy to evaluate for airway foreign bodies. Extra precautions need to be taken with personal protective equipment for these cases, as aerosolizing procedures may be a method of viral transmission [23]. In addition, extra precautions need to be taken when caring for children in the home or work setting. Several studies suggest a slightly longer incubation period from exposure to onset of symptoms in children (6.5–7.5 days in children compared to 5.4 days in adults) [16,20]. There is evidence that children may shed SARS-CoV-2 in the stool for a prolonged time (up to 30 days) [16].

Various treatment regimens including interferon, antivirals, and hydroxychloroquine therapies have been trialed on the pediatric population but there are currently no studies showing efficacy of one regimen over the other. The mortality rate of all children that were hospitalized with COVID-19 was 0.18%. This mortality rate is likely overestimated as it includes only patients who were tested positive and in most cases, only children who were symptomatic enough to be hospitalized were tested.

This review has several limitations, primary due to the nature of the design of the selected studies. The data from case series may be biased as the full population is not included. Many chart reviews were based solely on data of children that were symptomatic and were hospitalized, and do not represent the population as a whole. We attempted to remove any duplicate data from cases reports but it is possible that some case series may have duplicate data with another series or retrospective case review that was included from the same region.

Conclusions regarding the epidemiology of the COVID-19 global pandemic are difficult to make so soon after the disease was discovered. Future research should have a broader scope in terms of population surveillance to understand the clinical characteristics and natural history of the disease in children. Another area of future research is on manifestations of anosmia and dysgeusia in the pediatric population. None of the studies included in this review collected data regarding these symptoms in the pediatric population but they have been noted as possibly the first or only symptom manifestation of COVID-19 in some adults [24]. Early symptom identification may help decrease disease transmission. Finally, it is unclear why children have a milder course compared to adults. Further investigation may provide insight in developing treatment modalities for COVID-19.

5. Conclusion

There is limited data regarding the epidemiologic characteristics and clinical features of SARS-CoV-2 in children [8]. This Systematic Review represents the largest pooling of pediatric COVID-19 data throughout the world. It was performed to gain a better understanding of the global impact of COVID-19 on the pediatric population. This study shows that children can be asymptomatic carriers of the virus and suggests children may play a role in the community spread of COVID-19. There are no studies regarding the presence of anosmia or dysgeusia in the COVID-19 pediatric population. Hand-washing and preventive behaviors are recommended when taking care of the pediatric population to protect those are highest risk such as the elderly population and those with underlying medical conditions. Additional care may also be needed to care for COVID-19 positive children under 1 year of age and children with comorbidities. This review also suggests that unilateral CT chest imaging findings were seen in 36.4% pediatric COVID-19 patients. This is particularly concerning as the work-up of pediatric patients with cough may warrant a bronchoscopy to evaluate for airway foreign bodies. Extra precautions need to be taken with personal protective equipment for these cases, as aerosolizing procedures may be a method of viral transmission.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article to disclose.

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