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REVIEW

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Children with coronavirus disease 2019: A review of demographic, clinical, laboratory, and imaging features in pediatric patients

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Abstract

There is a current outbreak of coronavirus disease 2019 (COVID-19), with a global spread. With the rapid increase in the number of infections, an increase is observed in the number of children with COVID-19. Most research findings are regarding adult cases, which are not always transferrable to children. Evidence-based studies are still expected to formulate clinical decisions for pediatric patients. In this review, we included 2597 pediatric patients that reported recently and evaluated the demographic, clinical, laboratory, and imaging features of children with COVID-19. We found that even lymphopenia was the most common lab finding in adults; it infrequently occurred in children (9.8%). Moreover, elevated creatine kinase MB isoenzyme was much more commonly observed in children (27.0%) than that in adults, suggesting that heart injury would be more likely to occur in pediatric patients. Our analysis may contribute to determine the spectrum of disease in children and to develop strategies to control the disease transmission.

KEYWORDS

2019-nCoV, children, COVID-19, pediatric patients, SARS-CoV-2

1 | INTRODUCTION

In December 2019, a cluster of patients with pneumonia was epidemiologically linked to a seafood wholesale market in Wuhan, China. A previously unknown betacoronavirus (initially named 2019 novel coronavirus [2019-nCoV]) was discovered from bronchoalveolar lavage fluid samples of these patients.[1-3] As of 30 January 2020, 7736 cases infected with this novel coronavirus had been confirmed in China, and 98 cases had also been cumulatively reported from 18 countries outside China,[4] which prompted the World Health Organization (WHO) to declare this new coronavirus outbreak as a global health emergency.[5] On 11 February 2020, WHO named the illness associated with 2019-nCoV as coronavirus disease 2019 (COVID-19).[6] On the same day, the Coronavirus Study Group

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of the International Committee on Taxonomy of Viruses designated 2019-nCoV as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On 11 March 2020, WHO classified COVID-19 as a pandemic due to the rapid worldwide spread of SARS-CoV-2. Until 30 March 2020, WHO reported 693 224 confirmed cases, including 33 106 deaths all over the world.[7] Reported illnesses have ranged from mild symptoms to severe illness for COVID-19 cases. In most pediatric patients, SARS-CoV-2 causes mild or moderate symptoms, which can include fever and cough. However, the risk is statistically greater for older adults and people with other health problems. Nevertheless, a letter published in the *New England Journal of Medicine* by Lu et al[8] reported the death of a 10-month-old child with COVID-19. The infant suffered from intussusception and multiorgan failure and died 4 weeks after admission. Another study published on *Pediatrics* by Dong et al[9] recently examined 731 confirmed and 1412 suspected cases of children with COVID-19, which explored that children infected with nCoV showed less severe symptoms than adults; however, infants and toddlers were vulnerable to a moderate and severe infection. This study noted one death of a 14-year-old child with COVID-19 and found that 5.9% of cases were severe, compared with 18.5% of adults experiencing severe symptoms.[10] Given the above cases, the induction factor for the discrepancy of clinical manifestations among children and adults remains to be determined. In this review, we included 2597 pediatric patients with COVID-19, comprising 1185 confirmed and 1412 suspected cases that were reported recently. The analysis of demographic, clinical, laboratory, and imaging characteristics will help to understand the natural history of COVID-19 transmission in children, which would otherwise contribute to limit the threat of this human pandemic.

2 | DEMOGRAPHIC CHARACTERISTICS AND ILLNESS SEVERITY OF COVID-19 IN CHILDREN

In this study, 2597 cases of children with COVID-19 were collected from 24 articles,[8,9,11-32] comprising 1185 confirmed cases and 1412 suspected cases (Table 1). The COVID-19 cases were confirmed with positive SARS-CoV-2 nucleic acid in nasal and pharyngeal swab specimens or blood samples. However, if a child tested negative for SARS-CoV-2 RNA test, but had any two of abnormal conditions in clinical symptoms, laboratory tests, and chest X-ray imaging, the case was defined as a suspected case.[9] Meanwhile, all the suspected children had exposed to COVID-19 patients within the last 2 weeks.[9] All children had completed the vaccines recommended by the childhood immunization program. Among them, age information was available from 2517 cases. Most of them (2492 cases) followed the age distribution as follows: less than 1 year: 446 (17.9%), 1 to 5 years: 593 (23.8%), 6 to 10 years: 626 (25.1%), 11 to 15 years: 492 (19.7%), and more than 15 years: 335 (13.4%). The age distribution of another 25 cases was grouped by using different criteria,[32] and the related information is presented in Table 1. Gender information was available from 2566 cases, and the male/female ratio was 1453 to 1113 (Table 1).

The illness severity of COVID-19 was defined on the basis of the clinical characteristics, laboratory testing results, and chest radiographs, including asymptomatic infection, mild, moderate, severe, and critical.[9] According to our analysis of the 2597 cases (Table 1), 198 had an asymptomatic infection (7.6%), 1181 had mild illness (45.5%), 1079 had moderate illness (41.5%), 113 had severe illness (4.4%), 23 were critically ill (0.9%), and 3 could not survive (0.1%). Among them, 2558 children (98.5%) have an epidemiological link to the adult patients or an exposure to Wuhan or other epidemic areas. We also summarized the incubation period of 18 cases collected from seven articles; 16 (88.9%) of them showed symptoms within 2 to 10 days of exposure,[14,20,22,23,27] whereas the symptom onset occurred within 19[25] and 24 days,[21] respectively, for other two cases (11.1%).

3 | CLINICAL CHARACTERISTICS OF COVID-19 IN CHILDREN

The clinical information from 452 children with COVID-19 in 23 articles was collected and analyzed (Table 2). Although the signs and symptoms were presented in variety, over the course of disease, most children with COVID-19 experienced the following symptoms: fever (195/452, 43.1%), cough (196/452, 43.4%), sore throat (92/452, 20.4%), tachycardia (76/452, 16.8%), rhinorrhea (74/452, 16.4%), nasal congestion (69/452, 15.3%), tachypnea/shortness of breath (57/452, 12.6%), diarrhea (30/452, 6.6%), vomiting (26/452, 5.8%), myalgias or fatigue (23/452, 5.1%), hypoxemia (8/452, 1.8%), and chest pain (2/452, 0.4%). Among 23 critical cases, six of them (6/23, 26.1%) were complicated with underlying diseases: one case of 1-year-old boy with renal calculi and hydronephrosis; one case of 8-year-old boy with acute lymphoblastic leukemia and myelosuppression after chemotherapy; one case of 11-month-old boy with intussusception[11]; one case of 8-month-old boy with congenital heart diseases, malnutrition, and suspected hereditary metabolic diseases; one case of 1-year-old boy with congenital heart diseases[32]; and the last one was a premature infant with an acute respiratory distress syndrome (ARDS).[29] It was reported that the first severe COVID-19 child in China initially had gastrointestinal symptoms and unobvious early respiratory symptoms, which then progressed to ARDS, septic shock, and acute renal failure rapidly; however, there were no underlying diseases.[31] The clinical manifestations of neonates were atypical. For the five cases, three of them (60%) suffered from fever and vomiting, two of them (40%) had diarrhea, and one of them (20%) had cough.[24,26,29]

4 | LABORATORY CHARACTERISTICS OF COVID-19 IN CHILDREN

Laboratory indicators were available from 445 children with COVID-19 in 22 articles (Table 3), and the primary parameters were generalized. Concerning blood routine, the following observations were made: leukocytes were normal in 186 cases (186/249, 74.7%),

TABLE 1 Demographic characteristics and illness severity of coronavirus disease 2019 in children

Author	Journal[Ref.]	Case number (N)	Contact history (n/N)	Age distribution (n/N)					Male (n/N)	Illness severity (n/N)					Death (n/N)
				<1 y	1-5 y	6-10 y	11-15 y	> 15 y		Asymptomatic	Mild	Moderate	Severe	Critical	
Lu et al	*N Engl J Med*[8]	171	156/171	31/171	40/171	58/171	42/171	0/171	104/171	27/171	33/171	107/171	0/171	3/171	1/171
Dong et al	*Pediatrics*[9]	2143	2143/2143	379/2143	493/2143	523/2143	413/2143	335/2143	1213/2143	94/2143	1091/2143	831/2143	112/2143	13/2143	2/2143
Ma et al	*Chin J Contemp Pediatr*[11]	115	105/115	14/115	36/115	32/115	33/115	0/115	73/115	61/115	5/115	46/115	0/115	3/115	0/115
Wang et al	*Chin J Pediatr*[12]	34	28/34	N/A	N/A	N/A	N/A	N/A	14/34	3/34	9/34	22/34	0/34	0/34	0/34
Wang et al	*Chin J Pediatr*[13]	31	31/31	N/A	N/A	N/A	N/A	N/A	N/A	4/31	13/31	14/31	0/31	0/31	0/31
Cai et al	*Clin Infect Dis*[14]	10	10/10	2/10	2/10	4/10	2/10	0/10	4/10	0/10	6/10	4/10	0/10	0/10	0/10
Feng et al	*Chin J Pediatr*[15]	15	15/15	N/A	N/A	N/A	N/A	N/A	5/15	0/15	3/15	12/15	0/15	0/15	0/15
Su et al	*Emerg Microbes Infect*[16]	9	9/9	2/9	5/9	2/9	0/9	0/9	3/9	3/9	4/9	2/9	0/9	0/9	0/9
Zhou et al	*Chin J Contemp Pediatr*[17]	9	9/9	3/9	6/9	0/9	0/9	0/9	4/9	5/9	0/9	4/9	0/9	0/9	0/9
Wei et al	*JAMA*[18]	9	9/9	9/9	0/9	0/9	0/9	0/9	2/9	1/9	2/9	6/9	0/9	0/9	0/9
Zheng et al	*Curr Med Sci*[32]	25	21/25	16/25[a]		9/25[a]			14/25	0/25	8/25	15/25	0/25	2/25	0/25
Summary of the case reports[19-31]		26	22/26	6/26	11/26	7/26	2/26	0/26	17/26	0/26	7/26	16/26	1/26	2/26	0/26
Total (%)		2597	2558/2597 (98.5)	446/2492 (17.9)	593/2492 (23.8)	626/2492 (25.1)	492/2492 (19.7)	335/2492 (13.4)	1453/2566 (56.6)	198/2597 (7.6)	1181/2597 (45.5)	1079/2597 (41.5)	113/2597 (4.4)	23/2597 (0.9)	3/2597 (0.1)

[a]The age distribution was grouped by using different criteria in this study: 1 mo to 3 y, 3 to 6 y, ≥6 y. We regrouped these cases as <6 y and ≥6 y in our review.

TABLE 2 Clinical characteristics of coronavirus disease 2019 in children

Author	Journal[Ref.]	Case number (N)	Fever (n/N)	Cough (n/N)	Sore throat (n/N)	Tachycardia (n/N)	Rhinorrhea (n/N)	Nasal congestion (n/N)	Tachypnea (n/N)	Diarrhea (n/N)	Vomiting (n/N)	Myalgia or Fatigue (n/N)	Hypoxemia (n/N)	Chest pain (n/N)
Lu et al	*N Engl J Med*[8]	171	71/171	83/171	79/171	72/171	13/171	9/171	49/171	15/171	11/171	13/171	4/171	0/171
Ma et al	*Chin J Contemp Pediatr*[11]	115	29/115	47/115	0/115	3/115	47/115	47/115	3/115	3/115	3/115	0/115	3/115	2/115
Wang et al	*Chin J Pediatr*[12]	34	17/34	13/34	0/34	0/34	0/34	0/34	0/34	0/34	0/34	0/34	0/34	0/34
Wang et al	*Chin J Pediatr*[13]	31	20/31	14/31	2/31	0/31	2/31	0/31	0/31	3/31	2/31	3/31	0/31	0/31
Cai et al	*Clin Infect Dis*[14]	10	8/10	6/10	4/10	0/10	2/10	3/10	0/10	0/10	0/10	0/10	0/10	0/10
Feng et al	*Chin J Pediatr*[15]	15	5/15	1/15	0/15	0/15	0/15	1/15	0/15	0/15	0/15	0/15	0/15	0/15
Su et al	*Emerg Microbes Infect*[16]	9	2/9	1/9	0/9	0/9	0/9	0/9	0/9	0/9	0/9	0/9	0/9	0/9
Zhou et al	*Chin J Contemp Pediatr*[17]	9	4/9	2/9	0/9	0/9	1/9	0/9	0/9	0/9	0/9	0/9	0/9	0/9
Wei et al	*JAMA*[18]	7[a]	4/7	2/7	0/7	0/7	1/7	0/7	0/7	0/7	0/7	0/7	0/7	0/7
Zheng et al	*Curr Med Sci*[32]	25	13/25	11/25	0/25	0/25	0/25	2/25	2/25	3/25	2/25	0/25	0/25	0/25
Summary of the case reports[19-31]		26	22/26	16/26	7/26	1/26	8/26	7/26	3/26	6/26	8/26	7/26	1/26	0/26
Total (%)		452	195/452 (43.1)	196/452 (43.4)	92/452 (20.4)	76/452 (16.8)	74/452 (16.4)	69/452 (15.3)	57/452 (12.6)	30/452 (6.6)	26/452 (5.8)	23/452 (5.1)	8/452 (1.8)	2/452 (0.4)

[a]Nine cases were reported in this study but two of them had no clinical information available. So only seven cases were collected into this table.

TABLE 3 Laboratory characteristics of coronavirus disease 2019 in children

Author	Journal[Ref.]	Case number (N)	Normal WBC: 5.5-12.0 × 10^{9}/L (n/N)	Leukocytosis: >12.0 × 10^{9}/L (n/N)	Leukopenia: <5.5 × 10^{9}/L (n/N)	Lymphopenia: <1.2 × 10^{9}/L (n/N)	PCT: >0.046 ng/mL (n/N)	CRP: >10 mg/L (n/N)	LDH: >300 U/L (n/N)	ALT: >45 U/L (n/N)	AST: >50 U/L (n/N)	Creatinine: >62 μmol/L (n/N)	Blood urea nitrogen: >7.1 mmol/L (n/N)	CK: >170 U/L (n/N)	CK-MB: >25 ug/L (n/N)	D-dimer: >0.55 mg/L (n/N)
Lu et al	*N Engl J Med*[8]	171	N/A	N/A	45/171	6/171	105/171	33/171	N/A	21/171	25/171	N/A	N/A	N/A	N/A	21/171
Ma et al	*Chin J Contemp Pediatr*[11]	115	88/115	4/115	23/115	15/115	N/A	N/A	N/A	11/115	N/A	N/A	N/A	N/A	34/115	N/A
Wang et al	*Chin J Pediatr*[12]	34	28/34	5/34	1/34	1/34	1/34	1/34	10/34	N/A	N/A	N/A	N/A	N/A	N/A	3/34
Wang et al	*Chin J Pediatr*[13]	31[a]	26/31	3/31	2/31	2/31	1/28	3/30	2/26	6/27	6/27	0/27	0/27	4/27	4/27	2/21
Cai et al	*Clin Infect Dis*[14]	10[a]	6/10	3/10	1/10	0/10	0/10	3/10	2/10	1/10	2/10	0/10	0/10	N/A	5/10	2/5
Feng et al	*Chin J Pediatr*[15]	15	7/15	0/15	8/15	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Su et al	*Emerg Microbes Infect*[16]	9	8/9	1/9	0/9	0/9	0/9	0/9	N/A	0/9	0/9	0/9	0/9	N/A	6/9	0/9
Zhou et al	*Chin J Contemp Pediatr*[17]	9[a]	7/9	2/9	0/9	0/9	N/A	3/7	3/5	0/9	4/9	0/9	0/9	N/A	N/A	0/9
Zheng et al	*Curr Med Sci*[32]	25[a]	N/A	N/A	N/A	10/25	N/A	N/A	N/A	0/12	N/A	1/25	N/A	N/A	2/12	N/A
Summary of the case reports[19-31]		26[a]	16/26	4/26	8/26	8/26	4/20	11/26	3/23	3/23	6/23	1/11	1/11	1/20	2/23	5/23
Total (%)		445	186/249 (74.7)	22/249 (8.8)	88/420 (21.0)	42/430 (9.8)	111/272 (40.8)	54/287 (18.8)	20/98 (20.4)	42/376 (11.2)	43/249 (17.3)	2/91 (2.2)	1/66 (1.5)	5/47 (10.6)	53/196 (27.0)	33/272 (12.1)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CRP, C-reactive protein; LDH, lactate dehydrogenase; PCT, procalcitonin.

[a]The case number of each item may differ, as every patient had a distinct pattern of laboratory tests.

leukocytosis in 22 cases (22/249, 8.8%), leukopenia in 88 cases (88/420, 21%), and lymphopenia in 42 cases (42/430, 9.8%). Regarding inflammatory markers, the following observations were made: procalcitonin (PCT) increased in 111 cases (111/272, 40.8%), C-reactive protein (CRP) increased in 54 cases (54/287, 18.8%), and lactate dehydrogenase (LDH) increased in 20 cases (20/98, 20.4%). Concerning liver function, the following observations were made: alanine aminotransferase (ALT) increased in 42 cases (42/376, 11.2%) and aspartate aminotransferase (AST) increased in 43 cases (43/249, 17.3%). Regarding renal function, the following observations were made: blood creatinine increased in two cases (2/91, 2.2%) and urea nitrogen increased in one case (1/66, 1.5%).[31,32] Concerning myocardial enzyme detection, the following observations were made: creatine kinase (CK) increased in five cases (5/47, 10.6%) and CK-MB isoenzyme increased in 53 cases (53/196, 27.0%). Regarding blood coagulation function, the following observation was made: D-dimer increased in 33 cases (33/272, 12.1%). One of the above studies showed that in 115 pediatric patients, the elevated ALT and CK-MB mainly concentrated in infants, suggesting that the younger children are more likely to present higher levels of ALT and CK-MB.[11]

5 | IMAGING CHARACTERISTICS OF COVID-19 IN CHILDREN

Computed tomography (CT) screening was recommended for COVID-19 diagnosis in China. Lung CT information was available from 409 children with COVID-19 in 21 articles (Table 4), of which 178 cases (43.5%) had no obvious abnormality and 231 cases (56.5%) had inflammatory lesions of lung, including two cases (2/409, 0.5%) of white lung and three cases (3/409, 0.7%) of pleural effusion (Table 4). Furthermore, pulmonary imaging data from 294 cases were classified in 20 articles (Table 4): 87 (87/294, 29.6%) cases with ground-glass opacities, 60 (60/294, 20.4%) with a local patchy shadow, 43 (43/294, 14.6%) with a bilateral patchy shadow, and 2 (2/294, 0.7%) with interstitial lesions. One article reported that 47 cases (47/115) of lung CT showed ground-glass opacities, fibrous cord shadows, patchy lesions, and a pulmonary consolidation, but there was no specific classification.[11] After active treatment, pulmonary imaging lesions were absorbed to varying degrees (3-5 days). Children with severe symptoms may have multiple lobar lesions of both lungs and white lung,[11] which indicated that the inflammatory reaction is serious. The chest X-ray or CT manifestation of infants (17 days, 3, 6, and 9 months old) is not typical, and its mechanism is worth further studying.[13,21,26]

6 | NUCLEIC ACID TESTING OF SARS-CoV-2 RNA IN CHILDREN WITH COVID-19

Of 2597 cases from 24 articles, 1185 children with confirmed COVID-19 were diagnosed by testing SARS-CoV-2 nucleic acid with reverse transcription polymerase chain reaction from nasopharyngeal secretions or

TABLE 4 Imaging characteristics of coronavirus disease 2019 in children[a]

Author	Journal[Ref.]	Case number (N)	Normal	Ground-glass opacity	Local patchy shadow	Bilateral patchy shadow	Interstitial Lesions	White lung change	Pleural effusion
Lu et al	*N Engl J Med*[8]	171	60/171	56/171	32/171	21/171	2/171	0/171	0/171
Ma et al	*Chin J Contemp Pediatr*[11]	115	66/115	47/115 (no specific classification available)				2/115	2/115
Wang et al	*Chin J Pediatr*[13]	31	17/31	9/31	5/31	0/31	0/31	0/31	0/31
Cai et al	*Clin Infect Dis*[14]	10	6/10	0/10	4/10	0/10	0/10	0/10	0/10
Feng et al	*Chin J Pediatr*[15]	15	6/15	9/15	0/15	0/15	0/15	0/15	0/15
Su et al	*Emerg Microbes Infect*[16]	9	7/9	1/9	1/9	1/9	0/9	0/9	0/9
Zhou et al	*Chin J Contemp Pediatr*[17]	9	2/9	6/9	4/9	4/9	0/9	0/9	1/9
Zheng et al	*Curr Med Sci*[32]	24[b]	8/24	1/24	5/24	11/24	0/24	0/24	0/24
Summary of the case reports[19-31]		25[c]	6/25	5/25	9/25	6/25	0/25	0/25	0/25
Total (%)		409	178/409 (43.5)	87/294 (29.6)	60/294 (20.4)	43/294 (14.6)	2/294 (0.7)	2/409 (0.5)	3/409(0.7)

[a]Some patients may have two or more abnormalities of chest radiographs.
[b]There were 25 cases included in this study, only 24 of them were subjected to chest computed tomography scans.
[c]There were six cases included in the study reported by Liu et al,[19] only five of them had imaging information. In total, 25 cases were included in this group.

sputum samples. After analyzing the 731 confirmed cases, Dong et al[9] proposed that the median time from the symptom onset in patients to the diagnosis of SARS-CoV-2 infection was 2 days (0-42 days) (Table 5). Meanwhile, some other studies also concluded that the time to diagnose SARS-CoV-2 infection mainly ranged within 1 to 5 days, but longer time cannot be excluded for some unexpected cases (Table 5). The duration time of SARS-CoV-2 shedding would differ in different specimens. It was demonstrated that SARS-CoV-2 RNA could be detected from nasopharyngeal/throat swabs for 3 to 23 days after the illness onset. Extended time was reported in fecal samples, as the viral RNA could persist as long as 43 days in stools (Table 5).

7 | DRUG TREATMENT OPTIONS FOR CHILDREN WITH COVID-19

Once COVID-19 is confirmed in children, treatment in designated hospital would be recommended, as childhood infections are mainly caused by family clustering outbreaks and rapid deterioration. Treatment-related information was available from 309 children with COVID-19 in 17 articles,[8,12-14,16,17,19-21,23-25,27-29,31,32] all of which had supportive treatment and interferon atomization. In total, 37 cases were treated with lopinavir/ritonavir, 8 cases were treated with oseltamivir, 6 cases were treated with ribavirin, 22 cases were treated with oral Chinese medicine, and 28 cases received empirical antibiotic therapy. Also, eight children were admitted to the intensive care unit, seven cases were treated with glucocorticoid and human immunoglobulin, six cases were treated with tracheal intubation and ventilation, and two cases were treated with blood purification.

8 | DISCUSSION

Children have constituted a small fraction of recorded COVID-19 cases. However, relatively few cases of COVID-19 have been reported in children, compared with the total number of cases in the general population. The first confirmed pediatric case of SARS-CoV-2 infection was reported in a familial cluster in Shenzhen on 20 January 2020.[33] This was a 10-year-old child with no symptom but presented radiological ground-glass lung opacities. With the progression of COVID-19 outbreak, the first infant case was reported from Xiaogan, Hubei province.[21] This was a 3-month-old female infant who had fever for 1 day and was admitted on 26 January 2020. As COVID-19 had reached epidemic proportions worldwide, the number of pediatric infections also increased concomitantly. Several studies have reported that the signs and symptoms of COVID-19 in children are similar to adults and are usually milder as compared with adults.[8,9,14,18,19] However, no comprehensive data are available on the impact of COVID-19 on children. It is reasonable to consider that they might be at an increased risk of severe disease, even death.[34]

In this review, we collected 2597 cases and reported the demographic, clinical, laboratory and imaging characteristics of COVID-19 in children. Of the cases, most children had exposure to household members with confirmed COVID-19. Illness among pediatric cases appeared to be mild, as only 4.4% had severe and 0.9% had critical illness. Correspondingly, 14% had severe and 5% had critical illness in adults.[35] The primary symptoms in children are similar to those in adults,[36-39] but they have lower incidence rates: fever occurred in 82% to 98.6% of adults but in 43.1% of children, and cough occurred in 59.4% to 82% of adults but in 43.4% of children. Respiratory symptoms in children were mild, as 12.6% cases had tachypnea/shortness of breath, which occurred in 31% of adult cases.[38] Other studies also reported that 55% of adult patients developed dyspnea[36] and 17% patients developed ARDS, which were rarely observed in children. However, the digestive tract symptom appeared more common in children, as diarrhea occurred in 6.6% of pediatric patients from our analysis, but in 2% to 3.8% of adult cases from some clinical studies [36-38] The different patterns of clinical features in respiratory system and digestive tract might result from the maturity and functional discrepancy of SARS-CoV-2 receptor ACE2 between children and adults.[40] However, more studies are still required to prove this hypothesis.

There is a lack of particular laboratory findings on COVID-19 until now. However, some indicators presented in different patterns between children and adults should be considered. Lymphopenia is the most common lab finding in adults with COVID-19, which was found in as many as 70.3% to 83% of hospitalized patients.[36-39] But in children, lymphopenia was only observed in 9.8% cases. PCT increased in 40.8% pediatric patients in our review, but it appeared normal in some other cases.[28] It is worth pointing out that 0 to 0.05 ng/mL of PCT is the normal range for laboratory testing. However, the range between 0.05 and 0.5 ng/mL unlikely supports the diagnosis of a significant bacterial infection, as localized infections (without systemic signs) and allergic reaction may be associated with such low levels. For clinical diagnosis, the levels above 0.5 ng/mL are used, which are highly suggestive of systemic bacterial infection/sepsis or severe localized bacterial infection, such as severe pneumonia, meningitis, or peritonitis.[41] The discrepancy of reference ranges would result in different conclusions. PCT was typically normal in adults, but it may increase among those admitted to the ICU.[36,38,39] Some children had leukocytosis (8.8%), elevated serum ALT (11.2%), AST (17.3%), elevated LDH (20.4%), high CRP (18.8%), and elevated D-dimer (12.1%), which were similar to those in adults who may be associated with greater illness severity.[36,37,39,42-44] A recent study analyzed the CK-MB level in venous blood of 273 patients with COVID-19.[45] The researchers found that elevated CK-MB occurred in 3.03% of mild cases, 5.00% of severe cases, and 6.67% of critical cases, which indicated that a higher concentration of CK-MB is associated with the severity and case fatality rate of COVID-19. It is worth noting that elevated CK-MB occurred in 27.0% pediatric patients in our analysis, which implies that heart injury is more common to COVID-19 in children than that in adults. However, renal injury was rare in children, as the indicators of renal function were normal in most of cases (~98%) in our analysis.

TABLE 5 Nucleic acid testing of SARS-CoV-2 RNA in children with COVID-19

Author	Journal[Ref.]	Case number (N)	Time from illness onset to testing positive for SARS-CoV-2 nucleic acid testing in different types of specimens, d			The duration of SARS-CoV-2 shedding in different types of specimens, d		
			Nasal and pharyngeal swab	Sputum	Fecal	Respiratory swabs	Anal swab	Stool
Dong et al	*Pediatrics*[9]	2143	2 (0-42)	N/A	N/A	N/A	N/A	N/A
Wang et al	*Chin J Pediatr*[13]	31	N/A	N/A	N/A	11 (7-23)	N/A	N/A
Cai et al	*Clin Infect Dis*[14]	10	N/A	N/A	6 (3-13)	12 (6-22)	N/A	20 (18-30)
Su et al	*Emerg Microbes Infect*[16]	9	N/A	N/A	N/A	11.2 (8-16)	N/A	N/A
Wei et al	*JAMA*[18]	9	1-3	N/A	N/A	N/A	N/A	N/A
Liu et al	*N Engl J Med*[19]	6	4.7 (3-5)	N/A	N/A	7.5 (5-13)	N/A	N/A
Cai et al	*Chin J Pediatr*[20]	1	1	N/A	N/A	12	N/A	N/A
Zhang et al	*Chin J Pediatr*[21]	1	1	N/A	N/A	10	N/A	>14
Ji et al	*World J Pediatr*[22]	2	1.5	N/A	N/A	N/A	N/A	N/A
Zhang et al	*Chin J Contemp Pediatr*[23]	2	2	N/A	N/A	10	N/A	N/A
Wang et al	*Chin J Contemp Pediatr*[24]	1	7	N/A	N/A	3	5	N/A
Zhao et al	*Zhejiang Med J*[25]	1	N/A	5	N/A	17	>20	>20
Zeng et al	*Chin J Pediatr*[26]	1	8	N/A	N/A	N/A	N/A	N/A
Zhang et al	*World Latest Med Info*[27]	1	1	N/A	N/A	7	N/A	N/A
Zhang et al	*J Med Virol*[28]	3	7 (1-14)	N/A	N/A	11 (11-14)	N/A	37 (34-43)
Zeng et al	*JAMA Pediatr*[29]	3	2	N/A	N/A	4	5	N/A
Xing et al	*medRxiv*[30]	3	N/A	N/A	N/A	13	N/A	30 (23-33)
Chen et al	*Chin J Pediatr*[31]	1	14	N/A	N/A	N/A	N/A	N/A

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Bilateral air-space consolidation was demonstrated typically in patients with COVID-19, even though the chest radiographs are not remarkable in the early stage of disease.[36,37,46] Bilateral, peripheral ground-glass opacities were also demonstrated typically in adults with COVID-19,[38,42,46-55] which also occurred commonly in children. To date, there is still no specific CT imaging pattern for identifying COVID-19. Several studies identified chest CT abnormalities in patients before the detection of SARS-CoV-2 RNA.[46,56] In children, there was a report that a 10-year-old boy with an asymptomatic infection showed ground-glass opacities on CT scan.[33] Another report of 31 children with SARS-CoV-2 infection showed that three cases had no clinical manifestations, but had typical chest imaging manifestations. All these findings suggested that chest imaging changes may occur earlier than clinical symptoms, and they also showed the value of chest imaging in early infection recognition and diagnosis of children with COVID-19.[13] Given the much higher proportion of asymptomatic cases (7.6%) in children than that in adults (1%),[35] combining assessment of imaging features with clinical and laboratory findings could facilitate the early diagnosis of COVID-19 pneumonia in children.

Children may play a role in the spread of SARS-CoV-2 in the community. As for children in China, SARS-CoV-2 nucleic acid (RNA) was detected in respiratory specimens up to 23 days[13] and in stools up to 43 days[28] after the onset of symptoms. A case report of a 6-month-old infant with confirmed COVID-19 had no clinical signs or symptoms, except for a single transient temperature of 38.5°C. A high viral load of SARS-CoV-2 RNA was detected from the nasopharynx of this infant from the day of admission and remained positive up to 16 days.[57] Viral culture was not performed on specimens in the above reports. Therefore, it is uncertain whether persistent or asymptomatic RNA detection represented a potentially transmissible virus.

This review may have some limitations due to the limited number of children cases with COVID-19, as well as the possible overlap of cases among the regarding articles. However, we revealed a comprehensive description including demographic, clinical, laboratory, and imaging features of pediatric patients with COVID-19, especially the distinct pattern of manifestation for children when compared with adults, which provide a potent foundation for prevention, diagnosis, and treatment of COVID-19 epidemic in children.

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CONFLICT OF INTERESTS

The authors decare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

All authors contributed to the intellectual content of this manuscript and approved the final manuscript as submitted. XC and TZ drafted the initial manuscript. JZ, JZ, PS, YX, WG, ZL, WL, JM, and CD searched literatures and collated data. SH, CC, and YS, revised the article critically for important intellectual content.

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