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ORIGINAL ARTICLE

Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study

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Abstract

Background An outbreak of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 was first detected in Wuhan, Hubei, China. People of all ages are susceptible to SARS-CoV-2 infection. No information on severe pediatric patients with COVID-19 has been reported. We aimed to describe the clinical features of severe pediatric patients with COVID-19.

Methods We included eight severe or critically ill patients with COVID-19 who were treated at the Intensive Care Unit (ICU), Wuhan Children's Hospital from January 24 to February 24. We collected information including demographic data, symptoms, imaging data, laboratory findings, treatments and clinical outcomes of the patients with severe COVID-19.

Results The onset age of the eight patients ranged from 2 months to 15 years; six were boys. The most common symptoms were polypnea (8/8), followed by fever (6/8) and cough (6/8). Chest imaging showed multiple patch-like shadows in seven patients and ground-glass opacity in six. Laboratory findings revealed normal or increased whole blood counts (7/8), increased C-reactive protein, procalcitonin and lactate dehydrogenase (6/8), and abnormal liver function (4/8). Other findings included decreased CD16 + CD56 (4/8) and Th/Ts*(1/8), increased CD3 (2/8), CD4 (4/8) and CD8 (1/8), IL-6 (2/8), IL-10 (5/8) and IFN-γ (2/8). Treatment modalities were focused on symptomatic and respiratory support. Two critically ill patients underwent invasive mechanical ventilation. Up to February 24, 2020, three patients remained under treatment in ICU, the other five recovered and were discharged home.

Conclusions In this series of severe pediatric patients in Wuhan, polypnea was the most common symptom, followed by fever and cough. Common imaging changes included multiple patch-like shadows and ground-glass opacity; and a cytokine storm was found in these patients, which appeared more serious in critically ill patients.

Keywords Children · COVID-19 · Novel coronavirus · 2019-nCoV · Severe · Critical ill · Wuhan

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Introduction

The outbreak of coronavirus disease 2019 (COVID-19, previously known as 2019-nCoV) caused by SARS-CoV-2 infection in Wuhan City, China, has spread around the world [1]. As of 24 February, more than 77,262 confirmed patients have been reported in China, and several patients have been confirmed in 29 countries. Among the confirmed patients in china, 9915 were severe patients and 2592 died [2]. In addition, most of those who died had underlying health conditions such as hypertension, diabetes or cardiovascular disease which compromised their immune system [3].

Previous studies have shown that patients with COVID-19 present with fever, dry cough, dyspnea, fatigue and lymphopenia. SARS-CoV-2 is more likely to infect elderly adult men; and those with chronic comorbidities are at higher risk of severe acute respiratory syndrome and even death

in severe patients [4–6]. Infected children have relatively milder clinical symptoms compared with infected adults [7], and no deaths have been reported in the pediatric population up to now. Mildly affected pediatric patients have been reported with an age of onset ranging from 17 days to 17 years [8]. However, specific information characterizing severely affected pediatric patients remains unknown.

For better understanding of the clinical features of severe pediatric patients with COVID-19 and for improving the diagnosis and treatment, we aimed to describe epidemiological and clinical features, imaging data, laboratory findings, clinical treatments and outcomes of severely or critically ill pediatric patients with COVID-19 in Wuhan City, China.

Methods

Patients

We included eight severely or critically ill patients with COVID-19 who were treated at the Intensive Care Unit (ICU), Wuhan Children's Hospital from January 24 to February 24. COVID-19 was confirmed in all patients by positive results of real-time reverse transcription-polymerase chain reaction (RT-PCR) assay for nasopharyngeal swab specimens. Clinical staging of the patients was classified according to "Interim Guidance for Diagnosis and Treatment of Coronavirus Disease 2019 (the 6th edition)" released by National Health Commission [9].

Severe COVID-19 was defined when the pediatric patients met any of the following criteria: (1) increased respiratory rate: ≥ 30 times/min; (2) oxygen saturation < 93% under a resting state, and (3) arterial partial pressure of oxygen (PaO_2)/oxygen concentration (FiO_2) ≤ 300 mmHg (1 mmHg = 0.133 kPa).

Critically ill COVID-19 was defined when the pediatric patients met any of the following criteria: (1) respiratory failure which requires mechanical ventilation; (2) septic shock, and (3) accompanied by other organ failure that needs ICU monitoring and treatment.

Data collection

Demographic information and clinical characteristics including exposure history, anamnesis, signs and symptoms, chest computed tomographic (CT) scan or X-ray results, complications, treatments, clinical outcomes, and laboratory findings of each patient were obtained from the Electronic Medical Record System of Wuhan Children's Hospital. The dates of patients' disease onset and hospital admission, incubation period, days from illness onset to diagnosis confirmation, disease duration, as well as history of familial cluster were recorded.

Laboratory tests were conducted upon admission, including a complete blood count (leucocytes, neutrophils, lymphocytes, thrombocyte, hemoglobin), serum biochemistry (C-reactive protein, procalcitonin, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, creatine kinase, creatinine and D-dimer), TBNK test (CD16 + CD56 + CD3 +, CD4 + T, CD8 + T and Th/Ts), cytokine detection assays (IL-2, IL-4, IL-6, IL-10, TNF-α and IFN-γ) and identification of other respiratory pathogens such as influenza A virus (H1N1, H3N2, H7N9), influenza B virus, respiratory syncytial virus, parainfluenza virus and adenovirus.

Results

Demographic and baseline characteristics

Eight pediatric patients with COVID-19 treated in ICU were included in this study. Among them, three were critically ill patients, and five severely ill. Six were males and two females. The age ranged from 2 months to 15 years (Table 1). Five patients were family-clustered cases and had a close contact history with confirmed or suspected COVID-19 patients; one was infected during hospitalization. The transmission way was still unclear in two patients. The incubation period of four patients ranged from 5 to 10 days. Duration from illness onset to disease confirmation of seven patients ranged from 3 to 15 days. One patient (patient 8) who had a close contact history with infected patients was confirmed by RT-PCR test before symptoms appeared. Disease duration of all patients was over 10 days, and over 20 days in critically ill patients. All children were reported to be living in Wuhan during the outbreak period of COVID-19.

Clinical characteristics and chest imaging results

In the severe pediatric patients, the most common symptom was polypnea (8/8), followed by fever (6/8), cough (6/8), expectoration (4/8), nausea/vomiting (4/8), diarrhea (3/8), fatigue/myalgia (1/8), headache (1/8) and constipation (1/8) (Table 1). Lung auscultation revealed rales in the left or right lower lobe in five patients (5/8) and crackles in the others (3/8).

All patients had remarkable abnormalities in chest (CT) scanning or X-ray (Table 1). Six patients had bilateral pneumonia and two unilateral pneumonia. Imaging changes included multiple patch-like shadows (7/8), ground-glass opacity (GGO) (6/8), pleural effusion (1/8) and "white

Table 1 Demographics, baseline characteristics and symptoms of eight pediatric patients with coronavirus disease 2019 (COVID-19)

Variables	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Characteristics								
Age	8 y	10 mon	1 y, 1 mon	2 mon	2 y, 1 mon	15 y	13 y, 11 mon	13 y, 5 mon
Sex	Male	Female	Male	Male	Male	Female	Male	Male
Exposure history		Close contact with COVID-19 patient		Close contact with suspected COVID-19 patient		Close contact with COVID-19 patient	Close contact with COVID-19 patient	Close contact with COVID-19 patient
Anamnesis	Acute lymphocytic leukemia	Lacrimal sac dredge			Pharyngitis			
Incubation period (d)	NA	7	NA	10	NA	NA	5	5
Days from illness onset to diagnosis confirmation (d)	12	3	15	6	9	12	5	0
Disease duration (d)	28+	20+	24	20	16	19	12	9+
Familial cluster		Yes		Yes		Yes	Yes	Yes
Severely/critically ill	Critically ill	Critically ill	Critically ill	Severe	Severe	Severe	Severe	Severe
Symptoms								
Fever	Yes		Yes		Yes	Yes	Yes	Yes
Cough	Yes	Yes		Yes	Yes	Yes	Yes	
Fatigue/myalgia						Yes		
Headache						Yes		
Expectoration	Yes	Yes		Yes				Yes
Nausea/vomiting		Yes	Yes	Yes	Yes			
Diarrhea			Yes		Yes	Yes		
Constipation		Yes						
Polypnea	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lung auscultation	Rales	Crackles	Crackles	Rales	Crackles	Rales	Rales	Rales
Chest CT/X-ray								
Unilateral pneumonia				Yes				Yes
Bilateral pneumonia	Yes	Yes	Yes		Yes	Yes	Yes	

Table 1 (continued)

Variables	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Imaging changes	Multiple patch-like shadows, GGO, "white lung" appearance	Multiple patch-like shadows, pleural effusion, GGO	Multiple patch-like shadows, GGO	Multiple patch-like shadows	Multiple patch-like	Multiple patch-like shadows, GGO	GGO	Multiple mottling, GGO
Complications		Intussusception, toxic encephalopathy, status epilepticus, DIC, septic shock, MODS	Septic shock, MODS, Kidney stone, Hydronephrosis, Cardiac insufficiency, Coagulopathy	Hypoglobulinemia	Gastroenteritis			

NA not available, *COVID-19* coronavirus disease 2019, *CT* computed tomography, *DIC* disseminated intravascular coagulation, *GGO* ground-glass opacity, *MODS* multi-organ dysfunction syndrome

lung-like" change (1/8). The followings were imaging results of three typical patients.

Patient 1 was an 8-year-old boy, who was infected with COVID-19 when under blood transfusion for treating acute lymphoblastic leukemia during hospitalization. Chest CT demonstrated multiple patch-like shadows (January 31) and high density shadows and GGO (February 13). His condition deteriorated and chest X-rays demonstrated decreased brightness of the lung and "white lung" appearance on February 23 (Fig. 1).

Patient 2 was a 10-month-old infant, who had a close contact with a critically ill COVID-19 patient (her mother). Chest CT demonstrated small dense shadows and pleural effusion on February 4, GGO and consolidation shadow on February 9, and lesions deteriorated on February 12. Chest X-rays obviously improved until February 22 (Fig. 2).

Patient 6 was a 15-year-old girl, who had a close contact with a confirmed COVID-19 patient. Chest CT demonstrated multiple patch-like shadows and GGO bilateral both lungs (February 14), which was obviously improved on February 18 (Fig. 3).

Septic shock and multiple organ dysfunction syndrome (MODS) were the most common complications in critically ill patients. Patient 2 was complicated with septic shock, MODS, intussusception, toxic encephalopathy, status epilepticus and disseminated intravascular coagulation (DIC). Patient 3 was complicated with septic shock, MODS, kidney stone, hydronephrosis, cardiac insufficiency and coagulopathy. Patients 4 and 5 were complicated with hypoglobulinemia and gastroenteritis.

Laboratory assessments

COVID-19 was confirmed in all patients by RT-PCR. In this cohort (except patient 1 who had acute lymphocytic leukemia), leucocytes, neutrophils, lymphocytes, thrombocyte and hemoglobin counts were all normal or mildly increased (Table 2). Neutrophils, lymphocytes and hemoglobin were decreased in patient 1. Patient 1 was also infected with Influenza A virus. Increased C-reactive protein, procalcitonin and lactate dehydrogenase were found in five patients (5/8), and increased alanine aminotransferase (ALT) in four (4/8). Total bilirubin level in all patients was normal. Creatine kinase level decreased in one patient and increased in two; patient 2 had a far higher bilirubin level (20,702 U/L) than normal (normal range: 30–170 U/L). Creatinine level decreased in three patients and increased in two patients. Two patients (2/5) had high D-dimer level. TBNK lymphocyte subset analysis revealed decreased percentage of CD16 + CD56 + lymphocytes (4/8) and Th/Ts (1/8), and increased percentage of CD3 + (2/8), CD4 + (4/8) and CD8 + (1/8) lymphocytes. Cytokine detection assays showed increased levels of IL-6 (2/8), IL-10 (5/8) and IFN-γ (2/8).

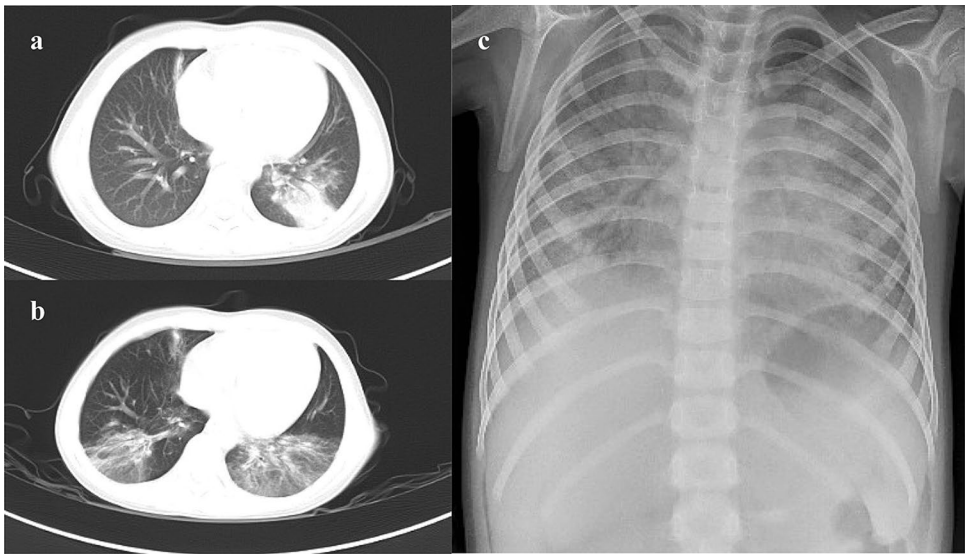

Fig. 1 Chest x-rays and chest CTs of patient 1. **a** Multiple patch-like shadows (Jan. 31). **b** High density shadows and ground-glass opacity (Feb.13). **c** Brightness of lung decreased and "white lung-like" changes appeared (Feb. 23)

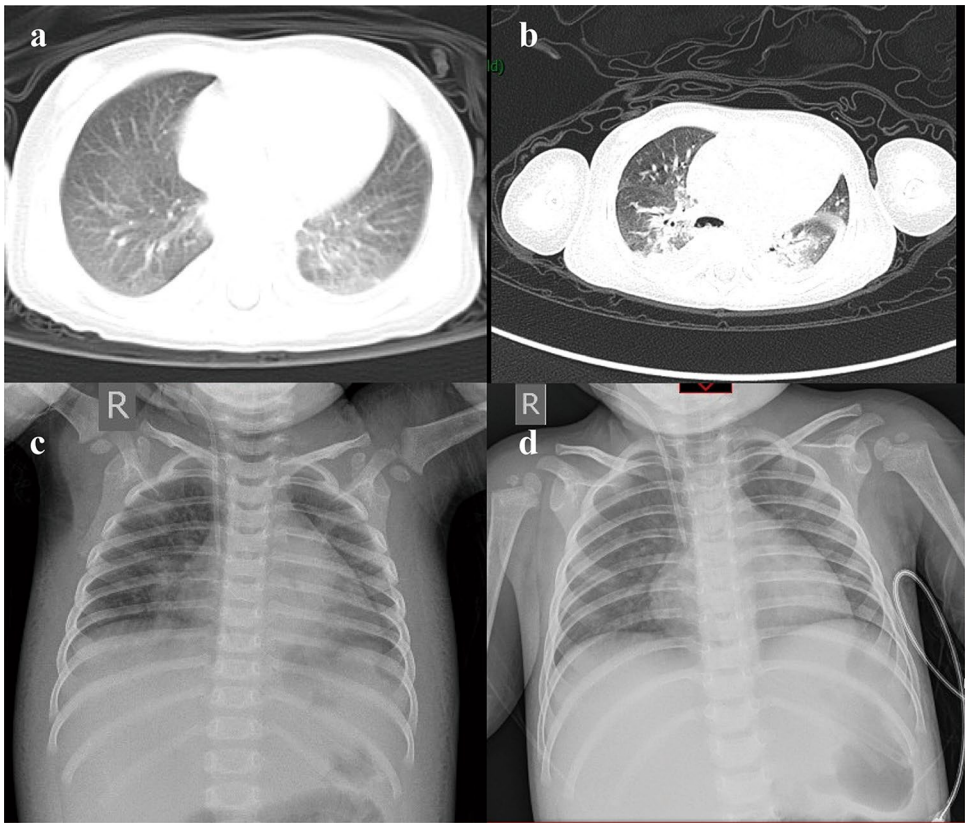

Fig. 2 Chest X-rays and chest CTs of patient 2. **a** Small dense shadows and pleural effusion (Feb. 4). **b** Ground-glass opacity and consolidation shadow (Feb. 9). **c** Lesions progress (Feb.12). **d** Chest X-rays obviously improved

Clinical treatment and outcomes

Treatments of COVID-19 remained focusing on symptomatic and respiratory supports (Table 3). Among the eight patients, six (6/8) received high-flow oxygen therapy and two critically ill (2/8) patients received mechanical ventilation. All patients received antiviral treatments (virazole, oseltamivir and interferon). Antibiotics, traditional Chinese medicine, intravenous glucocorticoids and immunoglobulin were also used dependent on patients' conditions. Symptomatic treatments were given for treating complications in patient 2 and 3. Up to February 24, 2020, three patients (patients 1, 2

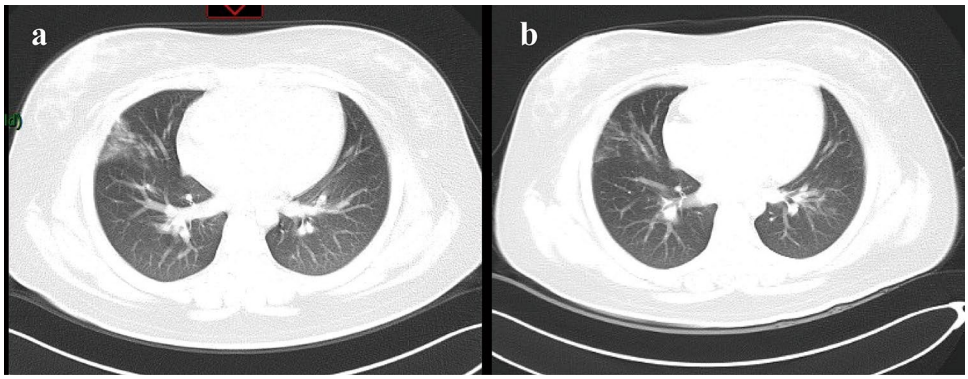

Fig. 3 Chest CTs of patient 6. **a** Multiple patch-like shadows and ground-glass opacity in both lungs (Feb. 8). **b** Lesions obviously improved (Feb. 14)

Table 2 Laboratory test results of eight pediatric patients with coronavirus disease 2019 (COVID-19)

Variables	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Leucocytes ($\times 10^9$/L; normal range 3.85–10)	1.65	14.95	9.19	8.32	8.8	10.6	3.85	7.6
Neutrophils ($\times 10^9$/L; normal range 1.08–5.8)	0.78	11.63	5.7	1.27	3.5	5.9	1.9	3.8
Lymphocytes ($\times 10^9$/L; normal range 1.15–4)	0.69	1.96	2.7	6.41	3.6	4.04	1.7	2.8
Thrombocyte ($\times 10^9$/L; normal range 100–320)	140	68	145	666	247	515	154	250
Hemoglobin (g/L; normal range 110–150)	83	90	103	111	123	150	159	136
C-reactive protein (mg/L; normal range 0–3)	6.48	57.9	103	0.75	27.02	1	9.9	0.5
Procalcitonin (ng/mL; normal range 0–0.05)	0.18	17.16	0.05	0.08	0.11	0.04	0.09	0.05
Lactate dehydrogenase (U/L; normal range 175–322)	394	888	282	891	471	370	209	187
Aspartate aminotransferase (U/L; normal range 21–72)	37	27	33	41	16	14	14	16
Alanine aminotransferase (U/L; normal range 15–46)	58	66	36	100	55	9	16	8
Total bilirubin (μmol/L; normal range 3–22)	11.8	20.4	16.5	12.4	5.3	7.8	8.1	8.1
Creatine kinase (U/L; normal range 30–170)	15	20,702	33	148	262	106	72	77
Creatinine (μmol/L; normal range 27–62)	27.1	43.4	21.3	15	24.8	64.5	58	72.1
D-dimer (mg/L FEU; normal range 0–0.55)	0.47	40.34	3.07				0.23	0.44
Other viruses	Influenza A virus							
TBNK test								
CD16+CD56+ (%; normal range 7.92–33.99)	5.80	1.36	2.30	18.06	5.97	5.08	10.00	10.12
CD3+ (%; normal range 38.56–70.06)	92.60	58.78	65.80	61.85	66.68	70.22	71.30	62.22
CD4+T (%; normal range 14.21–36.99)	33.39	37.85	39.38	21.54	39.42	40.24	29.66	30.34
CD8+T (%; normal range 13.24–38.53)	58.15	20.17	24.01	24.30	24.60	26.47	37.73	30.29
Th/Ts (normal range 0.96–2.05)	0.57	1.88	1.64	0.89	1.6	1.52	0.79	1
Cytokine detection assays								
IL-2 (pg/mL; normal range 0–11.4)	2.61	1.61	1.57	2.08	1.36		3.96	1.71
IL-4 (pg/mL; normal range 0–12.9)	3.42	2.45	2.63	2.98	2.13		6.24	4.88
IL-6 (pg/mL; normal range 0–20.9)	639.98	117.88	5.44	17.47	2.92		11.05	7.37
IL-10 (pg/mL; normal range 0–5.9)	9.24	17.42	6.94	8.84	2.5		6.25	3.31
TNF-α (pg/mL; normal range 0–5.9)	5.01	2.9	1.41	1.97	0.85		5.7	4.35
IFN-γ (pg/mL; normal range 0–17.3)	10.06	4.36	36.79	20.59	1.12		7.19	4.62

Table 3 Clinical treatments and outcomes of eight pediatric patients with coronavirus disease 2019 (COVID-19)

Variables	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Oxygen therapy	Yes	Yes	Yes	Yes			Yes	Yes
Mechanical ventilation (invasive)	Yes		Yes					
Antibiotic treatment	Yes	Yes	Yes		Yes	Yes		
Antiviral treatment	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Glucocorticoids	Yes	Yes	Yes			Yes	Yes	
Intravenous immunoglobulin therapy	Yes	Yes				Yes	Yes	
Other treatments	Traditional Chinese medicine	Enterostomy, hemopurification, transfusions of red blood cell, plasma and thrombocyte	Plasmapheresis			Traditional Chinese medicine	Traditional Chinese medicine	Traditional Chinese medicine
Clinical outcome	Remained in ICU	Remained in ICU	Discharged	Discharged	Discharged	Discharged	Discharged	Remained in ICU

ICU intensive care unit

and 8) remained in ICU (including two critically ill patients); the others recovered and were discharged home.

Discussion

Since December, 2019, COVID-19 caused by SARS-CoV-2 infection has spread rapidly around China and the world [5, 10–12]. SARS-CoV-2 is a coronavirus that belongs to the β-coronavirus cluster, which can cause the third known zoonotic coronavirus disease after severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) [13]. It has been reported that SARS-CoV-2 uses the same cell entry receptor (ACE2) to infect humans, as SARS-CoV, but the clinical features of COVID-19 seem to be more variable [3]. The number of COVID-19 patients currently exceeds SARS and MERS; however, most patients are infected mildly, and the overall case-fatality rate (CFR) was 2.3% (1023 deaths among 44,672 confirmed patients) [14], much lower than that of SARS (10%) and MERS (37%) [3, 15, 16].

In the early reports, all of the patients were adults (middle-aged and elderly) in Wuhan [5]. On entering the outbreak stage and improvement of pathogen detection, pediatric patients (even newborns) have been reported increasingly [17, 18]. According to the latest report from the Chinese Center for Disease Control and Prevention (CCDC), 965 confirmed patients under age 19 years (2.16%, 965/44,672) were reported nationwide [14]; no deaths have occurred in the group aged 9 years and younger, as of February 11. Children have special immune response system which is distinct from adults [19]; therefore, pediatric patients with COVID-19 have their own clinical features and therapeutic responses [20]. To our knowledge, this is the first report on pediatric patients with severe COVID-19.

The patients age ranged from 2 months to 15 years, and mostly were males (75%). Males seemed to be more susceptible to SARS-CoV-2 infection, which was similar to previous reports [5, 21–23]. Five patients (62.5%) were infected due to close contacts with family members confirmed with COVID-19; therefore, family daily prevention is an important way to prevent COVID-19. Disease duration is relative to the severity of the disease. Severely affected patients had a disease duration of over 10 days, but critically ill patients had a duration of over 20 days (two remained in ICU after over 20 days of treatment).

In our cohort, the most common symptoms were polypnea (100%), fever (75%), cough (75%), expectoration (50%) and nausea/vomiting (50%). Fatigue/myalgia and headache, commonly described in adults, were rarely described in children. The reason may be that these symptoms are difficult to be described by young children. Half of our patients were

infants or young children, who were unable to speak or speak clearly. So more data on clinical features of pediatric patients need to be studied. The ratio of patients with fever in this cohort of severe patients was lower than that of critically ill adult patients. Among the 52 critically ill adult patients reported by Yang et al. [22], common symptoms were fever (98%), cough (77%) and dyspnoea (63.5%). Nevertheless, the ratio of patients with fever in this series was higher than those children not treated in ICU. Among the 34 infected children (most are mild patients) reported by Wang et al. [24], fever (50%) and cough (38%) were the most common symptoms. According to our results, polypnea should be highlighted in severe pediatric patients, even without fever.

Infected patients who develop acute respiratory distress syndrome (ARDS) may present with characteristic pulmonary ground-glass changes on imaging [4, 6, 12, 25]. The CT images of our patients mainly showed multiple patch-like shadows and ground glass opacity, consistent with previous reports. Chest X-rays of patient 1 who remains in ICU demonstrate decreased brightness of the lung and "white lung-like" changes. This patient is still under intensive treatment and close monitoring.

Septic shock and MODS were common complications in critically ill patients. Multi-organ involvements were found in critically ill patients including the nervous, blood, urinary and cardiac systems. Complications were relatively mild in severe patients in our cohort, such as hypoglobulinemia and gastroenteritis.

The treatment modalities of COVID-19 infection were mainly symptomatic and respiratory supporting. High-flow oxygen therapy, invasive ventilation and antiviral treatments (virazole, oseltamivir and interferon) were given to the patients. Antibiotic therapy, traditional Chinese medicine, intravenous glucocorticoid and immunoglobulin therapies were also used according to the patients' conditions. Up to February 24, 2020, three patients remained in ICU (including two critically ill patients), the others recovered and were discharged without death. The overall case fatality rate of severe pediatric patients is far lower than those of adults (49.0%, 1023/2087) [14], which indicates a better clinical outcome in pediatric patients.

Leucocytes, neutrophils, lymphocytes, thrombocyte and hemoglobin counts were normal or mildly increased in severe patients. Among critically ill patients, patient 1 with acute lymphocytic leukemia, undergoing blood transfusion, showed low level of neutrophils, lymphocytes and hemoglobin; patient 2 with serious complications (septic shock, DIC, MODS) showed high level of leucocytes and neutrophils and low level of thrombocyte and hemoglobin. Blood purification and transfusion were performed to improve symptoms. Elevated C-reactive protein, lactate dehydrogenase, procalcitonin, ALT and D-dimer were also discovered in the cohort. The level of creatine kinase was significantly high in patient 2, which required high attention.

Coronaviruses of COVID-19, SARS and MERS can induce excessive and aberrant non-effective host immune responses that are associated with severe lung pathology. The lung injury is more pronounced in critically ill patients, associated with a cytokine storm, which is characterized by increased plasma concentrations of pro-inflammatory cytokines (IL-1β, IL-6, IL-12, TNF, IFN-γ) and anti-inflammatory cytokines (IL-4, IL-10, IL-13, TGF-β) [5, 6, 26–29]. In our cohort, decreased CD16 + CD56+ lymphocytes and increased IL-6, IL-10 and IFN-γ were observed. The levels of IL-6 and IL-10 were significantly increased in two critically ill patients, who remained in ICU with disease durations of over 20 days. More abnormalities in cytokine spectrum were seen in critically ill patients than in severe patients. Huang et al. [5] also found that COVID-19 patients in ICU had higher plasma levels of IL-2, IL-7, IL-10, GSCF, IP10, MCP1, MIP1A, and TNF-α, compared with non-ICU patients. Conversely, severe SARS patients had very low levels of IL-10 [30]. Different inflammatory responses were found between SARS and COVID-19, so more researches are needed. In addition, the level of CD4 increased, which indicating overactivation of the immune system leading to fatal immune disorders.

In conclusion, for severe or critically ill pediatric patients who survive intensive care, a number of specific laboratory abnormalities and aberrant and excessive immune responses may lead to long-term lung damage and severe health complications. Therefore, early identification of the specific features of severe pediatric patients and timely treatment are of crucial importance.

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Compliance with ethical standards

Ethical approval This study was approved by the Ethics Committee of Wuhan Children's Hospital. Informed consents for publication have been obtained from parents or guardians of patients.

Conflict of interest All the authors have no conflicts of interest.

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