

Clinical features and follow-up of pediatric patients hospitalized for COVID-19

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Abstract

Objective: This report summarizes the clinical features and 1-month follow-up observations for pediatric patients who were hospitalized with coronavirus disease 2019 (COVID-19) in Wuhan Women and Children's Hospital.

Methods: The 1-month follow-up data included clinical manifestations and results from serum severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) IgG and IgM tests, reverse-transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2, lung computed tomography (CT) scans, and laboratory tests.

Results: Between January 20 and March 15, 2020, 127 patients aged 0–15 years were hospitalized for COVID-19 treatment, including 3 severe cases and 124 mild or moderate cases. The main therapies included inhalation of aerosolized interferon- α (122/127) and additional antiviral drugs (28/127). Among the 81 patients who had pneumonia at admission, 35 with right lobe pneumonia had the longest hospital stay (mean 14.5 ± 7 days); 17 with left lobe pneumonia had the highest creatine kinase (154 \pm 106 U/L) and creatine kinase myocardial band (CK-MB, 43 \pm 48 U/L) levels; and 29 with bilateral pneumonia had the highest white blood cell counts ($8.3 \pm 4 \times 10^9$ /L). Among the 46 patients who were successfully followed up 1 month after discharge, two notable findings were right lobe pneumonia in 22% (95% confidence interval [CI]: 11%–37%) of patients and persistently elevated serum creatine kinase and CK-MB levels. The median duration of elevated CK-MB was 45 days. The mean concentrations of serum SARS-CoV-2 IgG and IgM in 41 patients were 8.0 ± 7.5 and 98 ± 40 ng/ml, respectively. At follow-up, four patients retested positive for SARS-CoV-2.

Conclusions: The involvement of different lung lobes in patients with COVID-19 was associated with variations in the persistence of pneumonia and elevation of CK-MB levels and body temperature.

KEYWORDS

coronavirus disease 2019 (COVID-19), follow-up, pediatric patients, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

1 | INTRODUCTION

In December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the pathogen responsible for a series of infections typical of pneumonia in the city of Wuhan in China.¹ This infectious disease soon became a global pandemic given the name coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO). By March 9, 2021, the WHO had reported 116 million cases and 2.6 million deaths due to COVID-19 worldwide.² A cohort study of 44,672 Chinese cases reported that 2.1% of patients were aged <20 years.³ It is well established now that COVID-19 can cause damage to several vital organs, including the lungs, heart, liver, and kidney,⁴ generating a variety of complex clinical features.

Compared with the clinical features and treatment outcomes observed in adult COVID-19 patients, pediatric patients with COVID-19 have presented with milder clinical manifestations.⁵ In the early stage of the pandemic, pediatric patients were sometimes treated with aerosolized interferon- α and sometimes with lopinavir/ritonavir syrup, and most recovered within 1 month of COVID-19 diagnosis.⁵ However, a few patients who were clinically cured later tested positive for SARS-CoV-2 again.⁶ These findings complicate the assessment of treatment outcomes and highlight the importance of a comprehensive follow-up. The pathogenic mechanisms of SARS-CoV-2 infection are analogous to those for the first SARS virus (SARS-CoV-1) because the viruses use the same receptors for cell entry. Thus, it is expected that SARS-CoV-2 infection may lead to long-term adverse outcomes as seen in SARS patients.⁴ As distinct immunological responses to SARS-CoV-2 infection may exist in pediatric patients and result in damage to vital organs,⁷ a follow-up of pediatric patients is necessary.⁸ This study aimed to analyze outcomes in pediatric patients hospitalized at Wuhan Women and Children's Hospital based on a 1-month follow-up after discharge. The following characteristics of pediatric COVID-19 cases at the 1-month follow-up were examined: (1) detection of SARS-CoV-2 by reverse-transcription (RT)-polymerase chain reaction (PCR); (2) clinical features, including symptoms and laboratory indices reflecting dysfunction of vital organs; and (3) differential outcomes in patients with different presentations on computed tomography (CT) scans.

2 | METHODS

2.1 | Study patients

This study was approved by the Ethics Committee of Wuhan Women and Children's Hospital and followed the principles of the Declaration of Helsinki. Written informed consent was acquired from the guardians of the patients. The study analyzed the clinical features of 127 pediatric patients aged 0–15 years who were hospitalized in Wuhan Women and Children's Hospital. These patients had RT-PCR-confirmed COVID-19 based on testing of nasopharyngeal swabs according to the diagnosis and treatment guidelines released by the National Health and Health Commission of the People's Republic of China.⁹ These patients received exclusive diagnoses of other possible infections, including influenza A,

influenza B, parainfluenza, *Chlamydomphila* pneumonia, and *Mycoplasma* pneumonia. Follow-up was performed after the patients were clinically cured according to the following criteria⁹: fever-free for 3 consecutive days, improvement in pneumonia in terms of CT scans and upper respiratory manifestations, and two 3-day-interval consecutive negative RT-PCR results for SARS-CoV-2.

2.2 | RT-PCR assay for SARS-CoV-2 detection

The sample collection, RT-PCR conditions, and results interpretation were conducted as previously described.¹⁰ Two sets of primers were used for the two target genes, that is, open reading frame1ab (ORF1ab) and nucleocapsid protein(N), according to the protocol released by the National Institute for Viral Disease Control and Prevention (China) (http://ivdc.chinacdc.cn/kyjz/202001/t20200121_211337.html).

2.3 | Chest CT scanning

Patients had nonenhanced chest CT examinations for pneumonia using a Siemens SOMATOM Definition AS128 instrument (Siemens Healthineers). CT features considered abnormal included cavitation, lymphadenopathy, pleural effusion consolidation, lesion, and infiltration suggestive of infection, as well as increased lung markings. CT scanning results were classified as no evidence of abnormality, increased lung markings, left and right lobe pneumonia, or bilateral pneumonia.

2.4 | Clinical classification and treatment

On admission, all cases were classified as mild, moderate, severe, or critically ill cases according to the guidelines for scoring pediatric patients with COVID-19.¹¹ Briefly, in addition to a positive RT-PCR test for SARS-CoV-2 for all cases, mild cases presented with or without upper respiratory symptoms and no abnormal radiographic presentation; moderate cases had additional mild pneumonia; severe and critical cases presented with manifestations suggesting injury to vital organs and rapid disease progression.⁵ The treatment included control of high fever, antiviral therapy, oxygen therapy as needed for hypoxia, and antibiotic therapy if a bacterial infection was suspected. The antiviral therapy involved inhalation of aerosolized interferon- α two times per day as well as anti-influenza drugs such as Abidor and Oseltamivir, as required.

2.5 | Collection of clinical data on admission

The data of patients at admission and after 1-month follow-up were retrospectively collected from electronic medical records and included demographic data, exposure history, underlying comorbidities, symptoms, laboratory examination results, CT scans, and therapy details. The laboratory examinations included immunological tests (C-reactive protein)

as well as the measurement of biomarkers for liver function (alanine aminotransferase, aspartate transferase), myocardial function (creatinine kinase myocardial band isoenzyme [CK-MB], creatine kinase, lactate dehydrogenase, and lactate dehydrogenase isoenzyme-1), and renal function (creatinine and blood urea nitrogen).

2.6 | Follow-up examination

At approximately 1 month after discharge, the following patient data were obtained: continued clinical manifestations, results from serum SARS-CoV-2 IgG and IgM measurements, results from RT-PCR detection of SARS-CoV-2, CT scans of the lungs, and results of laboratory tests (Tables 1–3). The SARS-CoV-2 IgG and IgM concentrations were measured using the iFlash SARS-CoV-2 IgG and IgM set (iFlash 3000 Chemiluminescence Immunoassay Analyzer, Shenzhen YHLO Biotech Co., Ltd.) and are reported in units of ng/ml.

2.7 | Data analysis and statistical methods

Data for continuous variables were described as mean and standard deviation (SD) and were compared between groups by independent group two-tailed *t* tests when values were normally distributed; otherwise, the Mann–Whitney *U* test was used. Data for categorical variables were described as number and percentage (%) and were compared between groups by Fisher's exact test. A two-sided α less than .05 was considered statistically significant. We defined elevated CK-MB as the initial event and normal CK-MB as the corresponding failure event. We compared the median duration of CK-MB elevation by Kaplan–Meier survival analysis to assess the treatment effect in different groups of patients. All data analyses were conducted using the R package (version 3.6).

TABLE 1 Demographic and clinical characteristics at admission for all included pediatric patients and pediatric patients who completed the 1-month follow-up examination

Features	All patients	Follow-up patients	<i>p</i> value
No. of patients	127	46	–
Age, years	5.1 ± 4.4	5.1 ± 4.3	>.99
Age, range (years)	2 days–15 years	20 days–14 years	–
<1	35 (28, 20–36)	13 (28, 16–44)	>.99
1–5	35 (28, 20–36)	13 (28, 16–44)	>.99
5.1–14	57 (45, 36–54)	20 (44, 29–59)	>.99
Female	63 (50, 41–59)	15 (33, 20–48)	.06
Family members with COVID-19	117 (92, 86–96)	43 (94, 81–98)	>.99
Chronic medical illness	9 (7, 4–13)	3 (7, 2–19)	>.99
Clinical classification			
Mild and asymptomatic	46 (36, 28–45)	14 (30, 18–46)	.6
Moderate	78 (61, 52–70)	32 (70, 54–82)	.4
Severe and critical	3 (2, 1–7)	0	–
Interferon- α	122 (96, 91–99)	46 (100, 100–100)	.3
More than one antiviral drug	28 (22, 15–30)	12 (26, 15–41)	.7
Antibiotics	40 (32, 24–40)	18 (39, 25–55)	.4
Hospital stay, days (range)	12.8 ± 6.0 [8, 39]	13.2 ± 4.9 [8, 30]	.69

Note: Data are presented as *n* (percentage [%] and 95% confidence interval [CI]) or mean ± SD, unless otherwise indicated.

Abbreviation: COVID-19, coronavirus disease 2019.

TABLE 2 Comparison of lung CT scan results for all patients at admission and the patients who completed the follow-up examination

Features	All patients (%; 95% CI)	Follow-up patients (%; 95% CI)	<i>p</i> value
No. of patients	127	46	–
Pneumonia	81 (64, 55–72)	10 (22, 11–37)	<.0001
Increased lung markings	35 (28, 20–36)	12 (26, 15–41)	>.99
Left lobe pneumonia	17 (13, 8–21)	0	<.001 ^a
Right lobe pneumonia	35 (28, 20–36)	10 (22, 11–37)	<.001 ^a
Bilateral pneumonia	29 (23, 16–31)	0	<.0001
No evidence of abnormality	7 (6, 2–11)	24 (52, 37–67)	<.0001
No CT scan	4 (3, 1–8)	0	–

Abbreviations: CI, confidence interval; CT, computed tomography.

^aThe numbers of patients with left or right lobe pneumonia at admission are represented by the sum (46 or 64) of the number (17 or 35) of patients with left or right lobe pneumonia and the number (29) of patients with bilateral pneumonia, as left lobe pneumonia at follow-up may have been derived from the bilateral pneumonia on admission.

TABLE 3 Comparison of clinical features at admission versus follow-up for 46 pediatric COVID-19 patients who completed the postdischarge follow-up

Features	Admission (n = 46)	Follow-up (n = 46)	p value
Symptoms			
Asymptomatic	10 (22, 11–37)	36 (78, 63–89)	<.0001
Dry cough	21 (46, 31–61)	1 (2, 1–12)	<.0001
Dyspnea or tachypnea	1 (2, 1–12)	0	NA
Pharyngeal congestion	5 (11, 4–24)	1(2, 1–12)	.2
Vomiting or diarrhea	3 (7, 2–19)	0	NA
Body temperature (°C)			
Fever (>37°C)	37.6 ± 1.0	36.8 ± 1.0	.0002
Fever (>37°C)	18 (39, 25–55)	1 (2, 1–12)	<.0001
Laboratory tests (reference values)			
WBC count (4–10×10⁹/L)			
WBC count (4–10×10 ⁹ /L)	7.3 ± 2.0	6.9 ± 1.8	.316
>10×10 ⁹ /L (n)	6 (13, 5–27)	0	NA
<4×10 ⁹ /L (n)	0	0	NA
C-reactive protein (<8 mg/L)			
C-reactive protein (<8 mg/L)	5.2 ± 1.5	3.2 ± 1.2	.01
Increased (n)	2 (4, 1–16)	0	NA
Creatine kinase (20–250 U/L)			
Creatine kinase (20–250 U/L)	123 ± 73	153 ± 88	.078
Increased (n)	3 (7, 2–19)	6 (13, 5–27)	0.5
Creatine kinase MB (< 25 U/L)			
Creatine kinase MB (< 25 U/L)	31 ± 21	32 ± 12	.780
Increased (n)	23 (50, 36–64)	34 (74, 59–85)	.03
Lactate dehydrogenase-L (120–300 U/L)			
Lactate dehydrogenase-L (120–300 U/L)	266 ± 88	245 ± 55	.173
Increased (n)	9 (20, 10–34)	7 (15, 7–29)	.8
Lactate dehydrogenase-1 (15–65 U/L)			
Lactate dehydrogenase-1 (15–65 U/L)	58 ± 18	59 ± 13	.761
Increased (n)	16 (35, 22–50)	17 (37, 23–52)	>.99
Alanine aminotransferase (<50 U/L)			
Alanine aminotransferase (<50 U/L)	23 ± 21	21 ± 12	.576
Increased (n)	6 (13, 5–27)	0	.03
Aspartate transferase (<50 U/L)			
Aspartate transferase (<50 U/L)	37 ± 21	32 ± 12	.164
Increased (n)	6 (13, 5–27)	4 (9, 3–22)	.7
Creatinine (27–88 μmol/L)			
Creatinine (27–88 μmol/L)	33 ± 11	30 ± 11	.194
Increased (n)	0	0	NA
Blood urea nitrogen (3–7 mmol/L)			
Blood urea nitrogen (3–7 mmol/L)	4.0 ± 1.4	4.1 ± 1.1	.704
Increased (n)	0	0	NA
SARS-CoV-2-IgM (ng/ml)		8.0 ± 7.5	NA
SARS-CoV-2-IgG (ng/ml)		98 ± 40	NA

Note: Data are presented as n (percentage [%] and 95% confidence interval [CI]) or mean ± SD, unless otherwise indicated.

Abbreviations: IgM, immunoglobulin M; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WBC, white blood cell.

3 | RESULTS

A total of 127 pediatric patients, aged 0–15 years (mean age, 5.1 ± 4.4 years; 63 females), who were hospitalized for COVID-19 treatment between January 20 and March 15, 2020, were included in this study (Table 1). There were 124 mild or moderate cases and 3 severe cases, including one that resulted in death, one that required continued treatment in the pediatric intensive care unit (PICU) at the time of follow-up, and one that was cured. A total of 125 patients were clinically cured and discharged with an average hospital stay of 12.8 days (SD, 6.0 days).⁹ For most patients (117/127, 92%, 95% confidence interval [CI]: 86%–96%), the transmission mode was a family cluster. The applied therapies included inhalation of aerosolized interferon- α (122/127, 96%, 95% CI: 91%–99%), antiviral drugs (28/127, 22.0%, 95% CI: 15%–30%, including Arbidol [n = 12], Ribavirin [n = 7], Oseltamivir [n = 5], and Ganciclovir [n = 4]), and antibiotics (40, 32%, 95% CI: 24%–40%).

Among the 123 patients who underwent CT scanning at admission, 81 patients were found to have pneumonia, including 17 (13%, 95% CI: 8%–21%) with left lobe pneumonia, 35 (28%, 95% CI: 20%–36%) with right lobe pneumonia, and 29 (23%, 95% CI: 16%–31%) with bilateral pneumonia. Among the 42 patients without pneumonia, 35 (28%, 95% CI: 20%–36%) had increased lung markings and 7 showed no evidence of abnormality on lung CT scans (Table 2). The 81 patients with pneumonia exhibited a significantly higher body temperature than those with increased lung markings or no evidence of abnormality in the lungs (Figure 1). The 35 patients with right lobe pneumonia had the longest mean hospital stay (14.5 ± 7 days). The 17 patients with left lobe pneumonia had the highest mean creatine kinase level (154 ± 106 U/L) and mean CK-MB level (43 ± 48 U/L). Patients with bilateral pneumonia showed the highest white blood cell counts (8.3 ± 4 × 10⁹/L). The prevalence of pneumonia decreased from 64% (81/127, 95% CI: 55%–72%) at admission to 22% (10/46, 95% CI: 11%–37%) at follow-up (p < .001; Table 2), and only right lobe pneumonia was present at the follow-up.

Of the 125 discharged patients, 46 patients were successfully followed for collection of symptom details and laboratory results after an average time of 26 ± 9.1 days since discharge. Mean patient age, sex, applied therapy, and hospital stay were comparable between the patients who completed the follow-up and the total hospitalized group (Table 1). Notably, the CK-MB, creatine kinase, lactate dehydrogenase, and lactate dehydrogenase isoenzyme-1 levels were not significantly reduced to normal reference ranges at the 1-month follow-up, in contrast to most clinical features for which the prevalence of abnormalities had significantly declined (Table 3). Moreover, the prevalence (34/46, 74%, 95% CI: 59%–85%) of CK-MB elevation at the follow-up was significantly greater than that at admission (23/46, 50%, 95% CI: 36%–64%, p = .03; Table 3). The CK-MB level increased after discharge in most patients in the follow-up group (Figure 2). Abnormalities among other laboratory indices

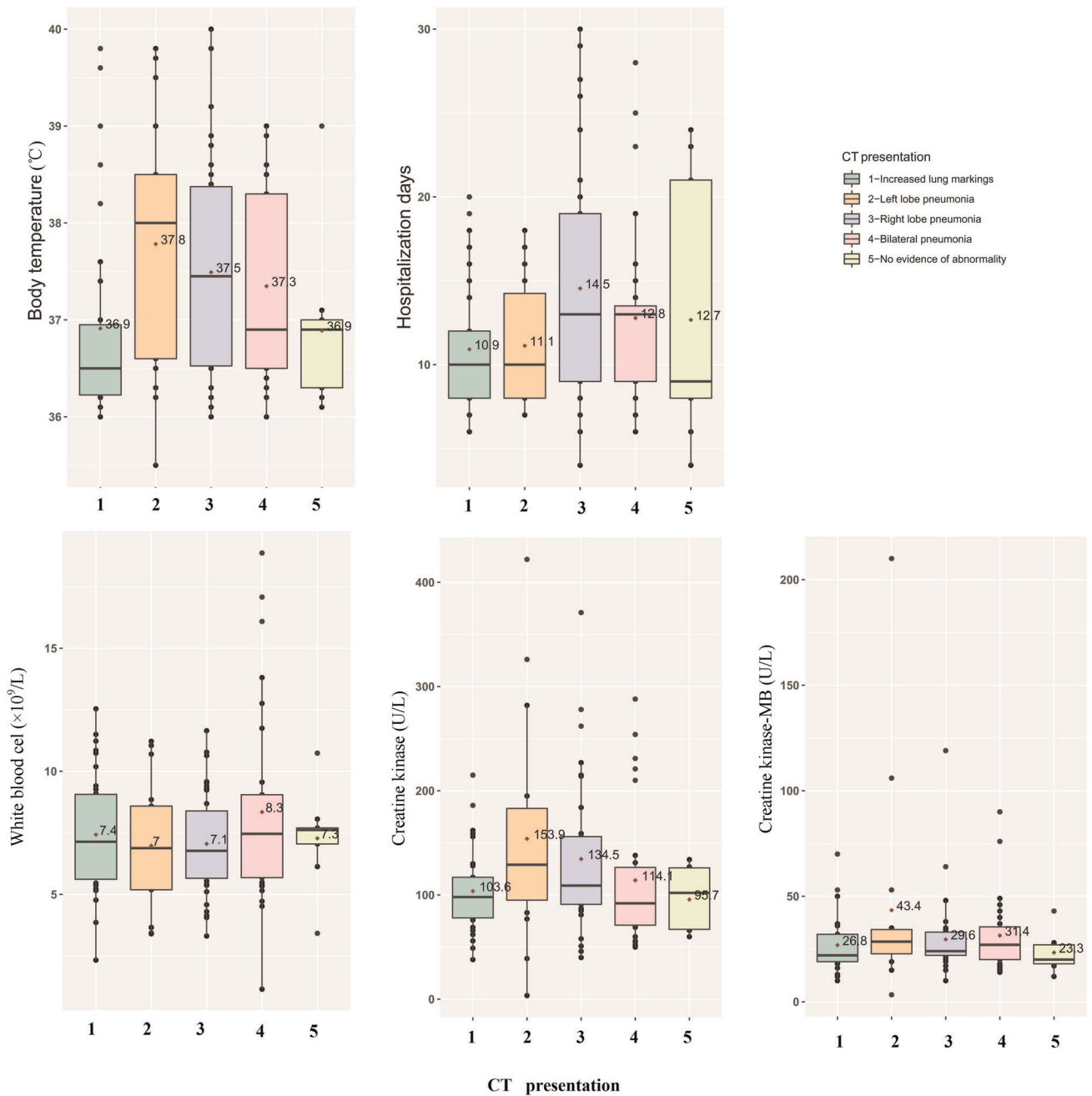


FIGURE 1 Comparisons of body temperature, length of hospital stay, white blood cell count, creatine kinase, and creatine kinase-MB among patients with different CT presentations. CT, computed tomography; MB, myocardial band [Color figure can be viewed at wileyonlinelibrary.com]

reflecting immune responses and liver and renal damage showed a low prevalence both at admission and at follow-up, including elevation of alanine aminotransferase ($n = 6$ at admission), aspartate transferase ($n = 6$ at admission), creatinine ($n = 0$), blood urea nitrogen ($n = 0$), C-response protein ($n = 2$ at admission), and white blood cells (above $10 \times 10^9/L$, $n = 6$ at admission) (Table 3).

As elevated CK-MB was the most prevalent and persistent clinical feature among the 46 patients in the follow-up group, we considered elevated CK-MB as the initial event and normal CK-MB as the failure event in performing survival analysis to demonstrate

the temporal trend (Figure 3). The median duration of elevated CK-MB was 45 days, meaning 50% of patients still had an elevated CK-MB level at 45 days after admission. Elevated CK-MB levels persisted long after discharge, as the mean hospital stay was 13.2 days. Although 0–1-year-old patients may have a higher reference range for CK-MB than >1-year-old patients, a longitudinal comparison between admission and follow-up showed slightly elevated creatine kinase and CK-MB levels at the follow-up time in most patients (Figure 2). At the follow-up examination, four patients again tested positive for SARS-CoV-2.

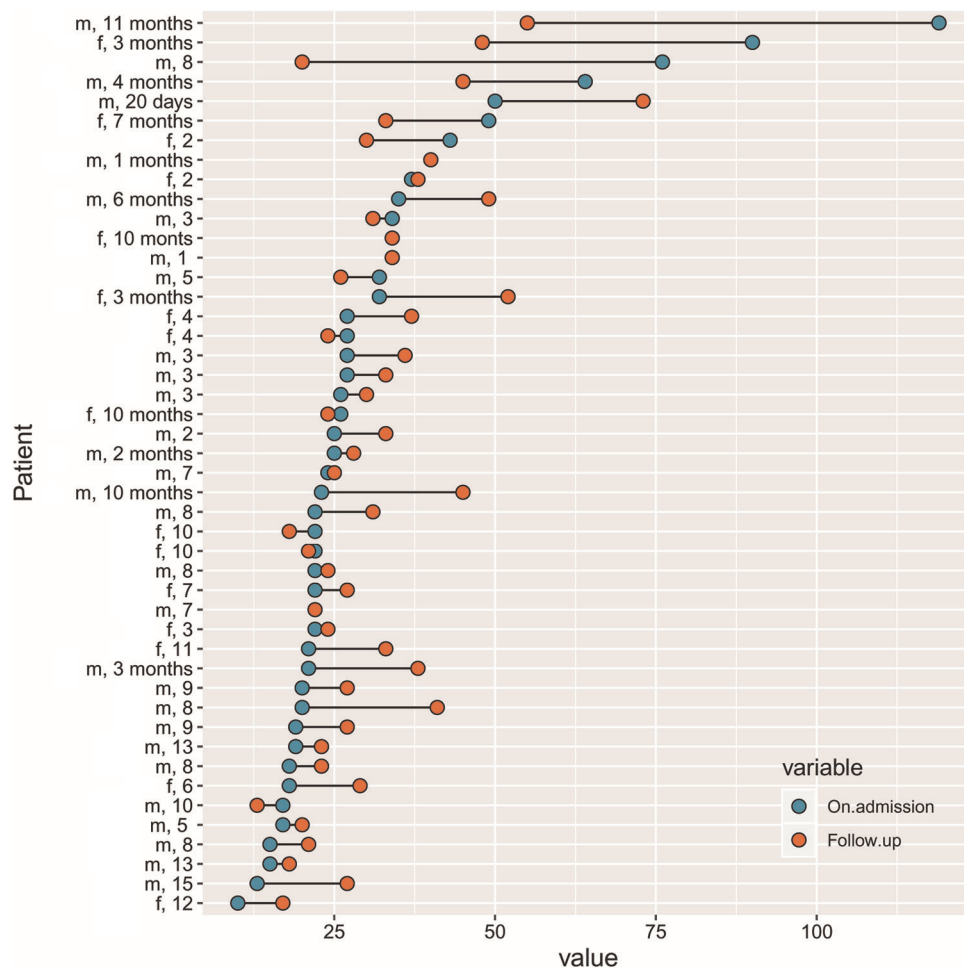


FIGURE 2 Creatine kinase-MB levels at admission and follow-up ($n = 46$). Letters “f” and “m” represent female and male, respectively. The age unit is year, unless otherwise indicated. MB, myocardial band [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

This study summarizes the clinical features and 1-month follow-up observations for 127 pediatric patients who were hospitalized for COVID-19. Among these patients, 125 were clinically cured and discharged. The other two patients included one critically ill patient who died and one critically ill patient who continued to receive treatment in the PICU at the end of the study. Lung CT images collected 1 month after discharge showed that right lobe pneumonia persisted in 22% of patients, whereas left lobe pneumonia had resolved. We observed persistently elevated creatine kinase and CK-MB levels in the 46 patients who completed the follow-up.

Because COVID-19 is still an emerging infectious disease, follow-up information for pediatric patients is scarce. Based on the criteria for cured COVID-19 in China,⁹ the length of hospitalization reflects the time required to achieve a negative SARS-CoV-2 RT-PCR test, the improvement of pneumonia and upper respiratory symptoms, and the end of fever. Therefore, the length of hospital stay is often used as an index to assess treatment effects. For the pediatric patients included in this study, the length of hospital stay varied from 8 to 39 days, indicating the varied severity of COVID-19 among these patients. The current 127 patients

were treated with aerosolized interferon- α (122/127, 96%) and antiviral drugs (28/127, 22.0%) according to the early version guidelines (the interim first to 7th edition) related to COVID-19. The current guideline (the interim 8th edition) suggested antiviral drugs only for severe and critically ill patients or rapidly progressing cases.¹²

Although RT-PCR has been used as the main method for COVID-19 diagnosis, the radiological examination was used as a diagnostic tool for screening and early diagnosis of COVID-19 pneumonia during the early stage of the COVID-19 pandemic according to the early version guidelines (the interim first to 7th edition). Nonetheless, previous studies reported inconsistent diagnostic values of CT on COVID-19. One study reported 98% sensitivity of chest CT scan during COVID-19 onset and diagnosis,¹³ while another study reported CT had limited sensitivity especially in the first 2 days after onset of symptoms, as 56% of patients had normal findings and chest CT therefore cannot be used to rule out infection from SARS-CoV-2.¹⁴ These previous findings indicated comprehensive consideration of an examination tool was essential owing to the complex presentations of COVID-19. In the current Chinese guideline (the interim 8th edition), CT scan is not recommended for mild and moderate patients, while the radiological examination is included as an assessment criterion of clinical severity types and hospitalization

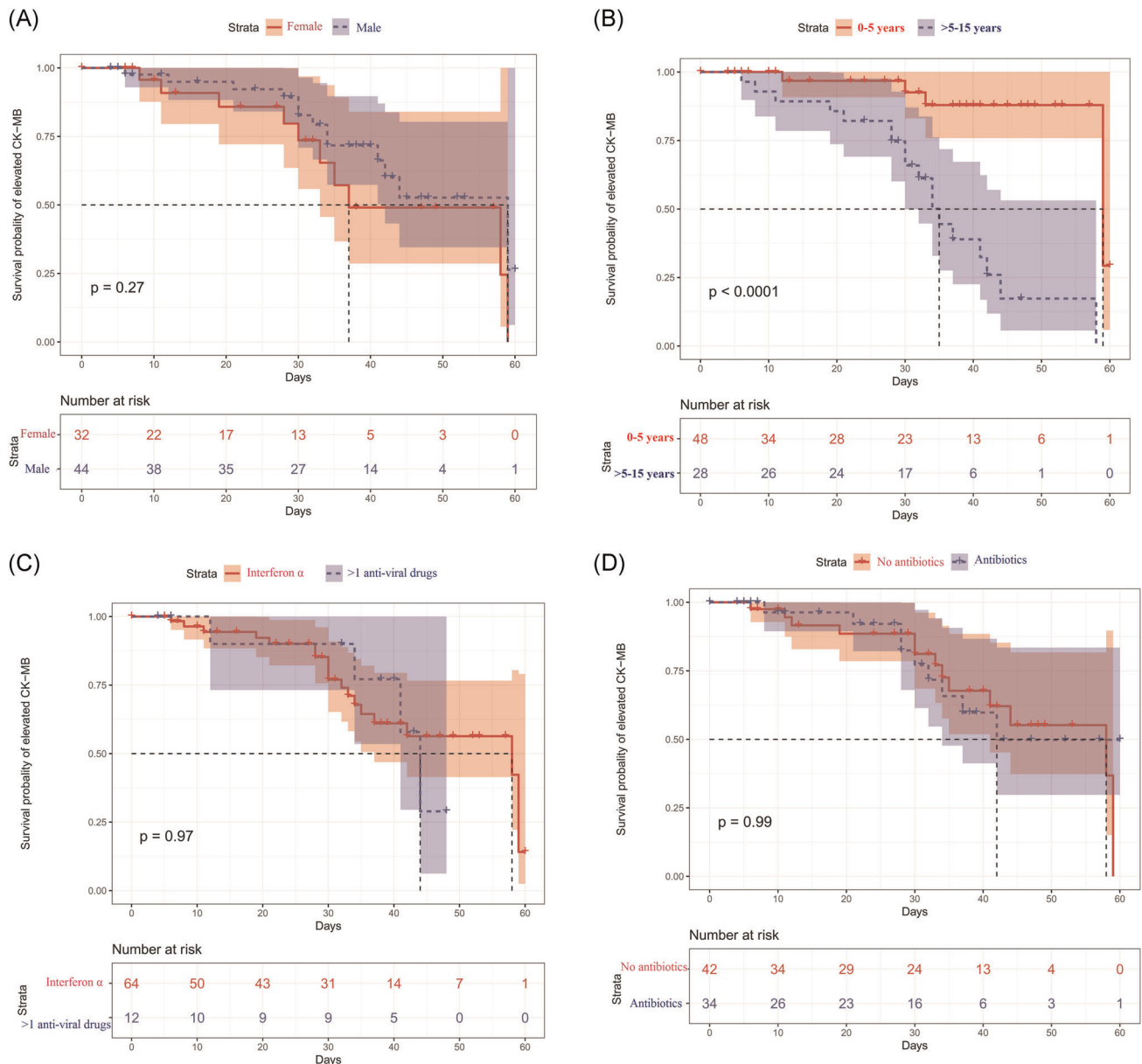


FIGURE 3 Survival analysis of the duration of creatine kinase-MB elevation among patient groups stratified by age, sex, use of additional antiviral drugs, and use of antibiotics. MB, myocardial band [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

discharge.¹² However, this study and literature suggested radiological evidence of pneumonia plays a role in the assessment of organ damage resulting from COVID-19.¹⁵ Notably, the 81 patients with pneumonia in this study had a significantly higher body temperature than patients without pneumonia ($p < .05$). We also observed distinct outcomes according to the different lobes where pneumonia occurred (Figure 1). Patients with right lobe pneumonia had the longest hospital stay, and right lobe pneumonia was present in all patients with persistent pneumonia at follow-up, suggesting that right lobe pneumonia predicted a worse outcome compared with nonright lobe pneumonia ($p = .003$). Patients with bilateral pneumonia often had a higher white blood cell count than those with pneumonia in a single lobe. Notably, 17 patients with left lobe pneumonia had much higher creatine kinase and CK-MB levels than patients with nonleft lobe pneumonia. The present findings support the

point of view that chest CT manifestations in children with COVID-19 are potentially a useful marker for early identification and severity assessment.¹⁶

Among the 46 patients who were successfully followed up 1 month after discharge, the prevalence of two common symptoms, dry cough and fever, decreased to 2% (Table 3). From the follow-up laboratory tests, notable findings included elevation of creatine kinase, CK-MB, lactate dehydrogenase, and lactate dehydrogenase isoenzyme-1 levels above normal ranges in most patients (Figure 2). This phenomenon was different from other clinical features, which no longer showed abnormality at the 1-month follow-up (Table 3).

Survival analysis demonstrated that 50% of the patients had elevated CK-MB levels for 45 days from the time of COVID-19 diagnosis (Figure 3). Elevated creatine kinase is often seen when the

heart muscle is damaged and thus defined as a cardiac biomarker in predicting the severity of patients with COVID-19.^{17,18} Persistently elevated creatine kinase and CK-MB levels suggest prolonged cardiac damage, which has been reported previously in some COVID-19 patients.^{19,20} Notably, in children with COVID-19, cardiac involvement has been linked to an abnormal inflammatory response.²¹ Our findings of persistently elevated CK-MB levels are consistent with the previous hypothesis that the heart is a primary target of injury in the multisystem inflammatory syndrome in children.²² The duration of elevated CK-MB for up to 45 days is very close to the 1-month time course of multisystem inflammatory syndrome.²³ Although mere elevation of CK-MB does not meet the criteria for the diagnosis of the multisystem inflammatory syndrome, this factor still provides evidence for the common occurrence of cardiac injury, possibly due to an uncontrolled immune response even in mild cases. Viral myocarditis or elevated CK-MB is often observed in various viral infections; examples include transient cardiac injury during H7N9 infection,²⁴ elevated CK-MB in rotavirus infection,²⁵ and viral myocarditis as a complication of acute upper respiratory tract infection.²⁶ We speculate a similar situation may exist in COVID-19, although more evidence is required to draw a sound conclusion.

Other laboratory indices reflecting the immune response and liver and renal damage, including C-reactive protein, alanine aminotransferase, aspartate transferase, creatinine, and blood urea nitrogen, showed a low prevalence of abnormality both at admission and at the 1-month follow-up (Table 3). Serum IgG and IgM against SARS-CoV-2 were detected in 41 patients at the 1-month follow-up. Notably, four pediatric patients with high levels of IgG and IgM tested positive for SARS-CoV-2 again at the 1-month follow-up.

This study has several limitations. First, this study was an early follow-up observational study. Longer follow-up is needed to observe the resolution or outcome of several clinical features, such as abnormal CT imaging and CK-MB levels. Second, only a proportion of patients were successfully followed up. Third, although the retrospective study observed persistently elevated creatine kinase in pediatric patients, we performed an echocardiogram only for three severe cases and observed abnormal presentations. For mild and moderate patients, no echocardiogram was performed, as COVID-19 was considered primarily a respiratory disease during the early stage of the pandemic. Because COVID-19 continues to spread rapidly in many countries around the world and is an urgent public health challenge, we believed an early follow-up report on pediatric patients would be valuable.

To summarize, we described the on-admission and follow-up clinical features of a cohort of hospitalized pediatric patients with COVID-19. Lung CT scans showed persistence of right lobe pneumonia at the 1-month follow-up. Most laboratory results reflecting the immune response or liver or renal damage showed a low prevalence of abnormality both at admission and at the 1-month follow-up. However, half of the pediatric patients who completed the follow-up had persistently elevated CK-MB levels at 1 month after discharge. The clinical implications of continued CK-MB elevation long after discharge require further investigation.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Feng Tang: conceptualization (equal); funding acquisition (equal); writing original draft (equal). **Wanjuan Luo:** data curation (equal); investigation (equal). **Xiaowen Wang:** data curation (equal); investigation (equal). **Hui Li:** methodology (equal); resources (equal). **Hong Mei:** methodology (equal); resources (equal). **Jianbo Shao:** data curation (equal); funding acquisition (equal); supervision (equal). **Qifa Song:** formal analysis (equal); writing review and editing (equal).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

1. Wu P, Hao X, Lau EHY, et al. Real-time tentative assessment of the epidemiological characteristics of novel coronavirus infections in Wuhan, China, as at 22 January 2020. *Euro Surveill.* 2020;25(3):2000044.
2. WHO. COVID-19 weekly epidemiological update. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20210309-weekly-epi-update_30.pdf. Accessed March 16, 2021.
3. Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. *Zhonghua Liu Xing Bing Xue Za Zhi.* 2020;41(2):145-151.
4. Chen YM, Zheng Y, Yu Y, et al. Blood molecular markers associated with COVID-19 immunopathology and multi-organ damage. *EMBO J.* 2020;39(24):e105896.
5. Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. *Lancet Infect Dis.* 2020;20:689-696.
6. Zou Y, Wang BR, Sun L, et al. The issue of recurrently positive patients who recovered from COVID-19 according to the current discharge criteria: investigation of patients from multiple medical institutions in Wuhan, China. *J Infect Dis.* 2020;222(11):1784-1788.
7. Buonsenso D, Sali M, Pata D, et al. Children and COVID-19: microbiological and immunological insights. *Pediatr Pulmonol.* 2020;55:2547-2555.
8. Yelin D, Wirtheim E, Vetter P, et al. Long-term consequences of COVID-19: research needs. *Lancet Infect Dis.* 2020;20(10):1115-1117.
9. National Health and Health Commission of the people's Republic of China. Diagnosis and treatment guidelines for 2019 novel coronavirus pneumonia (Draft version 7)[EB/OL]. 2020. <http://www.nhc.gov.cn/>

- zygj/s7653p/202002/3b09b894ac9b4204a79db5b8912d4440.shtml. (Chinese). Accessed March 5, 2020.
10. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323:1061.
 11. Chen Z, Fu J, Shu Q, et al. Diagnosis and treatment recommendation for pediatric coronavirus disease-19. *Zhejiang Da Xue Xue Bao Yi Xue Ban*. 2020;49(1):1-8.
 12. National Health and Health Commission of the people's Republic of China. Guidelines on diagnosis and treatment of novel coronavirus pneumonia (interim 8th edition). <http://www.nhc.gov.cn/zygj/s7652m/202008/475d0199d34c4cac840eb7998fad444f.shtml> (Chinese).
 13. Fang Y, Zhang H, Xie J, et al. Sensitivity of chest CT for COVID-19: comparison to RT-PCR. *Radiology*. 2020;296:200432-E117.
 14. Pata D, Valentini P, De Rose C, De Santis R, Morello R, Buonsenso D. Chest computed tomography and lung ultrasound findings in COVID-19 pneumonia: a pocket review for non-radiologists. *Front Med (Lausanne)*. 2020;7:375.
 15. Chen D, Tang F, Lu S, Song Q. Toward a clinically based classification of disease severity for paediatric COVID-19—Authors' reply. *Lancet Infect Dis*. 2021;21(1):22-23.
 16. Nino G, Zember J, Sanchez-Jacob R, Gutierrez MJ, Sharma K, Linguraru MG. Pediatric lung imaging features of COVID-19: a systematic review and meta-analysis. *Pediatr Pulmonol*. 2021;56(1):252-263.
 17. Qin JJ, Cheng X, Zhou F, et al. Redefining cardiac biomarkers in predicting mortality of Inpatients with COVID-19. *Hypertension*. 2020;76(4):1104-1112.
 18. Wu AH, Wang XM, Gornet TG, Ordonez-Llanos J. Creatine kinase MB isoforms in patients with skeletal muscle injury: ramifications for early detection of acute myocardial infarction. *Clin Chem*. 1992;38(12):2396-2400.
 19. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiology*. 2020;5:802.
 20. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin. *Eur Heart J*. 2021;42(2):206
 21. Snape MD, Viner RM. COVID-19 in children and young people. *Science*. 2020;370(6514):286-288.
 22. Jiang L, Tang K, Levin M, et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. *Lancet Infect Dis*. 2020;20(11):e276-e288.
 23. Yasuhara J, Watanabe K, Takagi H, Sumitomo N, Kuno T. COVID-19 and multisystem inflammatory syndrome in children: a systematic review and meta-analysis [published online ahead of print January 11, 2021]. *Pediatr Pulmonol*. 56(5):837-848. <https://doi.org/10.1002/ppul.25245>
 24. Han J, Mou Y, Yan D, et al. Transient cardiac injury during H7N9 infection. *Eur J Clin Invest*. 2015;45(2):117-125.
 25. Zheng J, Zheng H, Gupta RK, et al. Interrelationship of rotavirus infection and Creatine Kinase-MB isoenzyme levels in children hospitalized with acute gastroenteritis in Guangzhou, China, 2012-2015. *Sci Rep*. 2017;7(1):7674.
 26. Rezkalla SH, Kloner RA. Influenza-related viral myocarditis. *WMJ*. 2010;109(4):209-213.

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