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Original Article

Clinical features, laboratory findings and persistence of virus in 10 children with coronavirus disease 2019 (COVID-19)



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ABSTRACT

Background: A pandemic caused by SARS-CoV-2 infection (COVID-19) has rapidly spread across the globe. Although many articles have established the clinical characteristics of adult COVID-19 patients so far, limited data are available for children. The aim of this study was to reveal the clinical features, laboratory findings and nucleic acid test results of ten pediatric cases.

Methods: In this retrospective single-center cohort study, pediatric cases with COVID-19 infection were consecutively enrolled in one hospital in Huangshi, China from January 1 to March 11, 2020.

Results: A total of 10 children with COVID-19 were recruited. Of them, four were the asymptomatic type, one was the mild type, and five were the moderate type (including two subclinical ones). All patients were from family clusters. Only fever, nasal discharge and nasal congestion were observed. Lymphopenia and leukopenia were uncommon in our sample but elevated levels of lactate dehydrogenase (LDH) and alpha-hydroxybutyrate

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dehydrogenase (α -HBDH) were observed frequently. Of these laboratory test variables, no statistical difference was identified between asymptomatic and symptomatic patients. Abnormalities in radiological data were detected in five patients, and representative findings of chest CT images were patchy shadows and ground-glass opacities. There were two cases whose oropharyngeal nucleic acid tests reversed to positive after one negative result, and two patients whose oropharyngeal swabs tested negative but rectal swabs showed positive.

Conclusions: Clinical symptoms were mild in children with COVID-19. Increased levels of LDH and α -HBDH were potential clinical biomarkers for pediatric cases. More attention should be paid to the SARS-CoV-2 viral assessment of rectal swabs before patients are discharged.

At a glance commentary

Scientific background on the subject

A pandemic caused by SARS-CoV-2 infection (COVID-19) has rapidly spread across the globe. Although many articles have established the clinical characteristics of adult COVID-19 patients so far, limited data are available for children.

What this study adds to the field

Clinical symptoms were mild in children with COVID-19. Increased levels of LDH and α -HBDH were potential clinical biomarkers for pediatric cases. More attention should be paid to the SARS-CoV-2 viral assessment of rectal swabs before patients are discharged.

Since the first case reported in December 2019, a pandemic caused by the novel coronavirus (SARS-CoV-2) infection has been rapidly spreading [1,2]. Although China launched an emergency response early in the outbreak, the pandemic has spread around the world, with numerous countries reporting local cycles of transmission [3]. As of May 1, 2020, a total of 3,175,207 worldwide cases of Coronavirus Disease 2019 (COVID-19) have been confirmed, including 84,385 cases in China and 3,090,822 cases in other countries [4]. As of this time, a total of 224,172 patients have died from this disease [4]. The World Health Organization (WHO) has announced COVID-19 as a Public Health Emergency of International Concern, but the number of infected patients is still increasing globally [5]. How to control the spread of COVID-19 has become a global problem.

While many articles have established the clinical features of COVID-19 so far, most reports are about adults. However, it is now believed that people at all ages are generally susceptible to SARS-CoV-2, suggesting that it is equally important to understand the clinical features of pediatric patients of COVID-19 [6]. Data on COVID-19 infected children are limited, and studies focusing on the laboratory abnormalities and nucleic acid tests of pediatric patients are even fewer. In this report, we recruited 10 children with confirmed COVID-19 who were admitted to Huangshi Maternity and Children's Health Hospital in Hubei province, in order to delineate the

clinical characteristics, laboratory findings and nucleic acid tests for COVID-19 pediatric cases.

Material and methods

Subjects and data collection

In this retrospective single-center cohort study, pediatric cases with COVID-19 in Huangshi Maternity and Children's Health Hospital of Edong Healthcare Group were consecutively enrolled from January 1 to March 11, 2020. Data collection forms were generated to collect patients' general information, epidemiological history, clinical manifestations, laboratory examinations, imaging features and treatment. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Huangshi Maternity and Children's Health Hospital of Edong Healthcare Group (No.YXJYK-2020-001).

Clinical classifications

Severity of COVID-19 was defined according to the *Recommendations for the diagnosis, prevention and control of the 2019 novel coronavirus infection in children (first interim edition)* [7,8]. Based on patients' clinical features, laboratory tests and chest X-ray imaging, five severity levels were classified for children: asymptomatic, mild, moderate, severe, and critical.

Nucleic acid detection for SARS-CoV-2

Oropharyngeal swabs, rectal swabs and urine samples of patients were used to test for SARS-CoV-2 using the qRT-PCR kit (Sansure Biotech, Hunan, China). Patients were identified because of their close contacts with confirmed cases or acute fever with no clear predisposing factors. The viral nucleic acid detections were performed following the laboratory guidelines by the Chinese Center for Disease Control and Prevention. Specimens with positive results by both open reading frame 1 ab (ORF1a/b) and nucleocapsid protein gene site (N) would be considered laboratory-confirmed. The primers and probe set for ORF1a/b were as follows: forward primer 5'-CCCTGTGGGTTTACTACTAA-3'; reverse primer 5'-ACGATTGTGCATCAGCTGA-3'; and the probe 5'-FAM-CCGTCTGCGGTATGTGGAAGGTTATGG-BHQ 1-3'. The primers and probe target for N were as follows: forward primer 5'-GGGGAACCTCTCTGCTAGAAT-3';

reverse primer 5'-CAGACATTTTGCTCTCAAGCTG-3'; and the probe 5'-FAM-TTGCTGCTGCTTGACAGATT-TAMRA-3'. Conditions for the amplifications were 50 °C for 30 min, 95 °C for 1 min, followed by 45 cycles of 95 °C for 15 s and 60 °C for 30 s. A cycle threshold value (Ct-value) less than 37 was defined as a positive test, and a Ct-value of 40 or more was defined as a negative test. A medium load with Ct-value between 37 and 40 required a retest. If the Ct-value in the retest was less than 40 and the amplification curve had an obvious peak, the sample would be determined as positive; otherwise negative.

Laboratory tests

Laboratory test results were conducted upon admission, including routine blood test (absolute white blood cell count, neutrophil count and lymphocyte count, etc.; BC-6800 hematology analyzer, Mindray, China), C-reactive protein (CRP), procalcitonin (PCT; Fluorescence immunoassay, Wondfo Biotech, China), erythrocyte sedimentation rate (ESR) and other serum biochemistry including coagulation function (SF-8100 Fully Automated Coagulation Analyzer, Succeeder Technology, China), and liver and renal functions (BS-2000 Automated Biochemical Analyzer, Mindray, China). Detection results of other respiratory pathogens (influenza A virus, influenza B virus, respiratory syncytial virus, parainfluenza virus, mycoplasma pneumoniae, chlamydia pneumoniae, coxsackie virus group B, adenovirus and legionella pneumophila) were also included. Patients were discharged from hospital when their body temperature remained normal for three consecutive days, their respiratory symptoms substantially improved, and two consecutive results of respiratory pathogenic nucleic acid tests were negative.

Statistical analysis

Statistical analysis was performed with SPSS 17.0 statistical software package. Mann–Whitney *U* test was used to compare the laboratory test results and duration of virus shedding of asymptomatic patients (asymptomatic type) and symptomatic patients (mild and moderate type). Statistical significance level was set at *p*-values less than 0.05.

Results

Clinical manifestations and imaging examinations

A total of 10 children with COVID-19 were recruited in our study, two of whom were brother and sister (case 1 and case 2). General information, symptoms and imaging results are summarized in Table 1. Of these patients, 6 were boys and 4 were girls, with an age range of 1.5 months–120 months (median age = 25 months; mean age = 48 months). One child (case 7) was from Wuhan, and the other nine patients were local residents of Huangshi city (an epidemic region 100 km away from Wuhan). Case 8 was the youngest patient in Huangshi, diagnosed at 44 days after birth. All these children had close contact with adult family members with laboratory-confirmed SARS-CoV-2 infection. No history of underlying diseases was declared among these patients.

At illness onset, four children (case 7, case 8, case 9, and case 10) had fever, with peak body temperatures varying from 37.5 °C to 38.7 °C. None of them developed high fever (body temperature above 39 °C). Case 7 and case 9 presented nasal discharge and nasal congestion. No other symptoms frequently observed in adult patients, such as fatigue and myalgia, were found in these cases, and none of them developed dyspnea [9–11]. The remaining six children had no clinical symptoms at all and were diagnosed because of their household exposure to COVID-19.

Upon admission, abnormalities in radiological data were detected in five patients. Three of them (case 5, case 8 and case 9) had bilateral involvement, and the other two patients (case 6 and case 10) had abnormalities on only one side of their lungs. Representative findings of chest CT images were patchy shadows and ground-glass opacities. CT scans of the remaining five patients showed normal results.

Clinical classifications

Of the ten patients, four were classified as the asymptomatic type (case 1, case 2, case 3 and case 4) with normal clinical phenotypes and chest imaging results. One patient was classified as the mild type (case 7), showing symptoms but no signs of pneumonia based on chest imaging. The

Table 1 General information, symptoms and imaging results of ten pediatric patients.

	case 1	case 2	case 3	case 4	case 5	case 6	case 7	case 8	case 9	case 10
General information										
Sex	F	M	M	F	M	M	M	F	M	F
Age (month)	25	84	78	108	8	120	15	1.5	16	25
Clinical manifestations										
Peak of fever							38.7 °C	38.5 °C	37.5 °C	38.4 °C
fever	No	No	No	No	No	No	Yes	Yes	Yes	Yes
Nasal discharge	No	No	No	No	No	No	Yes	No	Yes	No
Nasal congestion	No	No	No	No	No	No	Yes	No	Yes	No
Radiological data										
	Normal	Normal	Normal	Normal	bilateral opacity	right lung opacity	Normal	bilateral opacity	bilateral opacity	left lung opacity

remaining five patients were considered as moderate type, showing abnormal chest imaging results and/or clinical symptoms. Children with the moderate type included two subclinical patients (case 5 and case 6), who had no clinical symptoms but had chest CT results that showed pulmonary lesions.

Detection results for SARS-CoV-2

For all patients, oropharyngeal swab specimens were detected for SARS-CoV-2 on their admission and during their hospitalization period. The duration of virus shedding in respiratory specimens, which is the interval from the first day of either symptom onset (symptomatic patients) or positive SARS-CoV-2 detection tests (asymptomatic patients) to the first day of two consecutive negative results, ranged from 7 days to 16 days after illness onset. The time of virus shedding in respiratory was longer in symptomatic patients than asymptomatic ones ($p = 0.019$). Of particular concern, two patients (case 2 and case 6) had oropharyngeal nucleic acid test reversed to positive after one negative result. Nucleic acid detection results of the 10 pediatric patients are shown in Fig. 1.

Six children had rectal swabs and urine samples tested for SARS-CoV-2 within 3–15 days after disease onset. The urine samples of all children but case 1 showed negative. Positive results of rectal swabs were observed in case 1, case 2, case 3, case 5, case 6 and case 8 on the 3rd, 3rd, 4th, 12th, 10th and 15th day since their illness onset, respectively. Interestingly, case 5 and case 8 tested positive on rectal swabs on the 12th and 15th day, but their oropharyngeal swabs showed negative.

Laboratory tests

Of the nine children who received routine blood test upon admission (case 4 did not receive any tests during hospitalization other than COVID-19 testing), the majority showed normal white blood cell and neutrophil count. Elevated levels of lymphocyte count were observed in five patients. As for biomarkers of infection, increased levels of serum CRP were detected in one patient and increased levels of ESR were detected in two patients. Normal serum levels of PCT were observed in all patients. Coagulation function parameters were normal in all patients but one (case 8), who showed increased D-dimer. Interestingly, decreased concentration of creatinine and carbon dioxide combining power were observed in all patients but case 6; levels of alkaline phosphatase (ALP), lactate dehydrogenase (LDH) and alpha-hydroxybutyrate dehydrogenase (α -HBDH) were increased in more than half of the detected patients (5/8, 6/8 and 6/8, respectively; case 9 did not receive serum biochemistry tests during hospitalization). Detection results of nine respiratory pathogens were negative, with the exception of one weak positive result for mycoplasma pneumoniae in case 2. No statistical difference of these laboratory test variables was identified between asymptomatic and symptomatic patients. The laboratory tests of nine pediatric patients upon admission are summarized in Table 2.

Treatment regimen and outcomes

All patients received antiviral therapy with α -interferon together with arbidol hydrochloride granules, oseltamivir

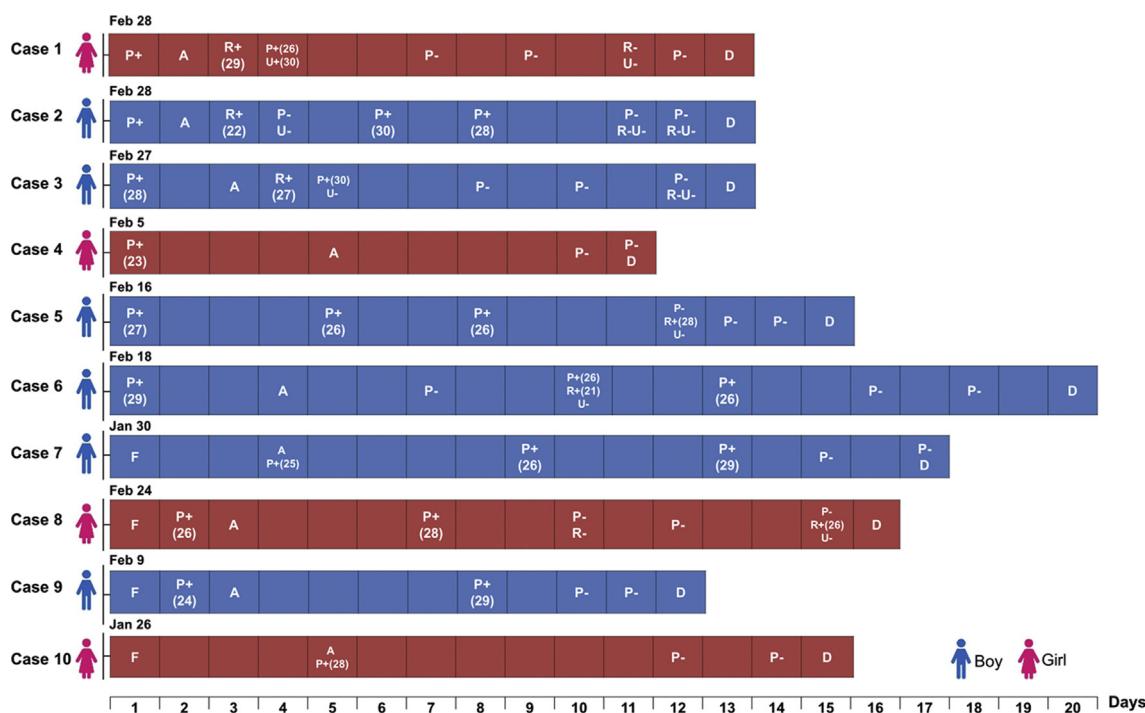


Fig. 1 Nucleic acid detection results of 10 pediatric patients. A: Admission; D: Discharge; F: Fever; P+: Pharyngeal swab positive; P-: Pharyngeal swab negative; R+: Rectal swab positive; R-: Rectal swab negative; U+: Urine sample positive; U-: Urine sample negative. Ct values of ORF1a/b for positive samples were in brackets.

Table 2 Laboratory tests of 9 pediatric patients on admission.

Variables	Normal Range	Asymptomatic type			Symptomatic type						p value
		case 1	case 2	case 3	case 5	case 6	case 7	case 8	case 9	case 10	
WBC	4.00–12.00 (109/L)	↑13.50	6.68	4.97	↑22.25	6.77	7.03	6.53	7.19	↓3.56	1.00
NEU	1.80–6.30 (109/L)	2.66	2.29	2.52	3.84	3.13	1.81	1.86	1.92	↓0.64	0.55
LYM	1.10–3.20 (109/L)	↑10.01	↑3.83	2.03	↑16.99	2.93	↑4.59	2.93	↑4.54	2.67	1.00
PLT	125–350 (109/L)	213	177	308	309	311	205	↑455	322	151	0.38
CRP	0–5.00 (mg/L)	<0.50	<0.50	<0.50	<0.50	1.3	↑5.30	<5.00	<0.50	<0.50	–
ESR	0–20.00 (mm/h)	18	11	6	NT	↑24.00	9	↑23.00	NT	12	0.40
PCT	0–0.50 (ng/mL)	0.13	0.23	<0.10	0.17	0.29	0.12	0.49	0.13	<0.10	–
TBIL	3.4–19.0 (umol/L)	↓3.0	4.5	6.4	6.3	10.3	4.5	6.7	NT	↓3.1	0.39
ALB	40.0–55.0 (g/L)	45.9	45	43.1	41.9	43.9	42.9	44.2	NT	44.5	0.25
ALT	5–50 (U/L)	15	40	11	28	19	20	29	NT	12	0.79
AST	15–40 (U/L)	33	↑47	27	↑54	30	39	15	NT	↑43	1.00
ALP	0–187 (U/L)	168	↑212	↑210	↑272	183	↑249	↑422	NT	174	0.39
CREA	57–97 (umol/L)	↓20	↓35	↓34	↓20	↓41	↓26	↓15	NT	↓27	0.57
UREA	2.6–7.5 (mmol/L)	5.49	4.38	2.88	3.62	7.05	↓2.58	4.23	NT	3.85	0.79
CO ₂ -CP	22.0–29.0 (mmol/L)	↓19.1	↓19.5	↓17.6	↓17.6	22.1	↓16.5	↓20.9	NT	↓15.2	0.79
CK	50–310 (U/L)	134	193	120	288	83	189	142	NT	114	1.00
LDH	120–250 (U/L)	↑285	↑271	235	↑311	212	↑290	↑264	NT	↑329	0.57
HBDH	72–182 (U/L)	↑228	↑214	181	↑257	151	↑240	↑196	NT	↑286	0.57
PT	11.00–16.00 (S)	13.7	13.3	14.6	14.4	13.9	14.3	12.2	NT	13.6	1.00
APTT	27.00–45.00 (S)	32.6	33.6	37.1	30.7	38.4	36.1	33.7	NT	35.6	0.79
TT	11.00–20.00 (S)	13.8	15	16.3	16.9	14	13.7	15.2	NT	14.8	1.00
D-Dimer	0–0.50 (ug/ml)	0.15	0.18	0.06	0.16	0.13	0.13	↑0.63	NT	0.31	0.57

Note: P values denoted the comparison between asymptomatic type and symptomatic type.

Abbreviations: WBC: White blood cell count; NEU: Neutrophil count; LYM: Lymphocyte count; PLT: Platelets; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; PCT: Procalcitonin; TBIL: Total bilirubin; ALB: Albumin; ALT: Alanine amino transferase; AST: Aspartate amino transferase; ALP: Alkaline phosphatase; CREA: Creatinine; UREA: Urea; CO₂-CP: Carbon dioxide combining power; CK: Creatine kinase; LDH: Lactate dehydrogenase; HBDH: α -Hydroxybutyrate dehydrogenase; PT: Prothrombin time; APTT: Partial thromboplastin time; TT: Thrombin time; D-Dimer: D-dimer.

phosphate, cetirizine hydrochloride, or lopinavir and ritonavir tablets. The duration of antiviral treatment ranged from 6 to 16 days. Empirical antibiotic (ceftazidime sodium or amoxicillin flucloxacillin sodium) treatment were performed on four symptomatic cases. Additionally, traditional Chinese medicine including Lianhua Qingwen capsule and Xiaochiqiao-qingre granule were prescribed to two children. None of the patients needed invasive respiratory support or extracorporeal membrane oxygenation. As of March 11, 2020, all the patients had been discharged after hospitalization for a median of 12 days (ranged from 7 to 17 days).

Discussion

Genetic analysis of SARS-CoV-2 has revealed that the virus is a beta-coronavirus that belongs to the family coronavirus within the order Nidovirales [11]. Coronaviruses mainly infect the respiratory tract and cause respiratory syndromes in humans, such as severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and COVID-19 [12,13], all of which are newly emerged infectious diseases that pose a great threat to international public health.

In the present study, we provided clinical and laboratory data of 10 pediatric COVID-19 cases from Huangshi Maternity and Children's Health Hospital in Hubei province. Of them, four were classified as the asymptomatic type, one was the mild type, and five were the moderate type (including two

subclinical cases). All patients in our study were infected through intrafamily transmission. Fever, nasal discharge and nasal congestion were the only symptoms observed upon their admission. All patients had a good prognosis and was discharged within 1–3 weeks after illness onset. These findings suggest that clinical symptoms tend to be mild among children with COVID-19, which is consistent with previous reports, which show that the frequency of confirmed severe and critical cases in children with COVID-19 is significantly lower (3%) compared with the overall frequency (18%) in all infected cases [8,14]. Similarly, during the outbreak of SARS and MERS, the numbers of overall pediatric cases and severe pediatric cases were far lower than those of adult cases; no fatal pediatric cases were reported [15].

Existing reports suggest that laboratory abnormalities frequently observed in COVID-19 patients include elevated white blood cell count, neutrophil count, alanine aminotransferase, LDH, D-dimer, PCT and deranged albumin, and lymphocyte count [16]. These abnormalities tend to be much more prominent in severe or critical adult patients [2,17], indicating their potential role in the assessment of disease severity. However, it remains unclear whether these abnormalities are also applicable to pediatric cases, whose phenotypes tend to be milder. In our report on pediatric cases, few cases with lymphopenia and leukopenia were detected. In contrast, increased lymphocyte count was observed in five patients. Considering that the proportion and absolute count of lymphocyte in children are typically higher than adults, the

significance of this index needs to be verified by a larger sample [18]. On the other hand, increased levels of serum CRP and ESR, which indicate inflammatory response, were observed in patients with symptoms, radiological changes, or a combination of both. However, no statistical difference in these laboratory test results was identified between asymptomatic and symptomatic patients.

It is worth noting that levels of LDH and α -HBDH were increased in six out of eight patients in our study, regardless of whether clinical symptoms were present. Similar findings emerged from the article published by Hu et al. [19] who demonstrated that lymphopenia, leukopenia and other abnormal laboratory findings were uncommon in asymptomatic cases, but relatively more cases (29%, 7/24) presented an elevated level of serum LDH. Zhao et al. [20] compared the abnormal laboratory tests between COVID-19 patients and other pneumonia patients and found that levels of LDH and α -HBDH were abnormal in a larger proportion of COVID-19 patients. Du et al. [21] enrolled 53 adult and 14 children cases with COVID-19 and found that the value and positive rate of LDH in children were more significantly increased than in adults ($p = 0.01$; $p = 0.02$). Additionally, Stockman et al. [15] demonstrated that an elevated level of LDH is one of the most common biochemical abnormalities in children with SARS. Our study further suggests that LDH and α -HBDH could be potential indicators of COVID-19 in pediatric cases;

LDH is a ubiquitously expressed enzyme that catalyzes the interconversion of pyruvic acid and lactic acid; LDH is composed of five isozymes (LDH1-5) [22,23]. α -HBDH has been considered to be an indirect reflection of LDH1 and LDH2 activity and is mainly found in heart muscle and red blood cells [24]. Considering that heart abnormalities are relatively common among patients with COVID-19 [25], elevations of serum LDH and α -HBDH in our report might be a reflection of cardiomyocyte damages. However, since abnormal LDH and α -HBDH have also been reported in other organ dysfunction [26], their practical clinical significance in COVID-19 requires further investigation.

Based on the *Novel Coronavirus Infection Pneumonia Diagnosis and Treatment Standards (Seventh Edition)* published by the National Health Committee, SARS-CoV-2 test results in respiratory samples were used as criteria for diagnosis and discharge. In our report, oropharyngeal swabs were examined for all patients, and two consecutive negative nucleic test results indicated that the patient could be discharged. The results of two patients are of particular note, as their oropharyngeal swabs tested negative but rectal swabs tested positive. One of the two patients even met the criteria of inpatient discharge despite testing positive on the rectal swab, which challenges the current guidelines for discharging COVID-19 patients. Similar results were shown by Cai et al. [27], who found that SARS-CoV-2 was detected in feces at a high frequency, and Xu et al. [28], whose viral RNA measurements suggested that viruses in feces might be greater in number and longer-lasting than those from the respiratory tract. Evidence has mounted of the transmission of SARS-CoV-2 through the digestive tract, and discharged patients may shed virus through defecation for a long time [29]. Chan and his colleagues performed studies on SARS-CoV shedding pattern and the diagnostic yield of

various specimen types [30]. They found that stool or rectal swab specimens provided the highest positive virologic rate and a prolonged viral shedding period. Compared with rectal sampling, another limitation of oropharyngeal sampling for COVID-19 patients is that the relatively invasive collection procedure of oropharyngeal swabs is uncomfortable and can induce coughing and sneezing. This will generate infectious aerosols and increase the risk of medical staff's exposure to virus. Non-standardized sampling procedure may lead to false negative results, especially for young children [31]. Therefore, both prolonged presence of SARS-CoV-2 in feces and potential false negative of the oropharyngeal sample might lead to the observed discrepancies in nucleic test results for rectal versus oropharyngeal swabs in our study. Considering the emergence of discharged patients of return positive nowadays, criteria for hospital discharge and methods for sampling should be reassessed [32,33]. Currently, medical institutions in some parts of China have already included negative nucleic acid testing result of fecal specimens as a criterion for releasing COVID-19 patients [34]. Findings in our study further suggest that SARS-CoV-2 nucleic test results in rectal swab should be considered for the discharge of pediatric cases.

This study has several limitations. First, nucleic tests were not performed daily during patients' hospitalization. Hence, it is difficult for us to monitor the exact dynamic changes of viral shedding. Second, there was a lack of patients with severe symptoms, rendering it impossible to compare the laboratory abnormalities of severe infection with mild infection. Finally, only ten children with confirmed COVID-19 were included in the sample. Our findings need to be verified by studies of larger scale for a more comprehensive understanding of pediatric patients' clinical features.

Conclusions

Even though children infected with SARS-CoV-2 tend to have mild symptoms or no symptoms at all, they can still release viruses. Until now, there is no unified treatment or specific vaccination available for COVID-19, so early identification, timely diagnosis and intense surveillance are vital. Our study suggests that increased levels of serum LDH and α -HBDH are potential clinically useful biomarkers for pediatric cases, and more attention should be paid to the SARS-CoV-2 viral assessment of rectal swabs before patients are discharged.

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Conflicts of interest

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

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