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Clinical characteristics of acute respiratory syndrome with SARS-CoV-2 infection in children in South China

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Abstract

Background: A retrospective study was conducted to summarize the clinical information of childhood infections during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic.

Methods: Children with SARS-CoV-2 infection in 11 hospitals from three provinces of South China were included in the study. Clinical information was collected and compared with children and adults infected by SARS-CoV-2 in Wuhan.

Results: In total, 52 children were enrolled, including 28 boys. The median age was 9 years (interquartile range [IQR], 4-12); 44.2% cases were of clustered occurrences, 40.4% patients had fever, 48.1% had cough, and 46.2% had a high lymphocyte count. No abnormalities were found in the liver and kidney function. Also, 82.7% of patients received antiviral therapy, but such therapy did not shorten the time to virus negativity or hospital stay (P = .082). The time to virus negativity was 12.0 days (IQR, 8.0-16.8) and hospital stay was 14.5 days (IQR, 10.3-17.9). Compared with reports in

Abbreviations: AKI, acute kidney injury; ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; AURTI, acute upper respiratory tract infection; BUN, blood urea nitrogen; CK, creatine kinase; CKMB, creatine kinase-MB; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CRRT, continuous renal replacement therapy; CT, computed tomography; ICU, intensive care unit; IMV, invasive mechanical ventilation; LDH, lactate dehydrogenase; NIV, noninvasive ventilation; PCT, procalcitonin; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Scr, serum creatinine; WBC, white blood cell.

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Wuhan, there were more acute upper respiratory tract infection (AURTI) and fewer pneumonia cases (*P* = .000). Compared with the non-ICU adult COVID-19 in Wuhan, these children's diseases were relatively mild, with fewer complications. **Conclusions:** Children with SARS-CoV-2 infection had a mild fever, lymphocyte elevation was more common than reduction, and antiviral treatment had no obvious effect. The overall clinical manifestations were mild, and the prognosis was good.

KEYWORDS

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

1 | INTRODUCTION

New coronavirus disease (COVID-19) cases caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have increased significantly since the end of 2019, guickly spreading to more than 200 countries and regions^{1,2} and resulting in more than 8000000 COVID-19 infections, with the death toll surpassing 400 000. SARS-CoV-2 is mainly transmitted through respiratory droplets and contact. The whole population is susceptible, and the disease has the characteristics of human-to-human transmission and family clustering.^{3,4} The clinical manifestations of infected patients are mainly fever, cough, and body aches. In severe cases, shortness of breath and cyanosis may occur. Severe symptoms such as respiratory failure, acute respiratory distress syndrome (ARDS), and shock can be life-threatening.⁵⁻⁸ Epidemiologic data have shown that children with SARS-CoV-2 infection have been relatively few as compared with adults so far,⁹⁻¹¹ but pediatric infections have been reported from newborns through 18 year olds.¹²⁻¹⁵ There have been few reports on clinical features and systematic summaries of diagnosis and treatment in children. Therefore, in this study, we collected the epidemiological characteristics, clinical data, diagnosis, therapeutic process, and prognosis in pediatric patients with SARS-CoV-2 admitted to 11 hospitals in the three southern provinces of China before the world epidemic. We conducted a retrospective analysis and compared these data with the reported cases of infection in the representative province of Wuhan.

2 | DATA AND METHODS

2.1 | Study subjects

From 21 January 2020 to 29 February 2020, SARS-CoV-2-infected children, aged 0 to 18 years (excluding newborns), were admitted to 11 hospitals (Guangdong Provincial People's Hospital [GDPH]; People's Hospital of Guangxi Zhuang Autonomous Region; Sanya Central Hospital, Hainan Province; Dongguan Children's Hospital; Affiliated Haikou Hospital of Xiangya Medical College [Central South University]; Jiangmen Central Hospital; Huizhou Third People's Hospital; The Second People's Hospital of Guangdong Province; ZhongShan Second People's Hospital; The First People's Hospital of Foshan; The

Ninth People's Hospital of DongGuan) in the three southern provinces of China. A total of 52 patients were enrolled in the study. These patients were found positive by the SARS-CoV-2 nucleic acid test in oropharyngeal swabs, either outside the hospital or after admission. The diagnostic criteria, diagnosis and treatment principles, and discharge criteria for children with COVID-19^{6,10} were determined according to the Expert Consensus on the Diagnosis and Treatment of Novel Coronavirus Pneumonia. Suspected patients and all patients with negative SARS-CoV-2 tests were excluded.

2.2 | Methods

The clinical data of children were collected from 11 hospitals in three provinces of South China retrospectively. Unified data collection forms were distributed to the researchers of the collaborating institutes, and they investigated and filled out the patients' medical records. The information was collected and summarized by Guangdong Province People's Hospital for statistical processing. The clinical data consisted of age, sex, weight, epidemiological investigation data, clinical symptoms and signs, laboratory and imaging examination data, main plans for diagnosis and treatment, and prognosis. The SARS-CoV-2 test was performed by sending the oropharyngeal swab specimen to the local Center for Disease Control for reversetranscription polymerase chain reaction (RT-PCR) to detect the SARS-CoV-2 nucleic acid. The data used in this study was anonymized before its use. This study protocol was reviewed and approved by the Medical Research Ethics Committee (No. GDREC2020019H) of Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences).

The data from this study of children in the three southern provinces were compared with representative literature data of children infected with SARS-CoV-2¹³ and non-ICU hospitalized adult patients with COVID-19⁵ in the Wuhan area.

To explore the effect of antiviral drugs on SARS-CoV-2 infection in children, all pediatric patients were divided into three groups according to the use of antiviral medications: the antiviral-free group (group A: 9 patients), the single-antiviral medication group (group B: 22 patients), and the two-or-more-antiviral medications group (group C: 21 patients). The differences in sex composition, clinical classification of the disease, time to virus negativity, and length of hospital stay were analyzed.

2.3 | Statistical analysis

This study was a multicenter retrospective study. Categorical variables are described as frequency rates and percentages, and continuous variables are described as mean, median, and interquartile range (IQR) values. Means for continuous variables were compared using one-way analysis of variance when the data were normally distributed; otherwise, the Kruskal-Wallis *H* test was used. Proportions for categorical variables were compared using the χ^2 test; however, Fisher's exact test was used when there were few data. The one-sample Wilcoxon signed rank test was used while comparing our patients with COVID-19 adults in Wuhan. All statistical analyses were done using SPSS (Statistical Package for the Social Sciences) version 19.0 software (SPSS Inc). For unadjusted comparisons, a two-sided α < .05 value was considered statistically significant.

3 | RESULTS

3.1 | Epidemiological characteristics

A total of 52 children from 11 hospitals in the three southern provinces of China were enrolled in the study, including 28 boys (53.9%). Their median age was 9 years (IQR, 4-12), and 11 children (21.1%) were aged 0 to 3. An epidemiological investigation found that 23 (44.2%) cases were of clustering occurrence, 19 (36.5) patients had a history of exposure to novel coronavirus-infected people, and 10 (19.2%) patients had no clear contact history. However, all of them had a history of travel in Wuhan (or Hubei province) or a contact history with relatives or friends in Wuhan. The incidence of SARS-CoV-2 children with clustered infection or exposure to confirmed patients in Wuhan reportedly is reportedly 90.1%, which was similar to the rate in our sample (P > .05).

3.2 | Clinical characteristics and the differences with infections in Wuhan

There were 21 (40.4%) cases of fever that lasted from 1 to 4 days, mainly moderate to low fever (<38.3°C). There were 25 (48.1%) patients with cough, 5 (9.6%) with systemic fatigue and soreness, 3 (9.6%) with sore throat, and 1 (1.9%) with gastrointestinal symptoms. No shortness of breath, cyanosis, or shock were reported in these patients; also, 13 patients were completely asymptomatic (23.1%). According to the classification of the children's SARS-CoV-2 infection consensus,⁶ there were 9 cases of mild pneumonia (17.3%), 30 cases of acute upper respiratory tract infection (57.7%), and 13 cases of asymptomatic infection (23.1%). In this study, there were no cases of severe pneumonia or critical pneumonia (Table 1). Compared with children with SARS-CoV-2 infection in Wuhan,¹³ there was no significant difference in age or sex distribution. The epidemiological findings were mainly clustered recurrence or confirmed contact history with diagnosed patients. In terms of clinical classification, in

the 171 reported pediatric cases in Wuhan, there were 111 cases of mild pneumonia (64.9%), 33 cases of acute upper respiratory infection (19.3%), and 27 cases of asymptomatic infection (15.8%), a distribution that was significantly different from the current study ($\chi^2 = 39.5$; P = .000). In terms of clinical manifestations. 41.5% of previously reported Wuhan children had fever, 48.5% had cough, and 7.6% had fatigue, similar to the results of this study. However, in Wuhan, 28.7% of patients suffered from shortness of breath, which was significantly different from our study (no shortness of breath). This suggests that pediatric infection of SARS-CoV-2 in the Wuhan area was relatively more severe than in the children in this study. In Wuhan, 98% of non-ICU adult inpatients with COVID-19⁵ had fever and 30.4% of the patients had experienced shortness of breath, which were significantly different from the rates in our sample; however, the proportions with symptoms of cough and headache were similar.

3.3 | Auxiliary inspection results and the differences with infections in Wuhan

In the auxiliary tests, 6 (11.5%) patients had low leukocyte counts in the first blood routine at admission, and the median leukocyte count was 6.6×10^{9} /L (IQR, 4.7-8.4). The lymphocyte count was high in 24 (46.2%) cases and low in 6 (11.5%) cases. The median lymphocyte count was 2.4×10^{9} /L (IQR, 1.8-4.3). The procalcitonin level in 28 (68.3%) patients was higher than 0.05 ng/mL, but it was less than 1 ng/mL in all patients. Other routine tests showed no abnormalities (Table 1). Among the reported non-ICU adult COVID-19 patients in Wuhan, the median leukocyte count was 4.3×10^{9} /L (IQR, 3.3-5.4) and the median lymphocyte count was 0.9×10^{9} /L (IQR, 0.6-1.2), which were significantly different from those in the pediatric COVID-19 patients in this study (Table 1). The results of PT, activated partial thromboplastin time (APTT), creatine kinase (CK), creatine kinase-MB (CKMB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and C-reactive protein (CRP) were similar to those of the children in this study. The X-ray or computed tomography (CT) of nine pediatric patients showed minor pulmonary exudation lesions (Figure 1). The changes in chest CT imaging examinations of adults were more obvious than in children.5

3.4 | Treatment process and outcomes; comparison with adult COVID-19 patients in Wuhan

In terms of treatment during hospitalization, all children were isolated and treated symptomatically. Antiviral drugs included ribavirin, arbidol tablets, lopinavir/ritonavir, and recombinant human interferon-alpha, which were appropriately selected by each hospital according to the specific conditions and experiences. In this study, 43 (82.7%) patients received antiviral therapy, 25 (48.1%) patients received antibiotics, and 12 (23.1%) patients received oxygen therapy (Table 2).

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	Clinical charact	Clinical characteristics of 52 children.	ldren, N (%) or median (IQR)	IQR)		A study of children SARS-CoV-2 infection in Wuhan	-CoV-2	A study of adult NCIP (non-ICU) in Wuhan	NCIP Tan
	Total (N = 52)	Mild pneumonia (N = 9)	AURTI (N= 30)	Silent infection (N = 13)	P value	Clinical characteristic (N = 171)	P value*	NCIP (N= 102)	P value**
Age									
1 mo to 3 y old	11 (21.2)	4	4	З	.13	6.7 y	÷	51 (37-62) y	:
4 to 18 y old	41 (78.8)	5	26	10					
Sex and epidemiologic characteristics									
Male	28 (53.9)	6	15	7	.68	104	.370	49	.284
Female	24 (46.1)	ę	15	6		67		53	
Cluster outbreak/contact with infected cases	42 (80.8)	ø	23	11	.54	154 (90.1)	.072	:	÷
Contact with suspected case or unidentified source	10 (19.2)	Ļ	7	2		17 (10)		:	
Comorbidities	0 (0)	0	0	0	:	:	:	:	:
Signs and symptoms									
Fever	21 (40.4)	6 (66.7)	15	0	:	71 (41.5)	.884	100 (98)	000.
Cough	25 (48.1)	8 (88.9)	17	0		83 (48.5)	.954	61 (65.7)	.085
Fatigue	5 (9.6)	1 (11.1)	4	0	:	13 (7.6)	.641	67 (65.7)	.001
Dyspnea	0 (0)	0 (0)	0	0	÷	49 (28.7)	:	31 (30.4)	÷
Pharyngalgia	3 (5.8)	1 (11.1)	2	0	:	:	:	20 (19.6)	.533
Headache	0 (0)	0 (0)	0	0	÷	:	:	12 (11.8)	÷
Abdominal pain/diarrhea/anorexia	1 (1.9)	0 (0)	1	0	÷	26 (15.2)	÷	10 (9.8)	:
Laboratory findings									
WBC, ×109/L	6.6 (4.7-8.4)	8.4 (5.6-10.6)	6.1 (4.2-7.0)	8.2 (4.5-9.0)	.53	:	:	4.3 (3.3-5.4)	.008
Lym, ×109/L	2.4 (1.8-4.3)	2.6 (1.3-5.4)	2.4 (1.8-3.2)	2.7 (1.7-5.0)	.62	:	:	0.9 (0.6-1.2)	.021
PT, s	12.5 (11.6-13.8)	12.1 (11.6-13.4)	12.7 (11.7-14.0)	12.3 (10.6-14.1)	.50	:	:	12.9 (12.3-13.4)	.173
APTT, s	35.4 (29.2-41.3)	34.2 (26.2-38.7)	36.3 (29.5-41.9)	34.1 (29.5-43.1)	.57	:	:	31.7 (29.6-33.5)	.866
CK, U/L	72 (53-110)	65 (32-110)	72 (46-97)	70 (60-149)	.65	:	:	87 (54-121)	.446
CKMB, U/L	17 (14-24)	15 (13-22)	17 (14-23)	17 (16-29)	.33	:	÷	13 (10-14)	.092
LDH, U/L	201 (167-252)	201 (169-337)	197 (166-232)	213 (178-231)	.56	:	:	212 (171-291)	.441
ALT, U/L	15 (12-24)	16 (13-32)	24 (19-37)	14 (10-25)	.50	:	÷	23 (15-36)	.043
AST, U/L	24 (19-36)	29 (22-41)	15 (12-23)	22 (19-37)	.60	:	:	29 (21-38)	.779
CRP	3.4 (0.5-7.5)	5.5 (1.7-10.0)	1.2 (0.5-5.0)	0.5 (0.5-10.0)	.26	:	:	:	:
PCT ≥ 0.05 ng/mL, <i>n</i> (%)	28 (68.3)	2 (33.3)	17	9	90.	:	:	22 (21.6)	.821

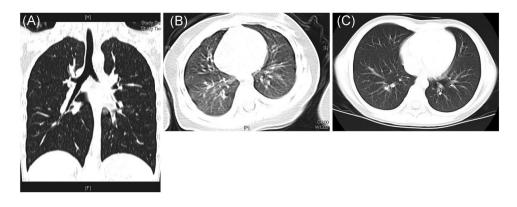


FIGURE 1 Computed tomography changes in lungs of three children with severe acute respiratory syndrome coronavirus 2 infection. A, A little patchy shadow can be seen under the pleura in the left lower lung. B, Ground glass opacity with reduced lung transparency. C, Decreased transparency bilaterally with thicker lung texture

No patients in this study were treated with intravenous glucocorticoids, ventilator-assisted breathing, blood purification, or extracorporeal membrane oxygenation. The clinical manifestations of all pediatric patients gradually improved, and there were no complications of shock, respiratory failure, ARDS, arrhythmia, or acute kidney injury (AKI) (Table 2). Children were discharged when the following criteria were met¹⁰: (a) the body temperature has been normal for more than 3 days; (b) the respiratory symptoms have clearly improved; (c) when criteria (a) and (b) have been met (the child is afebrile and symptoms are resolving), then daily PCR testing is begun and continued until two consecutive negative results are obtained. The median time from admission to the first negative SARS-CoV-2 PCR test on an oropharyngeal swab was 12.0 days (IQR, 8.0-16.8). All children were cured and discharged after a median hospital stay of 14.5 days (IQR, 10.3-17.0). However, five patients, during follow-up after discharge, tested positive again for SARS-CoV-2 on a PCR retest, but had no clinical symptoms or signs. They were rehospitalized, treated in isolation, and subsequently discharged when they tested negative on two consecutive PCR tests performed at 24-hour intervals.

The rates of oxygen therapy and intravenous glucocorticoid usage in the pediatric patients of this study were significantly lower than those of non-ICU adult inpatients with COVID-19 in Wuhan,⁵ whereas the proportion of antiviral usage was similar. The proportion of shock, arrhythmia, ARDS, or AKI of non-ICU adult COVID-19

	N (%) or median (IQR)							
	Total (N = 52)	Mild pneumonia (N = 9)	AURTI (N = 30)	Silent infection (N = 13)	P value	Adult NCIP, non- ICU (N = 102)	P value*	
Treatment								
Antiviral therapy	43 (82.7)	8 (88.9)	27	8		90 (88.2)	.716	
Antibiotics	25 (48.1)	5 (55.6)	17	3				
Glucocorticoid therapy	0 (0)	0	0	0		36 (35.3)	.004	
Oxygen inhalation	12 (23.1)	7 (77.8)	5	0		102 (100)	.006	
IMV/NIV/CRRT/ECMO	0 (0)	0	0	0		0		
Complications Shock/acute cardiac injury Arrhythmia/ ARDS/AKI	O (O)	O(O)	0	0		17 (16.7)	.199	
Prognosis								
Hospital stay, d	14.5 (10.3-17.0)	16.0 (11.0-19.0)	13.5 (9.8-17.0)	15.0 (11.0-18.5)	.66	10 (7.0-14.0)	.024	
Time to virus negativity, d	12.0 (8.0-16.8)	12.0 (9.0-16.5)	12.0 (8.0-17.0)	12.0 (7.0-16.0)	.53			
Virus changed from negative to positive	5 (9.6)	1	3	1				

TABLE 2 Treatments and complications of children infected with SARS-COV-2 and comparison with adults

Abbreviations: ARDS, acute respiratory distress syndrome; AURTI, acute upper respiratory tract infection; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IMV, invasive mechanical ventilation; NCIP, novel coronavirus (2019-nCoV)-infected pneumonia; NIV, noninvasive ventilation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. *Compared with mild pneumonia (N = 9) in our study.

Group No anti One an Two or P value ...

TABLE 3 The effect of antiviral drugs on the prognosis of children with SARS-CoV-2 infection

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		Sex (N) Clin		Clinical classifica	tions (N)		Prognosis (median) (IQR)	
roup	Total, N (%)	Male	Female	Mild pneumonia	AUR- TI	Silent infection	Time to virus negativity, d	Hospital stay, d
o antiviral	9 (17.3)	6	3	1	3	5	11.0 (6.5-14.0)	15.0 (9.0-17.0)
ne antiviral	22 (42.3)	12	10	6	11	5	11.0 (4.8-14.3)	13.0 (8.0-17.0)
wo or more antivirals	21 (40.4)	10	11	2	16	3	16.0 (10.0-19.0)	15.0 (11.5-19.0)

Abbreviations: AURTI, acute upper respiratory tract infection; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

.062

patients in the Wuhan area was as high as 16.7%, much higher than that of the children in this study.

In terms of antiviral efficacy, there was no statistically significant difference in the sex distribution of child patients among the groups that received no antiviral medication (group A), one antiviral medication (group B), and two or more antiviral medications (group C) (P = .629). The clinical classification of the disease was not significantly different (P = .062). The overall time to a negative result for the virus in group A, group B, and group C was 11.0 days (6.5-14.0), 11.0 days (4.8-14.3), and 16.0 days (10.0-19.0), respectively. The length of hospital stay in groups A, B, and C was 15.0 days (9.0-17.0), 13.0 days (8.0-17.0), and 15.0 days (11.5-19.0), respectively, with no significant difference (F = 0.282) (Table 3). This suggested that antiviral drugs had no significant benefit in reducing the time to virus negativity or the length of hospital stay in SARS-CoV-2-infected children.

4 | DISCUSSION

An unexplained viral pneumonia has gradually emerged since December 2019. A new beta-type coronavirus was discovered¹⁶ by etiological whole-genome sequencing of patients' alveolar wash. The World Health Organization and related organizations^{17,18} have named the causative virus SARS-CoV-2. SARS-CoV-2 is highly contagious, and existing patients are the main source of infection. The primary transmission routes are mainly respiratory droplets and contact. Currently, there is no sufficient evidence to confirm the presence of fecal-oral transmission or vertical transmission.¹⁹

Clustered occurrence is an important feature of SARS-CoV-2 infection in children. Children with a family cluster or a clear history of exposure to diagnosed patients make up 80.8% of child cases, whereas asymptomatic infection makes up 23.1% of positive cases. The symptoms of infected children are often mild and nonspecific; fewer than 50% of the children have fever or cough.^{5,20} This makes early diagnosis of SARS-CoV-2 infection in children challenging. A careful epidemiological investigation could help early diagnosis. At the end of the isolation period after discharge, five patients were found to be positive for SARS-CoV-2 infection, but they had no symptoms or signs. This phenomenon is not well understood. The existence of recurrent positive PCR testing after apparent recovery is a challenging feature of its epidemiology.

A few children included in this study were under 3 years of age (21.1%). The reason for the lower proportion of infants and young children is not clear, but it may be related to their limited mobility and low probability of contacting infected people. The role of their immune function cannot be excluded either. One of the consensus diagnostic criteria for novel coronavirus infection in children is normal or low leukocytes or low lymphocytes.⁶ However, this study showed that a normal or high lymphocyte count was more common than a reduction. Adult patients with COVID-19 are more likely to have a low lymphocyte count,⁵ and severe patients had more significant lymphocytopenia than mild patients. The reason for this difference is not clear and warrants further study. Children with SARS-CoV-2 had normal or low leukocyte counts and normal CRP, which is similar to those in children with common viral infections. SARS-CoV-2 may result in severe and critical cases, perhaps due to excessively activated inflammatory reaction^{21,22} and immune dysfunction.²³ In our study, however, the overall condition was mild, without respiratory complications, ARDS, AKI, or shock complications, and there were no severe or critical cases. Compared with children with SARS-CoV-2 infection in Wuhan, the clinical manifestations were similar, but the overall condition was milder.^{9,20} Similar to milder cases of adult COVID-19, no myocardial, liver, or coagulation dysfunction was apparent in children with mild pneumonia.

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Some drugs have been found to be possibly effective for the novel coronavirus pneumonia,²⁴ but there is neither enough evidence nor a specific drug for clinical treatment of COVID-19. The treatment is mainly isolation and symptomatic and supportive therapies.^{10,25} Ribavirin, arbidol, lopinavir/ritonavir, and recombinant human interferon-alpha⁶ are possible anti-SARS-CoV-2 drugs that have been tried during severe epidemics.^{5,26} In this study, 82.7% of patients were administered one or more of these drugs; 42.3% received monotherapy and 40.4% received multiple drugs. The use of antiviral drugs had no significant effect on shortening the length of hospitalization or shortening the time to virus negativity. In contrast, the results suggested that there was a trend toward a longer time for SARS-CoV-2 to turn negative in the patients treated by two or more antiviral drugs, suggesting that antiviral treatment is not beneficial, which is in line with the recent study of a large sample of severe COVID-19 patients treated with lopinavir/ritonavir.²⁶ The children in our study did not receive steroids, as their respiratory status did not deteriorate sufficiently enough to merit this treatment.

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5 | SUMMARY

This study investigated children with SARS-CoV-2 infection in parts of the three provinces in South China. The clinical characteristics were different from those of infected children and adults in Wuhan, Hubei. However, the number of cases in this study was relatively small and there were no severe or critical cases. The lack of representativeness is an obvious limitation.

Our study suggested that children with SARS-CoV-2 infection may have mild fever and no obvious cough; however, the lymphocyte count is more frequently high than low and asymptomatic infection is more common. Antiviral therapy was not beneficial. The overall clinical manifestations were mild, with rare complications and good prognosis. Careful epidemiological investigations are essential for the early diagnosis of new coronavirus infection in children. The phenomenon of virus reactivation after discharge may be a cause for concern, and the contagiousness of asymptomatic infection needs further study.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

GZ, BW, and YG designed and wrote the paper. All authors conducted the clinical studies; WG, YW, and YG analyzed the data. All authors contributed to the study implementation, interpretation, and reporting. All authors have read and approved the manuscript.

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2426 | WILEY-

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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