Comparison of Acute Pneumonia Caused by SARS-COV-2 and Other Respiratory Viruses in Children: A Retrospective Multi-Centered Cohort Study During COVID-19 Outbreak

Guangli Ren (guangliren@hotmail.com)
the genreral hospital of southem theater command of PLA

Xianfeng Wang
The Third People's Hospital of Shenzhen

Jun Xu
Wuhan Children's Hospital

Jun Li
Maternal and Child Health Hospital of Huangshi

Qiong Meng
The second Peoplel's Hospital of Guangdong Province

Guoqiang Xie
Gerneral hospital of Southern Theater Command of PLA

Bo Huang
The third affiliated hospital of Zunyi medical university

Weichun Zhu
Guangzhou Eighth People's Hospital

Jing Lin
Guangzhou Eighth People's Hospital

Chenghe Tang
Xinxiang Medical University First Affiliated Hospital

Sheng Ye
The children's hospital ZheJiang university school of medicine

Zhuo Li
Children's hospital of Nanjing medical university

Jie Zhu
General hospital of southern theater command of PLA

Zhen Tang
General hospital of southern theater command of PLA

Mingxin Ma
General hospital of southern theater command of PLA

Cong Xie
The second affiliated hospital of guangzhou medical university
Fang Yang
Jinan University First Affiliated Hospital
Yuzong Zhou
Maternal and child health hospital of Yangjiang
Ying Zheng
Shenzhen hospital affiliated to the university of Chinese academy of sciences
Shuling Lan
Southern Medical University Nanfang Hospital
Jianfeng Chen
Zhujiang Hospital of Southern Medical University
Feng Ye
Military hospital of 74 Group of PLA
Yu He
Chongqing Medical University Affiliated Children's Hospital
Benqing Wu
Shenzhen hospital affiliated to the university of Chinese academy of sciences
Simao Fu
Zhongshan Boai Hospital
Long Chen
Chongqing Medical University Affiliated Children's Hospital
Chengzhong Zheng
Strategic Support Force Medical Center of PLA
Yuan Shi
Chongqing Medical University Affiliated Children's Hospital

Research

Keywords: Severe Acute Respiratory Syndrome, COVID-19, Viral pneumonia, Cohort study, Children

DOI: https://doi.org/10.21203/rs.3.rs-42751/v1

Abstract

Background Coronavirus disease-2019 (COVID-19) has got more than 12 million infections and causing a certain degree of panic. We conducted this study to describe the clinical manifestations, treatment and outcome of COVID-19 in children, as compared to other viral pneumonia diagnosed during COVID-19 outbreak.

Methods Children with COVID-19 and viral pneumonia of 20 hospitals were enrolled in this retrospective multi-centered cohort study. 64 children with COVID-19 were defined as the COVID-19 cohort, of which 40 cases developed to pneumonia were defined as the COVID-19 pneumonia cohort, while 284 pneumonia cases caused by other viruses were defined as the viral pneumonia cohort.

Results Compared to the viral pneumonia cohort, children in the COVID-19 cohort were mostly exposed to confirmed family members (53/64 vs 23/284), with older median age (6.3 vs 3.2 yr), and shown higher proportion of ground-glass opacity (GGO) on computed tomography (18/40 *vs* 0/38), all *P*□0.001. Children in the COVID-19 pneumonia cohort had lower proportion of severe cases (1/40 *vs* 38/284, *P*=0.048), cases with high fever (3/40 *vs* 167/284, *P*□0.001), cases required intensive care (1/40 *vs*32/284, *P*□0.047) and the symptomatic duration was shorter (median 5 *vs* 8 days, *P*□0.001). The proportion of cases with evaluated inflammatory indicators, biochemical indicators related to organ or tissue damage, D-dimer and secondary infection with bacteria were lower in the COVID-19 pneumonia cohort than that of viral pneumonia cohort (all *P*□0.05). There was no statistic difference in the duration of positive PCR results from pharyngeal swabs when antiviral drugs (Lopinavir-ritonavir, ribavirin, and arbidol) were used in 25 children with COVID-19 as compared to 39 cases without antiviral therapy [median 10 *vs* 9 days, *P*=0.885].

Conclusions The symptoms and severity of COVID-19 pneumonia in children were no more severe than those of other viral pneumonia. Lopinavir-ritonavir, ribavirin and arbidol cannot shorten the duration of positive PCR results from pharyngeal swabs in children with COVID-19 in this study. Children with other pathogens infection should be paid attention to even though the COVID-19 outbreak.

Introduction

Coronaviruses are non-segmented positive-stranded RNA viruses, with protrusions on the surface resembling a corona, with a roughly 30 kb genome surrounded by a protein envelope[1]. Three coronavirus disease outbreaks have happened in the past two decades: severe acute respiratory syndrome (SARS)[2] in 2003, Middle East respiratory syndrome (MERS)[3] in 2012 and now the Corona Virus Disease 2019 (COVID-19)[4]. Since the first case of COVID-19 was reported in Wuhan, China on December of 2019, until 10 July, 2020, SARS-CoV-2 now has got more than 12 million people infected worldwide.

Generally, people from all age groups are susceptible to SARS-CoV-2. However, according to the data published by Chinese Center for Disease Control and Prevention (CCDC), the proportion of SARS-CoV-2

infection in children appears to be lower than that of adults[5]. Several studies[6–8] have described the epidemiologic characteristics and clinical features of children with COVID-19, and showed that most children cases had a clear exposure history and the symptoms were milder than adult infection cases.

Until now, very few studies have reported focus on the treatment of children with COVID-19 and how to identify serious cases during treatment. The similarities and differences between COVID-19 and other viral pneumonia in children, in terms of disease onset, clinical manifestations, characteristics of tests, and treatment responses, remain to be elucidated. So, we conducted a retrospective multi-centered cohort study of acute viral pneumonia in children during COVID-19 outbreak to answer the following three questions.

First, what are the clinical and epidemiological features of children with COVID-19 in our study? Second, what are the disease severity and characters of laboratory tests in children with COVID-19 pneumonia as compared to viral pneumonia caused by other viruses? Third, what are the treatment experience and outcome of COVID-19 as compared to other viral pneumonia in children

Methods

Study design and participants

This was a retrospective multi-centered cohort study. We enrolled children with COVID-19 and pneumonia caused by other viruses diagnosed during COVID-19 outbreak (from Dec 15 to Mar 15, 2020) from 20 hospitals in China. The locations of the 20 participating hospitals were shown on a simplified map (Fig. 1, online only).

Diagnosis of COVID-19 pneumonia was based on guidelines[9] issued by the National Health Commission of China. Cases had positive results on quantitative RT-PCR tests for SARS-CoV-2 sampled by nasopharyngeal or throat swabs were enrolled to the COVID-19 cohort, of which 40 cases developed to pneumonia were defined as the COVID-19 pneumonia cohort.

The children with pneumonia caused by other viruses but negative on SARS-CoV-2 related tests and were enrolled to the viral pneumonia cohort. In order to reduce bias caused by sampling, we reviewed all community acquired pneumonia (CAP) children admitted to the 20 hospitals during COVID-19 outbreak to screen viral pneumonia with identified viruses. The inclusion criteria of the viral pneumonia cohort: 1. Diagnosed with CAP based on the China guideline for diagnosis and treatment of CAP in children (2019 version)[10]; 2. Laboratory virus testing proved existence of viruses associated with pneumonia, including virus or viral antigen in upper-respiratory specimens (eg, nasopharyngeal aspirates) and lower respiratory samples (eg, induced sputum) by culture, immunofluorescence microscopy or molecular diagnostic assays (such as PCR, RT-PCR), and on measurement of antibodies in serum samples; 3. Clinically considered pneumonia mainly caused by the detected virus. The exclusion criteria: 1. Patients older than 18 years older or less than 28 days; 2.The initial pathogen of pneumonia were mycoplasma pneumonia

(MP), bacteria or others, and the detected viruses considered as secondary infection. 3. Parenchyma pathological lesions were found by CT or X-Ray at beginning time.

This study was reviewed and approved by the Medical Ethical Committee of General Hospital of Southern Theater Command of Chinese People's Liberation Army (approval number 2020-04). The written informed consent was waived.

Data Collection

Clinical data on epidemiology, signs and symptoms, underlying diseases, laboratory findings, disease diagnosis, and treatment records were retrospectively reviewed by doctors of the 20 hospitals. Information was recorded in a customized data collection form and was checked by two study investigators (RGL and XGQ) independently. X-ray and computed tomography (CT) images were reviewed and evaluated by two experienced radiologists (at least 5 years of experience in thoracic CT) of each hospital using uniform standards.

Clinical manifestations include respiratory symptoms and signs, gastrointestinal symptoms (diarrhea, vomiting, abdominal pain, and bloating), neurological symptoms (consciousness, response to stimulations, and convulsions), and systemic symptoms (fever, fatigue, and muscle aches). Laboratory findings include the whole blood cell tests, biochemical laboratory tests [liver enzymes, creatine kinase (CK), creatine kinase-MB (CK-MB), and lactate dehydrogenase (LDH)], coagulation function [prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, and D-dimer], humoral immune function (IgG, IgA, and IgM), cellular immune function ($CD4^+$/$CD8^+$ T cells) and infection indicators [C-reactive protein (CRP), procalcitonin (PCT), erythrocyte sedimentation rate (ESR), interleukin-6 (IL-6)]. PCT test value greater than 0.25 ng/mL was considered as elevated level[11]. The real-time reverse transcriptase polymerase chain-reaction (RT-PCR) test of SARS-CoV-2 was done as reported before[12] and was performed using nasopharyngeal swab, nasal swab and/or rectal swab at the local CCDC.

We classified the severity of SARS-CoV-2 infections to asymptomatic infection, mild infection (without pneumonia), moderate infection (with mild pneumonia), severe infection and critical infection, according to the diagnosis and treatment guidelines for COVID-19 (draft version 7)[9] issued by the National Health Commission of China. And, we used the same criteria to assess the severity of other viral pneumonia (mild and severe pneumonia) in children.

Drug usage (antiviral drugs, interferon alpha, antibiotics, glucocorticoids, etc.), immunotherapy (immunoglobulin, immunomodulator, etc.), blood transfusion, and needs for oxygen support were collected as the treatments indexes. Mortality, intensive care needs and symptomatic duration were collected as the outcome indicators.

Statistical analysis

Statistical analysis was done with SPSS, version 20.0. The Kolmogorov-Smirnov test was used to evaluate distribution type. Normally distributed data were expressed as mean ± standard deviation and independent sample t-test was used to make comparison between two cohorts. Non-normally distributed data and ordinal data were expressed as median (inter-quartile range) and Mann-Whitney U test was used to compare the differences between cohorts. Contingency table method was used to check the proportion of count data. *P*-value less than 0.05 was considered as statistically significant.

Results

We recruited 64 pediatric patients in the COVID-19 cohort, among which 33 patients were from Shenzhen, six patients were from Guangzhou, ten patients were from Wuhan, ten patients were from Huangshi, four were from Zunyi and one was from Hangzhou. From December 15th to March 15th, 2020, a total of 4335 cases of children with CAP have been diagnosed in the 20 hospitals, of which 626 cases were clinically diagnosed with viral pneumonia, and finally 284 viral pneumonia cases with confirmed virus were included in the viral pneumonia cohort. The flow chart of recruiting participants was shown in Fig. 2.

The epidemiological and baseline characteristics of over all 348 participants were shown in Table 1. Thirty-one children (48.4%) in the COVID-19 cohort and 161 cases (56.7%) in the viral pneumonia cohort were males, no difference was found among two cohorts, while the age of children in the COVID-19 cohort was older (median 6.3 *vs* 3.2 years). The epidemiological exposure histories of 64 children with COVID-19 were as follows: 53 cases were contacted with confirmed family members, three cases were contacted with other confirmed cases, seven cases had travel or residence in epidemic area of Hubei province, and one case had no clear history of exposure. House hold exposure was higher in the COVID-19 cohort as compared to the viral pneumonia cohort (53/64 *vs* 23/284, *P*0.001). Twelve children with COVID-19 were asymptomatic and 12 cases were with mild symptom but without pneumonia. The prevalence of pneumonia in children with COVID-19 was 62.5% (40/64). The ratios of cases developing from SARS-CoV-2 infection to pneumonia were 4/6 for children younger than 1 year old, 11/20 for 1–5 years old, 15/23 for 6–10 years old, and 10/15 for 11–18 years old in our study, respectively. No statistic difference was found among different age groups (*P* = 0.701).

Table 1
Epidemiological and baseline characteristics of over all 348 participants

General data	COVID-19 cohort (N = 64)	Viral pneumonia cohort (N = 284)	*P*
Age			
Median (range)	6.3 year (3 mon to 18 year)	3.2 year (1 mon to 13 year)	0.001
< 1 year [no. (%)]	6/64 (9.4)	44/284 (15.5)	0.001
1–5 year [no. (%)]	23/64 (35.9)	220/284 (77.5)	
6–10 year [no. (%)]	20/64 (31.2)	19/284 (6.7)	
11–18 year [no. (%)]	15/64 (18.8)	1/284 (0.4)	
Gender [male (%)]	31/64 (48.4)	161/284 (56.7)	0.230
Underlying chronic disease [no. (%)]	2/64 (3.1)	19/284 (6.7)	0.279
Chronic lung disease (repeated wheezing)	1/64 (1.6)	14/284 (4.9)	0.231
Heart disease	0/64 (0.0)	1/284 (0.4)	1.000
Others	1/64 (1.6)	5/284 (1.8)	1.000
Exposure history [no. (%)]*			
Contacted with confirmed family members	53/64 (82.8)	23/284 (8.1)	0.001
Contacted with other confirmed cases	3/64 (4.7)	15/284 (5.3)	
Travel or residence in epidemic area*	7/64 (10.9)	0/284 (0.0)	
No clear exposure history	1/64 (1.6)	246/284 (86.6)	
*No epidemic area was defined for other respiratory viruses.			

To ensure the comparability between cohorts, COVID-19 with pneumonia were filtered out (the COVID-19 pneumonia cohort) to compared to the viral pneumonia cohort in terms of clinical manifestations, the spectrum of disease severity and laboratory findings at admission (Table 2). There were no differences of gastrointestinal symptoms (3/40 *vs* 17/284) and dry cough (6/40 *vs* 35/284) between two cohorts, but the proportions of cases with fever (37.3°C, 22/40 *vs* 221/284), high fever (39.0°C, 3/40 *vs* 167/284), cough with sputum production (0/40 *vs* 229/284), rhinitis (1/40 *vs* 130/284), and wheezing (0/40 *vs* 43/284) were lower in the COVID-19 pneumonia cohort as compared with the viral pneumonia cohort (all

P□0.05). In addition, the duration of fever was shorter in the COVID-19 pneumonia cohort as compared to the viral pneumonia cohort [median (IQR), 2 (1-3.25) *vs* 4 (2–5) days, *P* = 0.004)].

Table 2
Symptoms, signs, disease severity, laboratory and radiographic findings of COVID-19 pneumonia and other viral pneumonia

Measures	COVID-19 pneumonia (N = 40)	Viral pneumonia (N = 284)	*P*
Symptoms and signs			
Fever [no. (%)]	22/40 (55.0)	221/284 (77.8)	0.001
Duration of fever [days, median (IQR)]	2.00 (1.00-3.25)	4.00 (2.00–5.00)	0.004
Highest temperature [no. (%)]			
< 37.3 °C	18/40 (45.0)	63/284 (22.2)	0.001
37.4–37.9 °C	8/40 (20.0)	8/284 (2.8)	
38.0–38.9 °C	11/40 (27.5)	46/284 (16.2)	
> 39.0 °C	3/40 (7.5)	167/284 (58.8)	
Cough [no. (%)]	6/40 (15.0)	256/284 (90.1)	0.001
Dry cough [no. (%)]	6/40 (15.0)	35/284 (12.3)	0.634
Cough with Sputum production [no. (%)]	0/40 (0.0)	229/284 (80.6)	0.001
Sore throat [no. (%)]	1/40 (2.5)	8/284 (2.8)	0.909
Rhinitis [no. (%)]	1/40 (2.5)	130/284 (45.8)	0.001
Short of breath [no. (%)]	1/40 (2.5)	22/284 (7.7)	0.226
Wheezing [no. (%)]	0/40 (0.0)	43/284 (15.1)	0.017
Gastrointestinal symptoms [no. (%)]	1/40 (2.5)	17/284 (6.0) (	0.709
Fatigue or muscle aches [no. (%)]	1/40 (2.5)	12/284 (4.2)	0.603
Neurological symptoms [no. (%)]	2/40 (5.0)	15/284 (5.3)	0.940
Three depression sign [no. (%)]	1/40 (2.5)	36/284 (12.7)	0.058

WBC: White blood cell; PCT: Procalcitonin; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IL-6: Interleukin-6; LDH: Lactate dehydrogenase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CK: Creatine kinase; CK-MB: Creatine kinase – MB; APTT: Activated partial thromboplastin time; MP: Mycoplasma pneumonia; GGO: Ground-glass opacity.

The denominator of the proportional count in the table was the total number of evaluated cases, and the numerator is the number of cases positive on this index.

Measures	COVID-19 pneumonia (N = 40)	Viral pneumonia (N = 284)	*P*
Low SaO2 of inhospital (95%) [no. (%)]	1/40 (2.5)	9/284 (3.2)	0.819
Severity [no. (%)]			
Moderate	39/40 (97.5)	246/284 (86.6)	0.048
Server or critical	1/40 (2.5)	38/284 (13.4)	
Blood routine			
WBC count [× 109/L; median (IQR)]	5.3 (4.4–7.8)	8.6 (6.3–12.1)	0.001
< 5.5 × 109/L [no. (%)]	19/40 (47.5)	38/284 (13.4)	0.001
Neutrophil count [× 109/L; median (IQR)]	2.5 (1.9–3.3)	3.2 (2.1–4.6)	0.029
< 1.1 × 109/L [no. (%)]	3/40 (7.5)	12/284 (4.2)	0.356
Platelet count [× 109/L; median (IQR)]	253.0 (217.3–320.0)	275.0 (209.0-350.0)	0.410
< 120 × 109/L [no. (%)]	1/40 (2.5)	9/284 (3.2)	0.819
Inflammatory indicators [no. (%)]			
PCT (> 0.25 ng/mL)	2/34 (5.9)	78/209 (37.3)	0.001
CRP (> 10 mg/L)	5/38 (13.2)	80/281 (28.5)	0.045
ESR (> 20 seconds)	5/36 (13.9)	35/62 (56.5)	0.001
IL-6 (> 20.9 ng/L)	5/34 (14.7)	62/168 (36.9)	0.012
Blood biochemistry			
LDH [U/L; median (IQR)]	210.0 (187.0-482.4)	349.0 (228.5-418.5) ()	0.001
> 300 U/L [no. (%)]	13/26 (36.1)	131/265 (49.4)	0.001
ALT [U/L; median (IQR)]	12.5 (9.25-24.0)	17 (13–23)	0.035
> 45 U/L [no. (%)]	4/40 (10.0)	18/275 (6.5)	0.432

WBC: White blood cell; PCT: Procalcitonin; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IL-6: Interleukin-6; LDH: Lactate dehydrogenase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CK: Creatine kinase; CK-MB: Creatine kinase – MB; APTT: Activated partial thromboplastin time; MP: Mycoplasma pneumonia; GGO: Ground-glass opacity.

The denominator of the proportional count in the table was the total number of evaluated cases, and the numerator is the number of cases positive on this index.

Measures	COVID-19 pneumonia (N = 40)	Viral pneumonia (N = 284)	*P*
AST [U/L; median (IQR)]	33.9 (19.8–41.3)	37.0 (31.0–45.0)	0.011
> 50 U/L [no. (%)]	4/40 (10.0)	36/276 (13.0)	0.588
CK [U/L; median (IQR)]	70.0 (57.0-91.8)	110.5 (79.3-155.8)	0.001
> 185 U/L [no. (%)]	2/35 (5.7)	48/276 (17.4)	0.076
CK-MB (> 27 U/L) [no. (%)]	5/35 (14.3)	165/270 (61.1)	0.001
Humoral immunity [g/L; median (IQR)]			
Ig G	8.1 (4.8–10.6)	8.4 (6.9–10.2)	0.712
Ig M	1.3 (1.0-1.6)	1.3 (0.9–1.6)	0.995
Ig A	1.0 (0.5–1.3)	0.9 (0.6–1.4)	0.218
Cellular immunity			
CD4+/CD8 + T cell [median (IQR)]	1.2 (0.9–1.6)	1.2 (0.9–1.8)	0.534
< 0.96 [no. (%)]	6/17 (35.3)	4/16 (25.0)	0.479
0.96–2.05 [no. (%)]	10/17 (58.8)	9/16 (56.2)	
> 2.05 [no. (%)]	1/17 (5.9)	3/16 (18.8)	
Coagulation			
Fibrinogen [g/L; median (IQR)]	2.5 (2.4-3.0)	3.1 (2.4–3.9)	0.114
D-dimer [mg/L; median (IQR)]	0.32 (0.25–0.42)	0.53 (0.33-1.00)	0.004
> 0.5 mg/L [no. (%)]	7/35 (20.0)	18/29 (62.1)	0.001
Prothrombin time [seconds; median (IQR)]	11.2 (10.2–13.3)	11.2 (10.3–13.0)	0.113
APTT [seconds; median (IQR)]	34.7 (31.3–36.4)	31.6 (25.8–35.7)	0.111
Co-infection [no. (%)]			
Virus	3/40 (7.5)	22/284 (7.7)	0.956

WBC: White blood cell; PCT: Procalcitonin; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IL-6: Interleukin-6; LDH: Lactate dehydrogenase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CK: Creatine kinase; CK-MB: Creatine kinase – MB; APTT: Activated partial thromboplastin time; MP: Mycoplasma pneumonia; GGO: Ground-glass opacity.

The denominator of the proportional count in the table was the total number of evaluated cases, and the numerator is the number of cases positive on this index.

Measures	COVID-19 pneumonia (N = 40)	Viral pneumonia (N = 284)	*P*
MP	9/40 (22.5)	61/284 (21.5)	0.883
Secondary-infection with bacteria [no. (%)]	0/40 (0.0)	52/284 (18.3)	0.003
Affected area on radiography [no. (%)]			
— no. (%)			
Left lung lobe	5/40 (12.5)	18/202 (8.9)	0.071
Right lung lobe	14/40 (35.0)	41/202 (20.3)	
Bilateral lung lobe	21/40 (52.5)	143/202 (70.8)	
CT images of the chest [no. (%)]			
GGO	18/40 (45.0)	0/38 (0.0)	0.001
Tiny nodules	6/40 (15.0)	2/38 (5.3)	0.297
Consolidation	5/40 (12.5)	21/38 (55.3)	0.001
Consolidation combined with GGO	4/40 (10.0)	1/38 (2.6)	0.387
Cable shadow	11/40 (27.5)	18/38 (47.4)	0.070
Light shadow	6/40 (15.0)	5/38 (13.2)	0.815
Streak shadow	6/40 (15.0)	6/38 (15.8)	0.923
Hydrothorax	1/40 (2.5)	1/38 (2.6)	1.000

WBC: White blood cell; PCT: Procalcitonin; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IL-6: Interleukin-6; LDH: Lactate dehydrogenase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CK: Creatine kinase; CK-MB: Creatine kinase – MB; APTT: Activated partial thromboplastin time; MP: Mycoplasma pneumonia; GGO: Ground-glass opacity.

The denominator of the proportional count in the table was the total number of evaluated cases, and the numerator is the number of cases positive on this index.

Only one child was in a critical condition in the COVID-19 pneumonia cohort, of whom the clinical manifestations including short of breath, neurological symptom (drowsiness), three depressions sign, low blood oxygen saturation and increased PCT, CRP, D-dimer and CK-MB on admission, and was received intubation and invasive ventilator-assisted ventilation immediately after admission.

The proportion of children who developed severe condition was lower in the COVID-19 pneumonia cohort as compared to the viral pneumonia cohort (1/40 *vs* 38/284, $P = 0.048$) and subgroup pneumonia caused by respiratory syncytial virus (RSV) (1/40 *vs*19/133, $P = 0.041$) and human adenovirus (1/40 *vs*7/25, $P = 0.002$), while no statistic difference was found as compared to pneumonia caused by influenza A and B

(1/40 *vs* 5/57, *P* = 0.182) or parainfluenza virus (1/40 *vs* 3/29, *P* = 0.168). The comparison between children with COVID-19 pneumonia and pneumonia caused by other four common types of respiratory viruses was shown in the Table 3 (online only).

Table 3
(online only). The comparison between pneumonia caused by SARS-COV-2 and other four common kinds of respiratory viruses

Measures	COVID-19 pneumonia (N = 40)	RSV pneumonia (N = 133)	Influenza A and B pneumonia (N = 57)	Parainfluenza virus pneumonia (N = 29)	Human adenovirus pneumonia (N = 25)
Age					
Median (yr)	7.0	2.6	4.0	3.4	3.9
< 1 year [no. (%)]	4/40 (10.0)	25/133 (18.8)	6/57 (10.5)	5/29 (17.2)	1/25 (4.0)
1–5 year [no. (%)]	11/40 (27.5)	108/133 (81.2)	42/57 (73.7)	23/29 (79.3)	17/25 (68.0)
6–10 year [no. (%)]	15/40 (37.5)	0/133 (0.0)	8/57 (14.0)	1/29 (3.4)	7/25 (28.0)
11–18 year [no. (%)]	10/40 (25.0)	0/133 (0.0)	1/57 (1.8)	0/29 (0.0)	0/25 (0.0)
Gender [male (%)]	18/40 (45.0)	73/133 (54.9)	30/57 (52.6)	19/29 (65.5)	16/25 (64.0)
Underlying chronic disease [no. (%)]	2/40 (5.0)	10/133 (7.5)	3/57 (5.3)	1/29 (3.4)	2/25 (8.0)
Chronic lung disease (repeated wheezing)	1/40 (1.6)	5/133 (3.8)	2/57 (3.5)	1/29 (3.4)	2/25 (8.0)
Heart disease	0/40 (0.0)	1/133 (0.8)	0/57 (0.0)	0/29 (0.0)	0/25 (0.0)
Others	1/40 (1.6)	4/133 (3.0)	1/57 (1.8)	0/29 (0.0)	0/25 (0.0)
Symptoms and signs					

WBC: White blood cell; PCT: Procalcitonin; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IL-6: Interleukin-6; LDH: Lactate dehydrogenase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CK: Creatine kinase; CK-MB: Creatine kinase – MB; RSV: respiratory syncytial virus; GGO: Ground-glass opacity.

*The blank in the column of co-infection was because viral pneumonia caused by multiple viruses was not included in this comparison. Of the 284 cases of viral pneumonia, 133 were caused by RSV, 57 were caused by influenza A or influenza B, 29 were caused by parainfluenza virus, 25 were caused by human adenovirus, 22 were caused by multiple viruses, six were caused by human rhinovirus, six were caused by human Boca virus and six cases were caused by other viruses. The comparison was made between pneumonia caused by SARS-COV-2 and other four common kinds of respiratory viruses.

Measures	COVID-19 pneumonia (N = 40)	RSV pneumonia (N = 133)	Influenza A and B pneumonia (N = 57)	Parainfluenza virus pneumonia (N = 29)	Human adenovirus pneumonia (N = 25)
Fever [no. (%)]	22/40 (55.0)	105/133 (78.9)	49/57 (86.0)	15/29 (51.7)	22/25 (88.0)
Duration of fever [days; median (IQR)]	2 (1–3)	3 (2–5)	4 (2.5-6)	3 (2–4)	5 (2-8.25)
Highest temperature [no. (%)]					
< 37.3 °C	18/40 (45.0)	28/133 (21.0)	8/57 (14.0)	14/29 (48.3)	3/25 (12.0)
37.4–37.9 °C	8/40 (20.0)	7/133 (5.3)	0/57 (0.0)	0/29 (0.0)	0/25 (0.0)
38.0–38.9 °C	11/40 (27.5)	23/133 (17.3)	12/57 (21.0)	4/29 (13.8)	0/25 (0.0)
> 39.0 °C	3/40 (7.5)	75/133 (56.4)	37/57 (64.9)	11/29 (37.9)	22/25 (88.0)
Cough [no. (%)]	6/40 (15.0)	119/133 (89.5)	53/57 (93.0)	26/29 (89.6)	19/25 (76.0)
Dry cough [no. (%)]	6/40 (15.0)	12/133 (9.0)	8/57 (14.0)	1/29 (3.4)	6/25 (24.0)
Cough with Sputum production [no. (%)]	0/40 (0.0)	119/133 (89.5)	45/57 (78.9)	25/29 (86.2)	13/25 (52.0)
Sore throat [no. (%)]	1/40 (2.5)	2/133 (1.5)	5/57 (8.8)	0/29 (0.0)	1/25 (4.0)
Rhinitis [no. (%)]	1/40 (2.5)	65/133 (48.9)	21/57 (36.8)	18/29 (62.1)	8/25 (32.0)

WBC: White blood cell; PCT: Procalcitonin; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IL-6: Interleukin-6; LDH: Lactate dehydrogenase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CK: Creatine kinase; CK-MB: Creatine kinase – MB; RSV: respiratory syncytial virus; GGO: Ground-glass opacity.

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Measures	COVID-19 pneumonia (N = 40)	RSV pneumonia (N = 133)	Influenza A and B pneumonia (N = 57)	Parainfluenza virus pneumonia (N = 29)	Human adenovirus pneumonia (N = 25)
Short of breath [no. (%)]	1/40 (2.5)	13/133 (9.8)	3/57 (5.3)	1/29 (3.4)	2/25 (8.0)
Wheezing [no. (%)]	0/40 (0.0)	28/133 (21.0)	3/57 (5.3)	2/29 (6.9)	2/25 (8.0)
Gastrointestinal symptoms [no. (%)]	1/40 (2.5)	7/133 (5.3)	4/57 (7.0)	2/29 (6.9)	1/25 (4.0)
Fatigue or muscle aches [no. (%)]	1/40 (2.5)	2/133 (1.5)	10/57 (17.5)	0/29 (0.0)	0/25 (0.0)
Neurological symptoms [no. (%)]	2/40 (5.0)	8/133 (6.0)	6/57 (10.5)	0/29 (0.0)	0/25 (0.0)
Three depressions sign [no. (%)]	1/40 (2.5)	20/133 (15.0)	3/57 (5.3)	3/29 (10.3)	5/25 (20.0)
Low SaO_2 of inhospital (< = 95%) [no. (%)]	1/40 (2.5)	4/133 (3.0)	1/57 (1.8)	1/29 (3.4)	3/25 (12.0)
Symptom duration [Days; median (IQR)]	5 (0–8)	8 (5–10)	8 (5–10)	9 (6–11)	9 (4–12)
Severity [no. (%)]					
Moderate	39/40 (97.5)	114/133 (85.7)	52/57 (91.2)	26/29 (89.7)	18/25 (72.0)
Server or critical	1/40 (2.5)	19/133 (14.3)	5/57 (8.8)	3/29 (10.3)	7/25 (28.0)
Blood routine					

WBC: White blood cell; PCT: Procalcitonin; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IL-6: Interleukin-6; LDH: Lactate dehydrogenase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CK: Creatine kinase; CK-MB: Creatine kinase – MB; RSV: respiratory syncytial virus; GGO: Ground-glass opacity.

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Measures	COVID-19 pneumonia (N = 40)	RSV pneumonia (N = 133)	Influenza A and B pneumonia (N = 57)	Parainfluenza virus pneumonia (N = 29)	Human adenovirus pneumonia (N = 25)
WBC [× 10^9/L; median (IQR)]	5.3 (4.4–7.8)	8.6 (6.3–11.5)	7.0 (5.7–9.8)	7.7 (6.0-12.3)	9.3 (6.9–14.3)
< 5.5 × 10^9/L [no. (%)]	19/40 (47.5)	17/133 (12.8)	14/57 (24.6)	4/29 (13.8)	2/25 (8.0)
Neutrophil count [× 10^9/L; median (IQR)]	2.5 (1.9–3.3)	3.5 (2.2–4.8)	2.3 (1.6–3.9)	3.3 (2.6–4.9)	3.0 (1.8–4.4)
< 1.1 × 10^9/L [no. (%)]	3/40 (7.5)	0/133 (0.0)	10/57 (17.5)	0/29 (0.0)	1/25 (4.0)
Platelet count [× 10^9/L; median (IQR)]	253.0 (217.2.0-320.0)	285.0 (224.0-366.8)	246.5 (187.3-298.5)	262.0 (173.5–325.0)	259.0 (193.0-313.8)
< 120 × 10^9/L [no. (%)]	1/40 (2.5)	5/133 (3.8)	2/57 (3.5)	1/29 (3.4)	1/25 (4.0)
Infection biomarkers[no. (%)]					
PCT (> 0.25 ng/mL)	2/34 (5.9)	28/88 (31.8)	15/46 (32.6)	7/19 (36.8)	14/21 (66.7)
CRP (> 10 mg/L)	5/38 (13.2)	25/131 (19.1)	24/57 (42.1)	4/28 (14.3)	16/25 (64.0)
ESR (> 20 seconds)	5/36 (13.9)	12/22 (54.5)	10/18 (55.6)	1/5 (20%)	9/12 (7.5)
IL-6 (> 20.9 ng/L)	5/34 (14.7)	25/80 (31.2)	9/31 (29.0)	6/17 (35.3)	15/23 (65.2)
Blood biochemistry					

WBC: White blood cell; PCT: Procalcitonin; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IL-6: Interleukin-6; LDH: Lactate dehydrogenase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CK: Creatine kinase; CK-MB: Creatine kinase – MB; RSV: respiratory syncytial virus; GGO: Ground-glass opacity.

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Measures	COVID-19 pneumonia (N = 40)	RSV pneumonia (N = 133)	Influenza A and B pneumonia (N = 57)	Parainfluenza virus pneumonia (N = 29)	Human adenovirus pneumonia (N = 25)
LDH [U/L; median (IQR)]	210.0 (187.0-482.4)	361.0 (303.5-418.5)	363.5 (269.5-489.8)	310.5 (288.0-361.8)	342.0 (286.0-405.0)
> 300 U/L [no. (%)]	13/36 (36.1)	97/125 (77.6)	33/50 (66.0)	18/28 (64.3)	17/25 (68.0)
ALT [U/L; median (IQR)]	12.5 (9.25-24.0)	18.0 (14.0–24.0)	15.0 (12.3–20.8)	16.5 (13.0–19.0)	15.5 (9.3–19.3)
> 45 U/L [no. (%)]	4/40 (10.0)	7/130 (5.4)	3/56 (5.4)	0/28 (0.0)	5/24 (20.8)
AST [U/L; median (IQR)]	33.9 (19.8–41.3)	38.5 (33.0–46.0)	39.0 (28.5–46.8)	36.5 (32.3–42.3)	29.0 (23.0-37.5)
> 50 U/L [no. (%)]	4/40 (10.0)	19/130 (14.6)	8/56 (14.3)	2/28 (7.1)	1/25 (4.0)
CK [U/L; median (IQR)]	70.0 (57.0-91.8)	113.0 (82.0-154.3)	122.5 (88.0-179.0)	110.5 (84.3–181.0)	86.0 (49.0-154.5)
> 185 U/L [no. (%)]	2/35 (5.7)	23/130 (17.7)	12/56 (21.4)	7/28 (25.0)	4/25 (16.0)
CK-MB (> 27 U/L) [no. (%)]	5/35 (14.3)	87/126 (69.0)	21/56 (37.5)	22/29 (75.9)	15/24 (62.5)
Humoral immunity [g/L; median (IQR)]					
Ig G	8.1 (4.8–10.6)	8.4 (6.4–10.2)	8.4 (6.9–10.6)	8.5 (6.5–10.6)	8.9 (7.2–9.9)
Ig M	1.3 (1.0-1.6)	1.3 (0.8–1.8)	1.2 (1.1–1.5)	1.3 (1.0-1.8)	1.3 (0.9–1.5)

WBC: White blood cell; PCT: Procalcitonin; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IL-6: Interleukin-6; LDH: Lactate dehydrogenase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CK: Creatine kinase; CK-MB: Creatine kinase – MB; RSV: respiratory syncytial virus; GGO: Ground-glass opacity.

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Measures	COVID-19 pneumonia (N = 40)	RSV pneumonia (N = 133)	Influenza A and B pneumonia (N = 57)	Parainfluenza virus pneumonia (N = 29)	Human adenovirus pneumonia (N = 25)
lg A	1.0 (0.5–1.3)	0.8 (0.5 – 0.1.3)	0.9 (0.5–1.4)	0.9 (0.6–1.4)	1.0 (0.7–1.2)
Co-infection [no. (%)]					
Virus*	3/40 (7.5)				
Mycoplasma pneumoniae	9/40 (22.5)	21/133 (15.8)	16/57 (28.1)	2/29 (6.9)	9/25 (36.0)
Secondary-infection with Bacteria [no. (%)]	0/40 (0.0)	25/133 (18.8)	6/57 (10.5)	6/29 (20.7)	5/25 (20.0)
Affected area on radiography [no. (%)] **— no. (%)**					
Left lung lobe	5/40 (12.5)	2/81 (2.5)	9/52 (17.3)	2/23 (8.7)	0/17 (0.0)
Right lung lobe	14/40 (35.0)	16/81 (19.7)	17/52 (32.7)	3/23 (13.0)	1/17 (5.9)
Bilateral lung lobe	21/40 (52.5)	63/81 (77.8)	26/52 (50.0)	18/23 (78.3)	16 (94.1)
CT images of the chest [no. (%)]					
GGO	18/40 (45.0)	0/12 (0.0)	0/9 (0.0)	0/2 (0.0)	0/7 (0.0)
Tiny nodules	6/40 (15.0)	0/12 (0.0)	1/9 (11.1)	0/2 (0.0)	0/7 (0.0)
Consolidation	5/40 (12.5)	2/12 (16.7)	8/9 (88.9)	1/2 (50.0)	4/7 (57.1)

WBC: White blood cell; PCT: Procalcitonin; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IL-6: Interleukin-6; LDH: Lactate dehydrogenase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CK: Creatine kinase; CK-MB: Creatine kinase – MB; RSV: respiratory syncytial virus; GGO: Ground-glass opacity.

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Measures	COVID-19 pneumonia (N = 40)	RSV pneumonia (N = 133)	Influenza A and B pneumonia (N = 57)	Parainfluenza virus pneumonia (N = 29)	Human adenovirus pneumonia (N = 25)
Consolidation combined with GGO	4/40 (10.0)	1/12 (8.3)	0/9 (0.0)	0/2 (0.0)	0/7 (0.0)
Cable shadow	11 (27.5)	5/12 (41.7)	4/9 (44.4)	0/2 (0.0)	5/7 (71.4)
Light shadow	6 (15.0)	1/12 (8.3)	2/9 (22.2)	1/2 (50.0)	0/7 (0.0)
Streak shadow	6 (15.0)	5/12 (41.7)	0/9 (0.0)	0/2 (0.0)	0/7 (0.0)
Hydrothorax	1 (2.5)	0/12 (0.0)	0/9 (0.0)	0/2 (0.0)	1/7 (14.3)

WBC: White blood cell; PCT: Procalcitonin; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IL-6: Interleukin-6; LDH: Lactate dehydrogenase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CK: Creatine kinase; CK-MB: Creatine kinase – MB; RSV: respiratory syncytial virus; GGO: Ground-glass opacity.

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On admission, counts of white blood cell and lymphocyte of COVID-19 pneumonia children were lower than those of other viral pneumonia (all P□0.05). The proportion of cases with leucopenia (white blood cell counts□5.5 × 10□/L) was higher in the COVID-19 cohort (19/40 *vs* 53/284). Levels of LDH (median 210.0 *vs* 349.0 U/L), ALT (median 12.5 *vs* 17.0 U/L), AST (median 33.9 *vs* 37.0 U/L), CK (median 70.0 *vs* 110.5 U/L), D-dimer (median 0.32 *vs* 0.53 mg/L), and the proportion of cases with elevated LDH (13/36 *vs* 131/265), CK-MB (5/35 *vs* 165/270), PCT (2/34 *vs* 78/209), CRP (5/38*vs*80/281), ESR (5/36 *vs* 35/62), IL-6 (5/34 *vs*62/168) and D-dimer (□0.5 mg/L, 7/35 *vs* 18/29) were lower in the COVID-19 pneumonia cohort as compared to the viral pneumonia cohort (all P□0.05). No statistic difference was noted between the two cohorts in terms of co-infection with other viruses (3/40 *vs* 22/284, P = 0.956) or co-infection with MP (9/40 *vs* 61/284, P = 0.883). However, secondary-infection with bacteria was less frequently detected in the COVID-19 pneumonia cohort (0/40 *vs* 52/284, P = 0.003).

Ground-glass opacity (GGO) was the most common radiographic presentation of children with COVID-19 pneumonia. The proportion of cases with GGO was significantly higher (18/40 *vs* 0/38, P□0.001), while the proportion of cases with consolidation (5/40 *vs* 21/38, P□0.001) was lower in COVID-19 pneumonia cohort as compared to the viral pneumonia cohort. Other radiographic presentations of COVID-19 pneumonia included tiny nodules, consolidation combined with GGO, cable shadow, light shadow, streak shadow and hydrothorax, had no statistical difference as compared to the viral pneumonia cohort (Table 2).

Treatments and outcome of children with COVID-19 pneumonia and other viral pneumonia were listed on Table 4. The proportion of received were higher in the COVID-19 pneumonia cohort, but the proportion of received oseltamivir was lower, as compared to the viral pneumonia cohort (all P<0.05). The proportion of children with COVID-19 pneumonia received oseltamivir (1/40 *vs* 65/284, P = 0.003), antibiotics (8/40 *vs* 261/284, P<0.001), corticosteroids (1/40 *vs* 50/284, P = 0.014), immunoglobulin (1/40 *vs* 39/284, P = 0.043) and needs for oxygen support (P = 0.024) were lower, but the proportion of cases received interferon alfa (2–4 ug/kg per day, 38/40 *vs* 15/284, P<0.001), lopinavir–ritonavir (9/40 *vs* 0/284, P<0.001) and ribavirin (4/40 *vs* 2/284, P<0.001) was higher than that of other viral pneumonia.

Table 4
Treatments and outcome of COVID-19 pneumonia and other viral pneumonia

Measures	COVID-19 pneumonia (N = 40)	Viral pneumonia (N = 284)	*P*
Antiviral therapy [Yes, no. (%)]	14/40 (35.0)	71/284 (25.0)	0.178
Lopinavir–ritonavir	9/40 (22.5)	0/284 (0.0)	0.001
Ribavirin	4/40 (10.0)	2/284 (0.7)	0.001
Arbidol	1/40 (2.5)	0/284 (0.0)	0.252
Oseltamivir	1/40 (2.5)	65/284 (22.9)	0.003
Paramive	0/40 (0.0)	4/284 (1.4)	1.000
Others	0/40 (0.0)	3/284 (1.1)	1.000
Interferon alfa [no. (%)]	38/40 (95.0)	15/284 (5.3)	0.001
Antibiotic therapy [Yes, no. (%)]	8/40 (20.0)	261/284 (91.9)	0.001
None	32/40 (80.0)	23/284 (8.1)	0.001
One kind	4/40 (10.0)	151/284 (53.2)	
Two kinds	3/40 (4.7)	99/284 (34.9)	
Three or more kinds	1/40 (2.5)	11/284 (3.9)	
Corticosteroids [no. (%)]	1/40 (2.5)	50/284 (17.6)	0.014
Immunoglobulin [no. (%)]	1/40 (2.5)	39/284 (13.7)	0.043
Blood transfusion [no. (%)]	1/40 (2.5)	4/284 (1.4)	1.000
Oxygen support [no. (%)]			
None	39/40 (97.5)	238/284 (83.8)	0.024
Nasal catheter, mask or other	0/40 (0.0)	22/284 (7.7)	
Non-invasive ventilation	0/40 (0.0)	8/284 (2.8)	
Invasive mechanical ventilation	1/40 (2.5)	16/284 (5.6)	
Mortality [no. (%)]	0/40 (0.0)	1/284 (0.4)	1.000
Required ICU support [no. (%)]	1/40 (2.5)	32/284 (11.3)	0.047
Symptomatic duration [Days; median (IQR)]	5 (0–8)	8 (4–12)	0.001

*The duration of hospital stay was not used as a prognostic indicator in this study, because many children with COVID-19 were observed in the hospital after the symptoms completely disappeared for the possibility of infectivity.

Measures	COVID-19 pneumonia (N = 40)	Viral pneumonia (N = 284)	*P*
Hospital stay [Days; median (IQR)]*	15 (10–23)	6 (5–8)	0.001

*The duration of hospital stay was not used as a prognostic indicator in this study, because many children with COVID-19 were observed in the hospital after the symptoms completely disappeared for the possibility of infectivity.

We evaluated the effects of three antiviral drugs by making comparison within COVID-19 cohort. Lopinavir–ritonavir (lopinavir 6–10 mg/kg and ritonavir 1.5–2.5 mg/kg per day, median for 9 days) was used in 12 (18.8%) cases, ribavirin (10–15 mg/kg per day, median for 8 days) was used in 8 (12.5%) cases, arbidol (5–8 mg/kg per day, median for 7 days) was used in 6 (9.4%) of children with COVID-19, respectively. The duration of positive PCR results from pharyngeal swabs was not significant different between 25 COVID-19 children used those antiviral drugs and that of 39 control cases without those antiviral drugs [median (IQR), 10 (5-13.5) *vs* 9 (7–11) days, $P = 0.885$]. Subgroup analysis was performed to evaluate the effectiveness of certain antiviral drug. Comparing children with COVID-19 who used lopinavir–ritonavir, ribavirin, or arbidol with non-antiviral therapy controls, no statistic difference was found in the duration of positive PCR results from pharyngeal swabs (all $P < 0.05$, Fig. 3).

Up until April 15, 2020, one patient in the viral pneumonia cohort was died and the other 347 patients were discharged, no statistical difference of mortality rate between two cohorts. As compared to the viral pneumonia cohorts, the proportion of cases required intensive care was lower (1/40 *vs* 32/284, $P = 0.047$) and the symptomatic duration was shorter [median (IQR), 5 (0–8) *vs* 8 (4–12) days, P 0.001] in the COVID-19 pneumonia cohort.

Discussion

Respiratory illnesses always the main trouble in the winter and the early spring time especially for children. SARS-CoV-2 is a newly detected emerging contagious pathogen causing a high prevalence of pneumonia. Understanding the clinical manifestations of children with COVID-19, especially those different from other similar diseases, is important for diagnosis, treatment and management of this disease. This was a multi-centered study that compared COVID-19 with acute pneumonia caused by other viruses in children, providing new insights into the clinical features and treatment of this disease.

Clear exposure histories, GGO on CT images were the characters of SARS-CoV-2 infection. Most children with COVID-19 (82.8%) were one of family clusters cases, but family clusters of pneumonia were not common for other virus infection, because most adults already have immunity against other common respiratory viruses and will not develop to pneumonia. GGO on CT images was a distinct characteristic of children with COVID-19, as it occurred in none of other 284 viral pneumonia cases. However, the proportion of the occurrence of GGO was obviously lower than that of adult cases[13], and 55% COVID-19 pneumonia cases without these typical radiographic changes. Moreover, we have observed that, after

several days, GGO can transform into lesions that cannot differentiate COVID-19 from other lung infections, which makes it more difficult to identify children COVID-19 by using CT images. The epidemiology and the PCR tests are very important in the diagnosis of COVID-19.

The prevalence of pneumonia in SARS-CoV-2 infection was 62.5%, similar with that of SARS (65%)[14], but much higher than that of H1N1 influenza (11%) and many other viruses. There was no difference in the proportion of children in different age groups who developed pneumonia after SARS-CoV-2 infection, and this situation can be observed in the research of Dong Y et al[15] and Wu Z et al[5], which indicated that younger age has no protective effect on preventing SARA-CoV-2 infection from developing COVID-19 pneumonia in children. Less exposure and milder symptom might be the reason for the lower detected incidence of children as compared to adults.

The symptoms and disease severity of COVID-19 pneumonia in children were no more severe than other common viral pneumonia. Fever and cough were the most common symptoms of children with COVID-19 pneumonia. The proportion of cases with fever in children COVID-19was significantly lower than that of adults with COVID-19[12,16] and children with other viral pneumonia in this study. The temperature was mainly low to moderate fever, the proportion of cases with high fever was only 7.5%, lower than that of other viral pneumonia (58.8%), and the duration of fever was shorter of children with COVID-19 than that of other viral pneumonia. The proportion of severe cases (1/40) in children with COVID-19 pneumonia in this study consistent with these data previous reported by Lu X et al[8] (3 of 171 children with COVID-19) and Dong Y et al[15] (21 of 731 children with COVID-19), which was significantly lower than that of adult cases[17] and lower than pneumonia caused by RSV (19/133) and human adenovirus (5/25) in this study. And, the proportion of cases required intensive care was lower and and the symptomatic duration was short as compared to the viral pneumonia cohort. So, we concluded that COVID-19 pneumonia in children were no more severe than pneumonia caused by common viruses from community. SARS-COV-2 infection is easy to be mixed up or missed with other respiratory virus infection.

Uncontrolled inflammatory innate responses may lead to tissue and organ damage in SARS-CoV-2 infection[18]. High amount of cytokines were detected in adults patients with severe illness cause by SARS-CoV[19], MERS-CoV[20] and SARS-CoV-2[17] infections. In addition, excessively increased inflammatory indicators (CRP, PCT) were observed in severe pneumonia caused by human adenovirus[21]. The only one case of critical COVID-19 child in our study, whose IL-6 (120.31 ng/L), IL-10 (33.38 ng/L), PCT (0.43 ng/mL) were significantly increased, and acute respiratory distress syndrome, acute renal failure and cardiac insufficiency were occurred. However, compared to pneumonia caused by other viruses, we found that the inflammatory indicators (CRP, PCT, ESR, IL-6, LDH), as well as biochemical indicators related to organ or tissue damage (ALT, AST, CK, CK-MB), and indexes related to disseminated intravascular coagulation were lower in the children with COVID-19 pneumonia. This indicates that SARS-CoV-2 infection have less effect on excessive activating the innate immune system in children and rarely triggered cytokine storm, which might relate to milder clinical manifestations of children with COVID-19.

Antiviral therapy, corticosteroid, immune therapy and antibiotics usage were the most concerned parts of COVID-19 treatment. By activating innate immunity, interferon was nebulized in more than 90% children COVID-19 in our data as well as other viral infection[22]. However, this study failed to evaluate its effect on SARS-CoV-2 infection. Lopinavir-ritonavir, ribavirin, and arbidol were used in about 1/3 children with COVID-19 in total, but they did not shorten the duration of positive PCR results from pharyngeal swabs for children with COVID-19. For other viral pneumonia, oseltamivir and paramivir were used in influenza A and influenza B related pneumonia, but antiviral drugs were rarely used in pneumonia caused by other viruses. Since all 64 children with COVID-19 have got good prognosis, we propose that it is not necessary to aggressively administer antiviral drugs in children COVID-19 before effective and safe antiviral drugs are confirmed. Several studies showed that immune therapy may be beneficial in dealing with cytokine storm syndromes in adults with sever COVID-19[23]. As mentioned above, cytokine storms were relatively rare and inflammatory indicators were lower in children with COVID-19 as compared to other viral pneumonia, corticosteroid is not a recommendation usage as other community-acquired viral pneumonia. Corticosteroid might be tried for critical children COVID-19 with obvious cytokine reactions, acute respiratory distress syndrome, multiple organ damages or with obvious wheezing. The percentage of viral-viral co-infection was 7.5% and viral-MP co-infection was 22.5% for children with COVID-19 pneumonia, which were similar to the viral pneumonia cohort and that reported by other studies on childhood viral pneumonia[24]. Secondary-infection with bacteria was detected in 18.5% cases of viral pneumonia cohort, whereas none was found in the COVID-19 pneumonia cohort. Few cases were administrated with penicillin for prophylactic treatment with possible bacteria infection. Milder symptom and shorter symptomatic duration of children with COVID-19 might be the reason of less secondary bacterial infection. For children with COVID-19, antibiotics cannot be used routinely, but multiple pathogen tests should be recommended because of high proportion co-infection in children with viral pneumonia.

The major limitation of our study was the selection bias. Firstly, not all the children with viral pneumonia were included since that clinicians failed to identify causative agents in some individuals with pneumonia. Although all participating hospitals routinely tested pathogens in children with pneumonia, the relatively severe cases have more chances of being detected for pathogens. Secondly, although the 64 SARS-CoV-2 infected cases contained cases from both Hubei province and outside Hubei province, their representativeness was limited due to a limited sample size.

Conclusions

Younger age has no protective effect on preventing SARS-CoV-2 infection from developing COVID-19 pneumonia in children. The symptoms and severity of children with COVID-19 pneumonia were no more severe than that of other viral pneumonia. Lopinavir-ritonavir, ribavirin, and arbidol cannot shorten the duration of positive PCR results from pharyngeal swabs in children with COVID-19 in our study. Multi-respiratory-pathogen test including SARS-COV-2 is necessary and children with other pathogens infection should be paid attention to even though COVID-19 outbreak.

Abbreviations

COVID-19
Coronavirus disease-2019; PCR:Polymerase chain-reaction; SARS:Severe acute respiratory syndrome; MERS:Middle East respiratory syndrome; CCDC:Chinese Center for Disease Control and Prevention; CAP:Community acquired pneumonia; MP:Mycoplasma pneumonia; CT:Computed tomography; WBC:White blood cell; CK:Creatine kinase; CK-MB:Creatine kinase-MB; LDH:Lactate dehydrogenase; PT:Prothrombin time; APTT:Activated partial thromboplastin time; CRP:C-reactive protein; PCT:Procalcitonin; ESR:Erythrocyte sedimentation rate; IL-6:Interleukin-6; GGO:Ground-glass opacity; RSV:Respiratory syncytial virus.

Declarations

Ethics approval and consent to participate

This study was reviewed and approved by the Medical Ethical Committee of General Hospital of Southern Theater Command of Chinese People's Liberation Army (approval number 2020-04). The written informed consent was waived.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

None of the authors declared potential conflict of interest.

Funding

This study was supported by Technology Project of Guangzhou City, Grant Award Number: 201607010123. The funders of this research had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Authors’ contributors

Guangli Ren, Guoqiang Xie, Long Chen, Chengzhong Zheng and Yuan Shi did literature search and designed the study. Guangli Ren, Xianfeng Wang, Jun Xu, Jun Li, Qiong Meng, Bo Huang, Weichun Zhu, Jing Lin, Chenghe Tang, Sheng Ye, Zhuo Li, Cong Xie, Fang Yang, Yuzong Zhou, Ying Zheng, Shuling Lan, Jianfeng Chen, Feng Ye, Yu He, Benqing Wu and Yuan Shi were responsible for disease diagnosis and

treatment and data collection. Guangli Ren, Guoqiang Xie, Jie Zhu, Zhen Tang and Mingxin Ma analysed data and wrote the report. Long Chen, Chengzhong Zheng and Yuan Shi did data interpretation and revised the paper.

Acknowledgements

Not applicable.

References

1. Chen Y, Liu Q, Guo D. Emerging coronaviruses: Genome structure, replication, and pathogenesis. J Med Virol. 2020;92:418–23.
2. Donnelly CA, Ghani AC, Leung GM, Hedley AJ, Fraser C, Riley S, et al. Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong Kong. Lancet. 361(9371). England,2003. 1761-6.
3. Cauchemez S, Fraser C, Van Kerkhove MD, Donnelly CA, Riley S, Rambaut A, et al. Middle East respiratory syndrome coronavirus: quantification of the extent of the epidemic, surveillance biases, and transmissibility. Lancet Infect Dis. 2014;14:50–6.
4. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med. 2020;382:1199–207.
5. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention [published online ahead of print, 2020 Feb 24]. JAMA. 2020. doi:10.1001/jama.2020.2648.
6. Cai J, Xu J, Lin D, Yang Z, Xu L, Qu Z, et al. A Case Series of children with 2019 novel coronavirus infection: clinical and epidemiological features [published online ahead of print, 2020 Feb 28]. Clin Infect Dis. 2020. doi:10.1093/cid/ciaa198.
7. 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 [published online ahead of print, 2020 Mar 25]. Lancet Infect Dis. 2020. doi:10.1016/S1473-3099(20)30198-5.
8. Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS-CoV-2 Infection in Children [published online ahead of print, 2020 Mar 12]. N Engl J Med. 2020. doi:10.1056/NEJMc2005073.
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). Mar 3. 2020. http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989.shtml (accessed May 8, 2020; in Chinese).
10. National Health Commission of the People's Republic of China. Guideline for diagnosis and treatment of community-acquired pneumonia in Children (2019 version). Chin J Clin Infect Dis. 2019;12:6–13.

11. Stockmann C, Ampofo K, Killpack J, Williams DJ, Edwards KM, Grijalva CG, et al. Procalcitonin Accurately Identifies Hospitalized Children With Low Risk of Bacterial Community-Acquired Pneumonia. J Pediatric Infect Dis Soc. 2018;7:46–53.
12. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China [published online ahead of print, 2020 Feb 07]. JAMA. 2020. doi:10.1001/jama.2020.1585.
13. Xu X, Yu C, Qu J, Zhang L, Jiang S, Huang D, et al. Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2. Eur J Nucl Med Mol Imaging. 2020;47:1275–80.
14. Babyn PS, Chu WC, Tsou IY, Wansaicheong GK, Allen U, Bitnun A, et al. Severe acute respiratory syndrome (SARS): chest radiographic features in children. Pediatr Radiol. 2004;34:47–58.
15. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China. Pediatrics. 2020. doi:10.1542/peds.2020-0702.
16. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China [published online ahead of print, 2020 Feb 28]. N Engl J Med. 2020. doi:10.1056/NEJMoa2002032.
17. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506.
18. Cao X. COVID-19: immunopathology and its implications for therapy. Nat Rev Immunol. 2020;20:269–70.
19. Wong CK, Lam CW, Wu AK, Ip WK, Lee NL, Chan IH, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clin Exp Immunol. 2004;136:95–103.
20. Falzarano D, de Wit E, Rasmussen AL, Feldmann F, Okumura A, Scott DP, et al. Treatment with interferon-α2b and ribavirin improves outcome in MERS-CoV-infected rhesus macaques. Nat Med. 2013;19:1313–7.
21. Shen CF, Wang SM, Ho TS, Liu CC. Clinical features of community acquired adenovirus pneumonia during the 2011 community outbreak in Southern Taiwan: role of host immune response. BMC Infect Dis. 2017;17:196.
22. Mesev EV, LeDesma RA, Ploss A. Decoding type I and III interferon signalling during viral infection. Nat Microbiol. 2019;4:914–24.
23. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395:1033–4.
24. Haq IJ, Battersby AC, Eastham K, McKean M. Community acquired pneumonia in children. BMJ. 2017;356:j686.

Figures

Figure 1

Locations of hospitals for participants screening. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

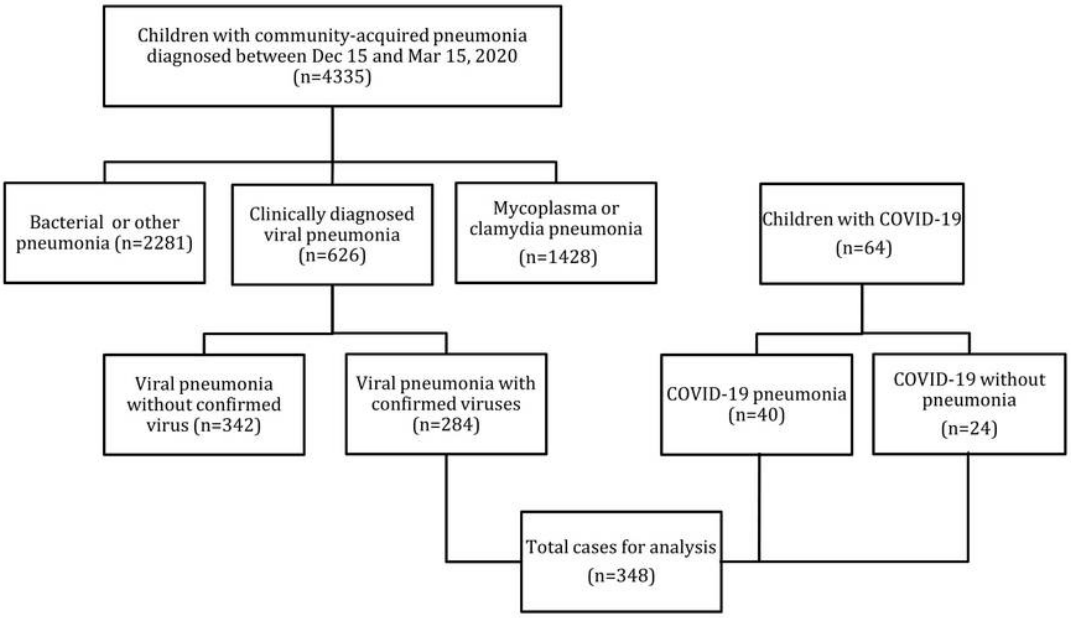

Figure 2

The flow diagram of recruiting participants

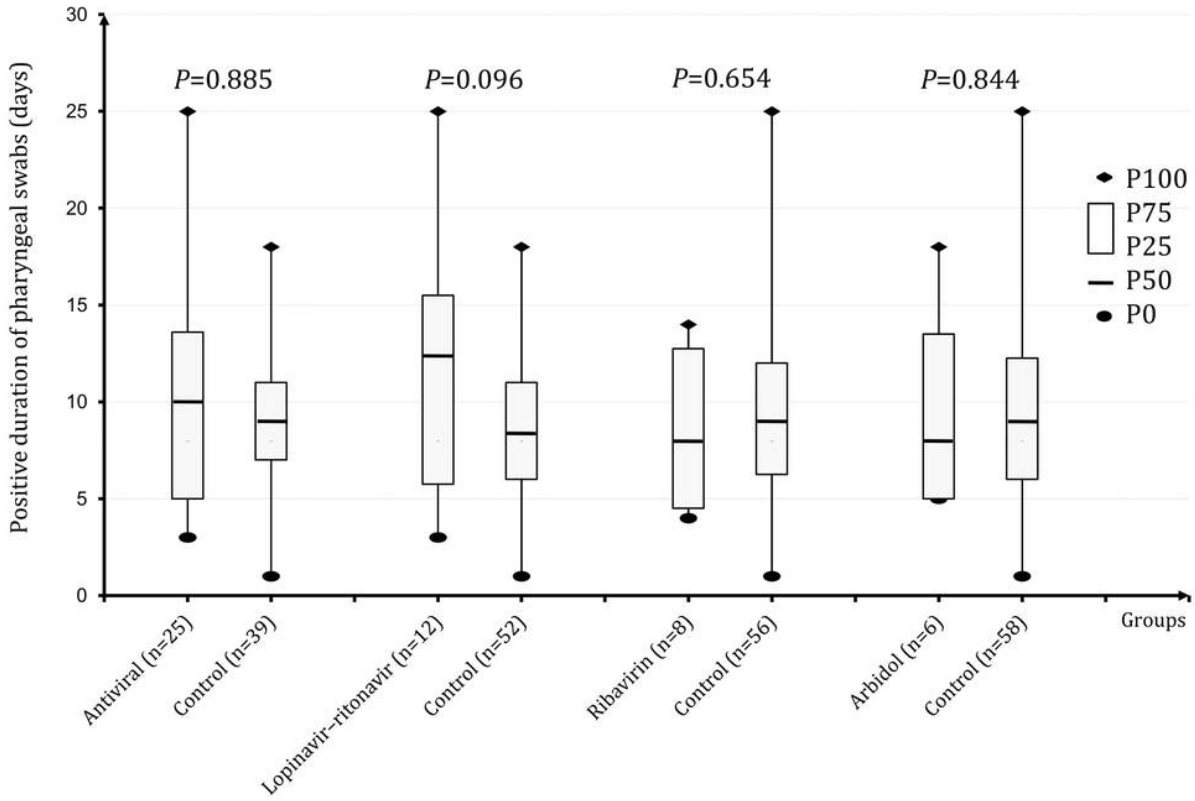

Figure 3

Effect of lopinavir–ritonavir, ribavirin and arbidol on children with COVID-19