



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study

Haiyan Qiu*, Junhua Wu*, Liang Hong, Yunling Luo, Qifa Song, Dong Chen



Summary

Background Since December, 2019, an outbreak of coronavirus disease 2019 (COVID-19) has spread globally. Little is known about the epidemiological and clinical features of paediatric patients with COVID-19.

Methods We retrospectively retrieved data for paediatric patients (aged 0–16 years) with confirmed COVID-19 from electronic medical records in three hospitals in Zhejiang, China. We recorded patients' epidemiological and clinical features.

Findings From Jan 17 to March 1, 2020, 36 children (mean age 8·3 [SD 3·5] years) were identified to be infected with severe acute respiratory syndrome coronavirus 2. The route of transmission was by close contact with family members (32 [89%]) or a history of exposure to the epidemic area (12 [33%]); eight (22%) patients had both exposures. 19 (53%) patients had moderate clinical type with pneumonia; 17 (47%) had mild clinical type and either were asymptomatic (ten [28%]) or had acute upper respiratory symptoms (seven [19%]). Common symptoms on admission were fever (13 [36%]) and dry cough (seven [19%]). Of those with fever, four (11%) had a body temperature of 38·5°C or higher, and nine (25%) had a body temperature of 37·5–38·5°C. Typical abnormal laboratory findings were elevated creatine kinase MB (11 [31%]), decreased lymphocytes (11 [31%]), leucopenia (seven [19%]), and elevated procalcitonin (six [17%]). Besides radiographic presentations, variables that were associated significantly with severity of COVID-19 were decreased lymphocytes, elevated body temperature, and high levels of procalcitonin, D-dimer, and creatine kinase MB. All children received interferon alfa by aerosolisation twice a day, 14 (39%) received lopinavir–ritonavir syrup twice a day, and six (17%) needed oxygen inhalation. Mean time in hospital was 14 (SD 3) days. By Feb 28, 2020, all patients were cured.

Interpretation Although all paediatric patients in our cohort had mild or moderate type of COVID-19, the large proportion of asymptomatic children indicates the difficulty in identifying paediatric patients who do not have clear epidemiological information, leading to a dangerous situation in community-acquired infections.

Funding Ningbo Clinical Research Center for Children's Health and Diseases, Ningbo Reproductive Medicine Centre, and Key Scientific and Technological Innovation Projects of Wenzhou.

Copyright © 2020 Elsevier Ltd. All rights reserved.

Introduction

Coronaviruses are non-segmented positive-stranded RNA viruses with a roughly 30 kb genome surrounded by a protein envelope. Most coronaviruses cause diseases in their particular host species;¹ those that can infect humans through cross-species transmission have become an important threat to public health. Two serious coronavirus disease outbreaks have happened in the past two decades: severe acute respiratory syndrome (SARS) in 2003,² and Middle East respiratory syndrome (MERS) in 2012.³

Since December, 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been recognised as the causal factor in a series of severe cases of pneumonia originating in Wuhan in Hubei province, China.⁴ This disease has been named coronavirus disease 2019 (COVID-19) by WHO. SARS-CoV-2 has been shown to cause disease via a mechanism analogous to the SARS

coronavirus, with potential damage to vital organs such as lung, heart, liver, and kidney, and infection poses a considerable risk to patients by the high prevalence of pneumonia.⁵ By March 1, 2020, SARS-CoV-2 had led to 80 981 confirmed cases of COVID-19 in China, and 44 067 cases in 117 countries.⁶ A cohort study of 44 672 Chinese cases reported that 2·1% of patients were younger than 20 years, and 1·2% were asymptomatic.⁷

Pneumonia is the leading cause of mortality in children.⁸ Distinct immunological responses to viral infections can exist in children and result in severe damage to vital organs.⁹ Although short-to-medium-term outcomes for children who recovered from SARS seemed good, the disease caused exercise impairment after more than 6 months.¹⁰ A comprehensive literature search indicated that MERS was rare in children (31 cases identified between 2012 and 2016),¹¹ because transmission depends heavily on animal exposure and direct contact

Lancet Infect Dis 2020; 20: 689–96

Published Online
March 25, 2020
[https://doi.org/10.1016/S1473-3099\(20\)30198-5](https://doi.org/10.1016/S1473-3099(20)30198-5)
See [Comment](#) page 633

For the Chinese translation of the abstract see Online for appendix

*Contributed equally

Department of Pediatrics, Ningbo Women and Children's Hospital, Ningbo, Zhejiang, China (Prof H Qiu MD, J Wu MD); Department of Infectious Diseases, The Third Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China (L Hong MD, Y Luo MD); Department of Microbiology, Ningbo Municipal Centre for Disease Control and Prevention, Ningbo, Zhejiang, China (Prof Q Song MSc); and Department of Infectious Diseases, Wenzhou Central Hospital and Sixth People's Hospital of Wenzhou, Wenzhou, Zhejiang, China (Prof D Chen MSc)

Correspondence to: Prof Qifa Song, Department of Microbiology, Ningbo Municipal Centre for Disease Control and Prevention, Ningbo 315010, Zhejiang, China
songqf@nbcdc.org.cn

or Prof Dong Chen, Department of Infectious Diseases, Wenzhou Central Hospital and Sixth People's Hospital of Wenzhou, Wenzhou 325000, Zhejiang, China
chendong_wz@126.com

Research in context

Evidence before this study

We searched PubMed from Nov 1, 2019, to March 1, 2020, for studies published in any language using the terms “COVID-19”, “coronavirus disease 2019”, “novel coronavirus”, “paediatric patients”, “children”, “transmission”, “clinical feature”, and “epidemiological features”. We found 13 studies about coronavirus disease 2019 (COVID-19) in children. These studies were related to treatment recommendations, CT features in 15 children, case reports, and COVID-19 in infants. To our knowledge, no study has been done to comprehensively investigate a cohort of paediatric patients with COVID-19 and their distinctive clinical features. Published work about adult patients has shown that manifestations vary strikingly by individual. Since children are different from adults in many aspects, such as immunological development, we aimed to investigate the clinical and epidemiological features of paediatric patients with COVID-19.

Added value of this study

Between Jan 17 and March 1, 2020, 661 cases of COVID-19 were reported in Ningbo and Wenzhou (Zhejiang province, China). Of these cases, 36 were in children. All children with COVID-19

had been infected either by close contact with adults infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or by exposure to the epidemic area. Although fever, cough, and pneumonia were the most common signs, about half the children had mild disease with no presenting symptoms. Fewer children with COVID-19 had obvious symptoms compared with adult patients with COVID-19 and paediatric patients with H1N1 influenza described in previous studies.

Implications of all the available evidence

By contrast with findings in adults, children with COVID-19 had milder clinical manifestations; nearly half of paediatric patients were asymptomatic (ie, no fever and no cough). This asymptomatic condition is relevant if community-acquired transmission becomes the primary mode; identification of paediatric patients without presenting symptoms will become a great challenge. Fortunately, the number of children infected with SARS-CoV-2 accounted for a small proportion of total people infected, and paediatric patients also had clear epidemiological information. Devising measures to protect children from infection with SARS-CoV-2 is very important.

in the household or health-care facilities. Collectively, these two coronavirus diseases did not widely affect children because of the short-term epidemic of SARS and the strict transmission route of MERS. In a study of 15 children with COVID-19 (aged 4–14 years), six patients had small nodular ground-glass opacities in the lungs.¹² At the time of the COVID-19 outbreak, all schools were on the spring festival holiday, which might have prevented children from exposure to transmission sources. However, the school community is a place that can enhance rapid spread of the highly infectious SARS-CoV-2.

Ningbo and Wenzhou are two cities in Zhejiang province, located 900 km east of Wuhan. On Jan 17, 2020, the first COVID-19 case was reported in Wenzhou. Up to March 1, 2020, 661 cases of COVID-19 had been reported in Ningbo and Wenzhou, of which 36 were in children. We aimed to describe the epidemiological and clinical features of these paediatric patients, information that is urgently needed for prevention and treatment of COVID-19 in children.

Methods

Study population

We did an observational cohort study at three hospitals in Zhejiang province, China (Ningbo Women and Children’s Hospital, The Third Affiliated Hospital of Wenzhou Medical University, and Wenzhou Central Hospital of Wenzhou). We included all paediatric patients (aged 0–16 years) with laboratory confirmed COVID-19. The diagnosis of COVID-19 was based on guidelines issued by the National Health Commission of the People’s Republic

of China.¹³ We screened all patients who had cough, fever, and radiographic presentation at the initial assessment, or who underwent epidemiological investigation because of a history of exposure to epidemic areas or close contact with an infected individual. We confirmed SARS-CoV-2 infection by RT-PCR of samples taken from upper nasopharyngeal swabs. Epidemiological investigation was focused on the route of transmission, and we assessed travel history, residence in epidemic areas, and close contact with patients with confirmed COVID-19 within 14 days.

This study was approved by the ethics committee of Ningbo Women and Children’s Hospital and followed the Declaration of Helsinki. Written consent was obtained from the guardians of the patients.

Procedures

Sample collection, RT-PCR, and interpretation of results was done as previously described.¹⁴ Two sets of primers were used for two target genes (ie, open reading frame 1ab [*ORF1ab*] and nucleocapsid protein [*N*]) according to the protocol issued by the National Institute for Viral Disease Control and Prevention in China (panel 1).¹⁵

On admission, patients were assessed for clinical type, according to guidelines for scoring paediatric patients with COVID-19 (recommendations issued by the paediatrics branch of the Chinese Medical Association; panel 2).¹⁶ The therapeutic principles included general support therapy; monitoring of lung, liver, kidney, and myocardial functions; active control over high fever; oxygen uptake if necessary; and antiviral treatment with interferon alfa and lopinavir–ritonavir. Treatment

Panel 1: Primers for targets**Target 1: open reading frame 1ab (ORF1ab)**

Forward primer: CCCTGTGGGTTTTACTTAA

Reverse primer: ACGATTGTGCATCAGCTGA

Probe: 5'-VIC-CCGCTGCGGTATGTGGAAAGTTATGG-BHQ1-3'

Target 2: nucleocapsid protein (N)

Forward primer: GGGGAACCTTCCTGCTAGAAT

Reverse primer: CAGACATTTTGTCTCAAGCTG

Probe: 5'-FAM-TTGCTGCTGCTTACAGATT-TAMRA-3'

Panel 2: Definitions of clinical types of COVID-19 in paediatric patients**Mild disease**

- Upper respiratory symptoms (eg, pharyngeal congestion, sore throat, and fever) for a short duration or asymptomatic infection
- Positive RT-PCR test for SARS-CoV-2
- No abnormal radiographic and septic presentation

Moderate disease

- Mild pneumonia
- Symptoms such as fever, cough, fatigue, headache, and myalgia
- No complications and manifestations related to severe conditions

Severe disease

Mild or moderate clinical features, plus any manifestations that suggest disease progression:

- Rapid breath (≥ 70 breaths per min for infants aged < 1 year; ≥ 50 breaths per min for children aged > 1 year)
- Hypoxia
- Lack of consciousness, depression, coma, convulsions
- Dehydration, difficulty feeding, gastrointestinal dysfunction
- Myocardial injury
- Elevated liver enzymes
- Coagulation dysfunction, rhabdomyolysis, and any other manifestations suggesting injuries to vital organs

Critical illness

Rapid disease progression, plus any other conditions:

- Respiratory failure with need for mechanical ventilation (eg, ARDS, persistent hypoxia that cannot be alleviated by inhalation through nasal catheters or masks)
- Septic shock
- Organ failure that needs monitoring in the ICU

COVID-19=coronavirus disease 2019. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. ARDS=acute respiratory distress syndrome. ICU=intensive care unit.

	Total (n=36)	Mild cases (n=17)	Moderate cases (n=19)	p value*
Epidemiological data				
Female patients	13 (36%)	7 (41%)	6 (32%)	0.70
Male patients	23 (64%)	10 (59%)	13 (68%)	..
Age, years (SD, range)	8.3 (3.5, 1-16)	7.5 (3.2, 1-16)	9.0 (3.6, 3-16)	0.099
Age ≤ 5 years	10 (28%)	8 (80%)	2 (20%)	..
History of exposure to epidemic area	12 (33%)	5 (29%)	7 (37%)	0.70
Family members with COVID-19	32 (89%)	16 (94%)	16 (84%)	0.60
Symptoms				
Dry cough	7 (19%)	3 (18%)	4 (21%)	..
Dyspnoea or tachypnoea	1 (3%)	..	1 (5%)	..
Pharyngeal congestion	1 (3%)	1 (6%)
Sore throat	2 (6%)	1 (6%)	1 (5%)	..
Vomiting or diarrhoea	2 (6%)	..	2 (10%)	..
Body temperature, °C	37.8 (0.4)	37.6 (0.3)	38.0 (0.4)	0.0020
Fever (body temperature $> 37^{\circ}\text{C}$)	13 (36%)	4 (24%)	9 (47%)	..
Headache	3 (8%)	1 (6%)	2 (10%)	..
Laboratory tests (reference values)				
White blood cells ($4-10 \times 10^9$ cells per L)	6.1 (2.1)	6.5 (2.3)	5.8 (1.9)	0.32
Decreased (n)	7	2	5	..
Lymphocytes ($1.1-3.2 \times 10^9$ cells per L)	2.4 (0.8)	2.8 (1.0)	2.0 (0.7)	0.0083
Decreased (n)	11	2	9	..
Procalcitonin (< 0.5 ng/mL)	0.24 (0.17)	0.15 (0.13)	0.32 (0.19)	0.0039
Increased (n)	6	1	5	..
C-reactive protein (< 8 mg/L)	5 (2)	4 (1)	5 (2)	0.072
Increased (n)	1	0	1	..
D-dimer (< 0.5 $\mu\text{g/mL}$)	0.29 (0.20)	0.21 (0.18)	0.36 (0.21)	0.028
Increased (n)	3	1	2	..
Erythrocyte sedimentation rate (0-20 mm/h)	7 (2)	6 (2)	7 (2)	0.14
Increased (n)	0	0	0	..
Creatine kinase (55-170 U/L)	96 (47)	80 (44)	110 (56)	0.085
Increased (n)	1	0	1	..
Creatine kinase MB (< 18 U/L)	19 (10)	14 (9)	24 (12)	0.0084
Increased (n)	11	4	7	..
Alanine aminotransferase (< 40 U/L)	21 (14)	21 (12)	20 (13)	0.82
Increased (n)	2	2	0	..
Aspartate transferase (< 40 U/L)	30 (11)	32 (10)	28 (11)	0.26
Increased (n)	3	2	1	..
Creatinine (40-110 $\mu\text{mol/L}$)	56 (12)	58 (11)	54 (13)	0.32
Increased (n)	0	0	0	..
Blood urea nitrogen (3-7 mmol/L)	3.8 (0.5)	3.7 (0.4)	3.9 (0.5)	0.20
Increased (n)	0	0	0	..
Oxygen saturation (92-100%)	98.1 (0.4)	98.2 (0.3)	98 (0.3)	0.054
Decreased (n)	0	0	0	..
Radiography				
Pulmonary ground-glass opacities	19 (53%)	..	19 (100%)	..

(Table 1 continues on next page)

outcomes were defined as improved, cured, and failed. Improved outcome referred to the end of fever and improvement in pneumonia (via CT scan) and improvement in upper respiratory manifestations. Cured outcome referred to normal body temperature for 3 days,

plus improved outcomes and two negative results on RT-PCR for SARS-CoV-2. Failed outcome referred to disease progression to critical illness or death. Patients who were discharged from hospital had to be quarantined for 2 weeks.

	Total (n=36)	Mild cases (n=17)	Moderate cases (n=19)	p value*
(Continued from previous page)				
Treatment				
Oxygen inhalation	6 (17%)	1 (6%)	5 (26%)	..
Interferon alfa	36 (100%)	17 (100%)	19 (100%)	..
Lopinavir-ritonavir	14 (39%)	2 (12%)	12 (63%)	..
Time taken to become SARS-CoV-2 PCR-negative, days (SD, range)	10 (2, 7–22)	9 (2, 7–12)	11 (2, 8–22)	0.0050
Duration of fever after admission, days (SD, range)†	3 (2, 2–5)	2 (2, 2–4)	3 (2, 2–5)	0.14
Duration of hospitalisation, days (SD, range)	14 (3, 10–20)	12 (3, 10–16)	15 (4, 12–20)	0.017

Data are n (%) or mean (SD), unless otherwise indicated. COVID-19=coronavirus disease 2019. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. *p values indicate the difference between paediatric patients with mild clinical type (asymptomatic or upper respiratory infection) and those with moderate clinical type with pneumonia. †Data for 13 patients.

Table 1: Epidemiological and clinical features of paediatric patients with COVID-19 stratified by two clinical types

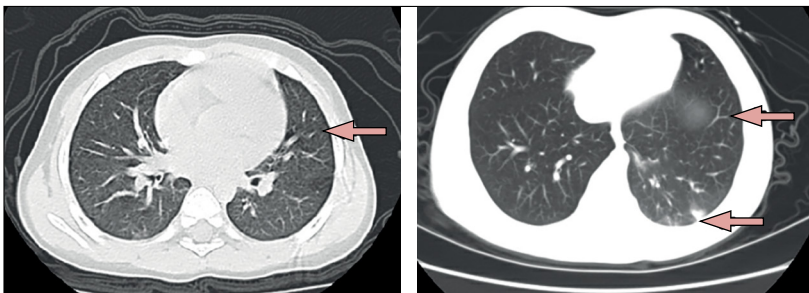


Figure 1: Chest CT scans from two paediatric patients with coronavirus disease 2019
(Left) CT of 10-year-old boy showing multiple opacities in lower lobes of both lungs (arrow). (Right) CT of 1.5-year-old girl showing multiple ground-glass opacities with a big patchy opacity in the right lung (arrows).

We obtained data retrospectively from electronic medical records, and these were reviewed by two trained doctors (LH and YL). Information retrieved included demographic data, medical history, exposure history, underlying comorbidities, symptoms, laboratory examinations, chest CT scans, and treatment. Laboratory examinations included routine testing, analysis of immunological responses, and measurement of biomarkers for monitoring lung, liver, myocardial, and renal functions. We compared the prevalence of abnormal clinical indices of the paediatric patients with previously reported data for 175 adults with COVID-19 in Wenzhou,¹⁷ 44 paediatric patients with SARS in Hong Kong,^{10,18} and 167 Chinese paediatric patients with H1N1 influenza.¹⁹

Statistical analysis

We presented continuous variables as mean (SD) and categorical variables as number (%). We compared means of continuous variables between groups using independent group *t* tests when values were normally distributed; otherwise, we used the Mann-Whitney *U* test. We compared proportions for categorical variables

between groups using Fisher's exact test, because of limited numbers. We judged a two-sided α less than 0.05 statistically significant. All data analyses were done with SPSS version 20.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 17 and March 1, 2020, 661 COVID-19 cases were reported in Ningbo and Wenzhou in China; of these cases, 36 (5%) were in children (aged 1–16 years; mean age 8.3 [3.5] years). 13 (36%) of 36 patients were female (table 1). The route of transmission for paediatric patients was either by close contact with family members with COVID-19 (32 [89%]) or a history of exposure to epidemic areas (12 [33%]), or both (eight [22%]). 17 (47%) of 36 children had mild clinical type, with ten (28%) patients asymptomatic and seven (19%) showing acute upper respiratory symptoms. The remaining 19 (53%) paediatric patients had moderate clinical type, characteristic of mild pneumonia (table 1). No severe and critically ill cases were seen.

On admission, frequent symptoms were fever (13 [36%]) and dry cough (seven [19%]). Of 13 patients with fever, four (11%) had a body temperature of 38.5°C or higher and nine (25%) had a body temperature of 37.5–38.5°C. Other symptoms were recorded infrequently, including sore throat (two [6%]), pharyngeal congestion (one [3%]), dyspnoea or tachypnoea (one [3%]), and vomiting or diarrhoea (two [6%]). Neither neurological symptoms nor signs of cardiac, liver, or renal failure were recorded.

Generally, two types of abnormal radiographic presentations were seen: multiple opacities and patchy opacities. 19 (53%) paediatric patients had pulmonary ground-glass opacities on CT scan, suggesting pneumonia (figure 1). Pneumonia plus either fever or cough was seen in 11 (30%) paediatric patients and eight (22%) had pneumonia as the only symptom. Ten (28%) children showed no symptoms of pneumonia, five (14%) reported fever only, and two (5%) only had a dry cough.

Table 1 shows findings of laboratory examinations related to immunological responses and cardiac, liver, and renal damage, according to mild or moderate clinical type. Abnormal findings in paediatric patients were increased serum creatine kinase MB (11 [31%]), decreased lymphocytes (11 [31%]), leucopenia (seven [19%]), and increased procalcitonin (six [17%]). Some features differed significantly between mild and moderate clinical type of COVID-19, including decreased lymphocytes ($p=0.0083$), raised body temperature ($p=0.0020$), and high levels of procalcitonin ($p=0.0039$), D-dimer ($p=0.028$), and creatine kinase MB ($p=0.0084$). Children

with moderate clinical type also had a positive PCR result for longer ($p=0.0050$) and spent more days in hospital ($p=0.017$) than did those with mild clinical type.

Table 2 shows findings of laboratory examinations related to immunological responses and cardiac, liver, and renal damage, according to age group. Ten patients were aged 5 years or younger and 26 patients were 16 years or younger but older than 5 years. The older children had decreased lymphocytes ($p=0.029$), elevated procalcitonin ($p=0.032$), and decreased creatine kinase ($p=0.032$) compared with the younger patients.

Treatments and primary manifestations were traced to assess disease progression and outcome, and four case types were identified: asymptomatic, upper respiratory symptoms or fever only, pneumonia only, and both pneumonia and upper respiratory symptoms or fever (figure 2). On admission, all children were treated with interferon alfa by aerosolisation twice a day, 14 (39%) received lopinavir–ritonavir syrup twice a day, and six (17%) needed oxygen inhalation (table 1). In the 13 patients with fever, mean duration of fever was 3 (SD 2) days. Improvement in pneumonia was seen 4–10 days after treatment initiation. SARS-CoV-2 RT-PCR results became negative after a mean of 10 (SD 2) days of treatment, regardless of the various initial manifestations of patients (figure 2). The mean number of days in hospital was 14 (SD 3) days. By Feb 28, 2020, all patients were cured, according to the criteria for cured outcome, and quarantined for a further 2 weeks. Follow-up is continuing every week, with samples taken to measure serum IgG and IgM and SARS-CoV-2 in blood, faeces, and nasopharyngeal swabs.

The comparison of paediatric patients with COVID-19 with adult patients with COVID-19 in the same city (table 3) showed that paediatric patients had a significantly lower prevalence of abnormal values of several variables indicating disease severity, such as fever (36% for children and 86% for adults), cough (19% and 62%), pneumonia (53% and 95%), elevated C-reactive protein (3% and 49%), and severe disease type (0% and 23%; $p<0.0001$ for all features). Nevertheless, no differences were noted between children and adults in prevalence of leucopenia, lymphopenia, and elevated myocardial enzymes. When compared with children with SARS, paediatric patients with COVID-19 had much milder disease in terms of the prevalence of fever, cough, pneumonia, and severe case type. Compared with children with H1N1 influenza, paediatric patients with COVID-19 had fewer upper respiratory symptoms (eg, cough and pharyngeal congestion) but pneumonia was more frequent. Notably, when the three groups of patients with coronavirus infections were compared with the paediatric patients with H1N1 influenza, the most striking difference was that patients with H1N1 influenza had a much higher prevalence of pharyngeal congestion and a lower prevalence of pneumonia.

	Age 0 to ≤5 years (n=10)	Age >5 to ≤16 years (n=26)	p value
Epidemiological data			
Female patients	4 (40%)	9 (35%)	..
Male patients	6 (60%)	17 (65%)	..
History of exposure to epidemic area	2 (20%)	10 (38%)	..
Family members with COVID-19	10 (100%)	22 (85%)	0.60
Symptoms			
Dry cough	1 (10%)	6 (23%)	..
Body temperature, °C	37.7 (0.3)	37.9 (0.4)	0.16
Fever (body temperature >37°C)	3 (30%)	10 (38%)	..
Radiography			
Pulmonary ground-glass opacities	6 (60%)	13 (50%)	0.70
Laboratory tests (reference values)			
White blood cells ($4-10 \times 10^9$ cells per L)	6.5 (2.2)	5.9 (2.0)	0.44
Decreased (n)	2	5	..
Lymphocytes ($1.1-3.2 \times 10^9$ cells per L)	2.9 (1.1)	2.2 (0.7)	0.029
Decreased (n)	2	9	..
Procalcitonin (<0.5 ng/mL)	0.13 (0.15)	0.28 (0.19)	0.032
Increased (n)	1	5	..
C-reactive protein (<8 mg/L)	4 (1)	5 (2)	0.14
Increased (n)	0	1	..
D-dimer (<0.5 µg/mL)	0.20 (0.18)	0.32 (0.20)	0.11
Increased (n)	0	3	..
Creatine kinase (55–170 U/L)	124 (54)	85 (44)	0.032
Increased (n)	1	0	..
Creatine kinase MB (<18 U/L)	21 (14)	18 (7)	0.40
Increased (n)	5	6	..
Oxygen saturation (92–100%)	98.2 (0.3)	98.1 (0.3)	0.38
Decreased (n)	0	0	..
Mild cases	4 (40%)	13 (50%)	0.70
Therapy and outcomes			
Oxygen inhalation	1 (10%)	5 (19%)	..
Interferon alfa	10 (100%)	26 (100%)	>0.99
Lopinavir–ritonavir	1 (10%)	13 (50%)	..
Time taken to become SARS-CoV-2 PCR-negative, days (SD, range)	9 (2, 7–14)	11 (2, 8–22)	0.011
Duration of hospitalisation, days (SD, range)	13 (3, 10–18)	15 (4, 13–20)	0.16

Data are n (%) or mean (SD), unless otherwise indicated. COVID-19=coronavirus disease 2019. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. *p values indicate the difference between paediatric patients with mild clinical type (asymptomatic or upper respiratory infection) and those with moderate clinical type (mild pneumonia).

Table 2: Comparison of clinical features between paediatric patients, by age group

Discussion

SARS-CoV-2 is an emerging contagious pathogen causing a high prevalence of pneumonia in infected individuals. Understanding the clinical features in paediatric patients is important for diagnosis and effective treatment of this illness. The findings of our study show that the main clinical features of COVID-19 in children were fever, dry cough, and pneumonia. Paediatric patients acquired COVID-19 by clear transmission routes, including close contact with family members, a history of exposure to epidemic areas, or both of these. No other sources, such as a hospital stay or

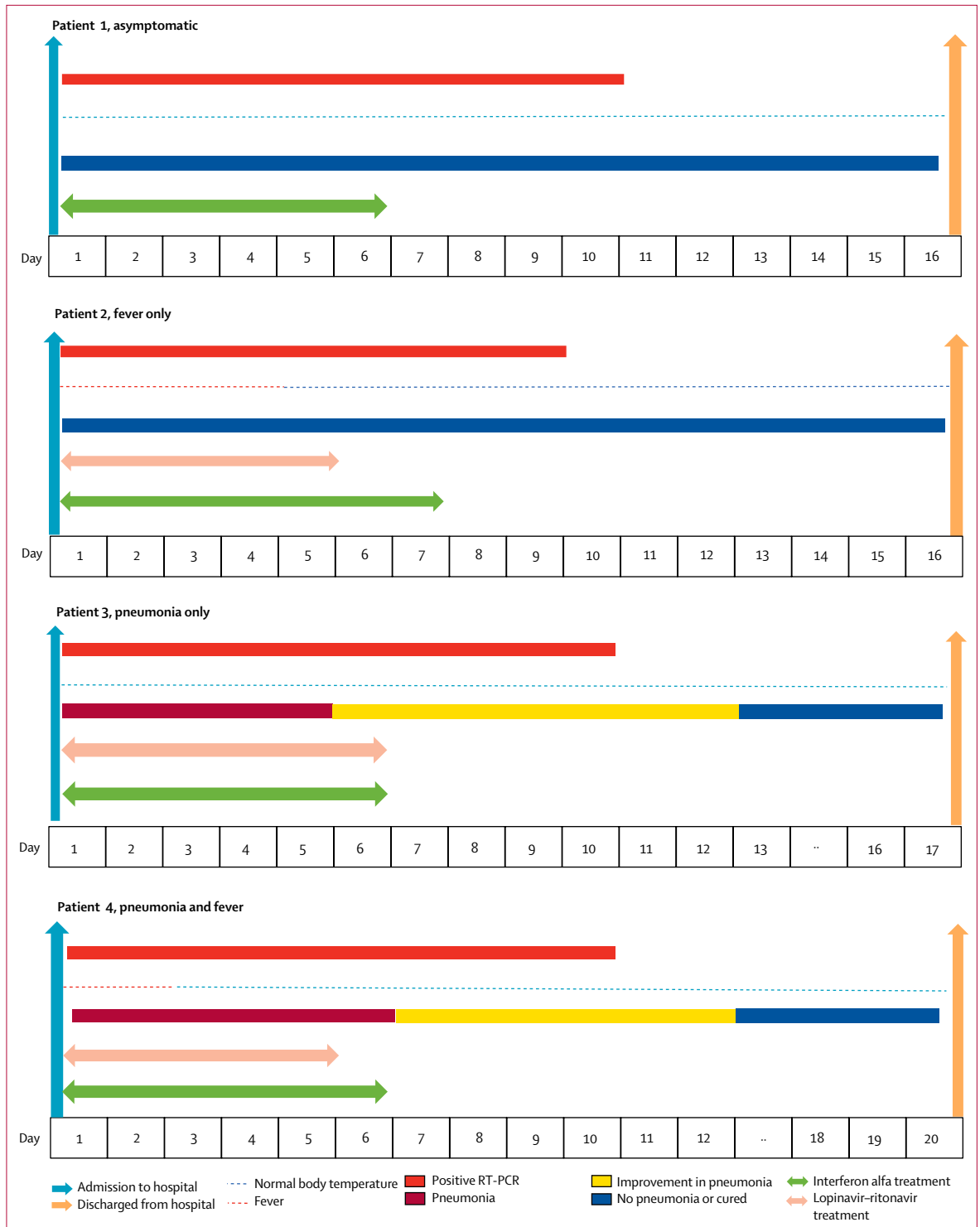


Figure 2: Trajectory of COVID-19 disease progression and treatment in four paediatric patients with different manifestations
 Patient 1: male (aged 1.5 years), asymptomatic; 10 days to become SARS-CoV-2 PCR-negative. Patient 2: male (aged 5.2 years), only symptom was fever for 4 days; 9 days to become SARS-CoV-2 PCR-negative. Patient 3: male (aged 6 years), only symptom was pneumonia for 12 days; 10 days to become SARS-CoV-2 PCR-negative. Patient 4: female (aged 7.5 years), symptoms were fever for 3 days and pneumonia for 12 days; 10 days to become SARS-CoV-2 PCR-negative. COVID-19=coronavirus disease 2019. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

unclear routes of transmission, were identified. This transmission feature means that identification of these paediatric patients was straightforward. However, previous work has shown that potential transmission routes of SARS-CoV-2 can be highly variable,²⁰ compared with MERS coronavirus, which is less transmissible.¹¹ This situation could be altered if COVID-19 persists for a long time in an area with increased risk for community-acquired infections.

Among the paediatric patients in our study, just under a third were asymptomatic. Moreover, a fifth had pneumonia only and needed radiographic examination to be identified. Symptoms seen on admission were variable, including cough and fever. All asymptomatic patients and children who did not present with pneumonia needed laboratory and radiographic examinations for diagnosis. The large proportion of children with asymptomatic SARS-CoV-2 infection contrasts with paediatric patients with H1N1 influenza¹⁹ and SARS,¹⁰ and adult patients with COVID-19,¹⁷ in terms of presenting symptoms such as cough and pharyngeal congestion (table 3), indicating SARS-CoV-2 has little effect on the upper respiratory tract of children. COVID-19 is highly transmissible, similar to SARS and H1N1 influenza, but can have a covert presentation in children.

Pneumonia is the leading infectious cause of death in children younger than 5 years.²¹ Although COVID-19 in children seemed to be mild in term of presenting symptoms, the prevalence of pneumonia with COVID-19 (53%) was higher than with H1N1 influenza (11%), but very similar to the prevalence with SARS (65%).¹⁸ A striking characteristic of COVID-19 is that it affects several vital organs (eg, lungs and heart), as shown by increased amounts of myocardial enzymes, even though all children with COVID-19 had the mild or moderate clinical type (table 3). With high mortality in adult patients with COVID-19 in epidemic areas⁸ (eg, >4% mortality in Wuhan), paediatric patients should continue to be monitored after discharge from hospital.

Compared with adults, children rarely have comorbidities such as hypertension, cardiovascular disease, and diabetes. Paediatric patients in our study had a lower prevalence of pneumonia and symptoms such as fever, cough, and dyspnoea compared with adult patients with COVID-19 (table 3). However, in our study, the prevalence of leucopenia, lymphopenia, and increased myocardial enzymes in children with COVID-19 was similar to that in adults. Notably, adults have a much higher prevalence of increased C-reactive protein than do children, suggesting a much milder immunological response in children and less immune damage.²² Except for antiviral drugs, no special treatments (eg, glucocorticoid therapy and invasive mechanical ventilation) were administered, and few children needed inhaled oxygen. Taking all these findings into consideration, the presentation of COVID-19 in paediatric patients is much milder than in adults. It is noteworthy that few patients with coronavirus disease (ie, COVID-19 and SARS) have pharyngeal congestion or

	Children with COVID-19 (n=36)	Adults with COVID-19 (n=175) ¹⁷	Children with SARS (n=44) ¹⁰	Children with H1N1 influenza (n=167) ¹⁹
Age, years	8.3 (3.5)	45 (14)	12.2 (4.1)	4.1 (3.5)
Fever	13 (36%)	150 (86%)	44 (100%)	153 (92%)
Cough	7 (19%)	109 (62%)	28 (64%)	138 (83%)
Pharyngeal congestion or sore throat	1 (3%)	8 (5%)	6 (14%)	159 (95%)
Dyspnoea	1 (3%)	23 (13%)	4 (9%)	12 (7%)
Asymptomatic*	10 (28%)	<5%	0	<5%
Pneumonia	19 (53%)	166 (95%)	40/62 (65%)†	18 (11%)
Comorbidities or complications (except pneumonia and bronchitis)	0	10 (6%)	5 (11%)	7 (4%)
Mild and moderate cases	36 (100%)	136 (77%)	35 (79%)	135 (81%)
Severe cases	0	39 (23%)	9 (21%)	32 (19%)
Leucopenia	7 (19%)	44 (25%)	15 (34%)	65 (39%)
Lymphopenia	11 (31%)	61 (35%)	34 (77%)	NA
Myocardial enzymes elevated	11 (31%)	39 (22%)	3 (7%)	18 (11%)
Liver enzymes elevated	2 (6%)	32 (18%)	21 (48%)	12 (7%)
Elevated C-reactive protein	1 (3%)	86 (49%)	NA	42 (25%)
Antiviral therapy	14 (39%)	170 (97%)	42 (96%)	167 (100%)

Data are n (%) or mean (SD). COVID-19=coronavirus disease 2019. SARS=severe acute respiratory syndrome. NA=not available. *No pneumonia, no upper respiratory symptoms, and no fever. †The prevalence of abnormal radiographic presentations in children with SARS was obtained from reference 18.

Table 3: Comparison of prevalence of clinical features between children with COVID-19, adults with COVID-19, children with H1N1 influenza, and children with SARS

sore throat, which contrasts with patients with H1N1 influenza, despite the high prevalence of cough and fever in all patients. Pharyngeal congestion is more like an upper respiratory symptom than is fever (which is a systemic symptom) and cough, which can also be induced by a lower respiratory infection.

The findings of our study also showed that, although all paediatric cases were mild or moderate, the number of days spent in hospital and time needed for these patients to have negative PCR results was still considerable (table 1, figure 2). The time to achieve a negative PCR result seemed to be unaffected by severity of disease in terms of symptoms and the presence of pneumonia and treatment choices. Nevertheless, fever resolved faster in mild cases than in moderate cases (figure 2). Considering that delayed clearance of viral RNA in patients' stools is a potential risk for transmission,²³ particularly in patients in rehabilitation, the reliability of viral RNA-negative criteria in asymptomatic patients, in the long run, needs further investigation.

The major limitation of our study was the small sample size. However, most results were consistent within the study and, with several case reports on children with COVID-19, we believe our conclusions are valid. Since COVID-19 is spreading in more countries and has become an urgent public health event, we present an early report on paediatric patients and expect additional data to improve our findings.

In conclusion, our study shows that paediatric patients with COVID-19 have a simple transmission mode, either by close contact with infected adults or by exposure to epidemic areas. Although fever, dry cough, and mild pneumonia are common manifestations, nearly half of patients have neither obvious symptoms nor abnormal radiological findings. The proportion of asymptomatic cases indicates the difficulty in identifying paediatric patients without clear epidemiological information. This finding suggests a dangerous situation if community-acquired infections occur.

Contributors

HQ and JW designed the study and did the literature search. LH and YL were responsible for disease diagnosis and treatment and data collection. DC collected and analysed data. QS analysed data and wrote the report.

Declaration of interests

We declare no competing interests.

Acknowledgments

This study was funded by Ningbo Clinical Research Center for Children's Health and Diseases, Project of Ningbo Reproductive Medicine Centre (PPXK2018-06), and Key Scientific and Technological Innovation Projects of Wenzhou (ZY202004).

References

- Shi Z, Hu Z. A review of studies on animal reservoirs of the SARS coronavirus. *Virus Res* 2008; **133**: 74–87.
- Donnelly CA, Ghani AC, Leung GM, et al. Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong Kong. *Lancet* 2003; **361**: 1761–66.
- Cauchemez S, Fraser C, Van Kerkhove MD, et al. Middle East respiratory syndrome coronavirus: quantification of the extent of the epidemic, surveillance biases, and transmissibility. *Lancet Infect Dis* 2014; **14**: 50–56.
- Wu P, Hao X, Lau EHY, et al. Real-time tentative assessment of the epidemiological characteristics of novel coronavirus infections in Wuhan, China, as at 22 January 2020. *Euro Surveill* 2020; **25**: 2000044.
- Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus: a first step in understanding SARS pathogenesis. *J Pathol* 2004; **203**: 631–37.
- WHO. Coronavirus disease 2019 (COVID-19): situation report—41. March 1, 2020. <https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200301-sitrep-41-covid-19.pdf> (accessed March 12, 2020).
- Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. *Zhonghua Liu Xing Bing Xue Za Zhi* 2020; **41**: 145–51.
- Dagan R, Bhutta ZA, de Quadros CA, et al. The remaining challenge of pneumonia: the leading killer of children. *Pediatr Infect Dis J* 2011; **30**: 1–2.
- Campbell H, Nair H. Child pneumonia at a time of epidemiological transition. *Lancet Glob Health* 2015; **3**: e65–66.
- Leung CW, Kwan YW, Ko PW, et al. Severe acute respiratory syndrome among children. *Pediatrics* 2004; **113**: e535–43.
- Al-Tawfiq JA, Kattan RF, Memish ZA. Middle East respiratory syndrome coronavirus disease is rare in children: an update from Saudi Arabia. *World J Clin Pediatr* 2016; **5**: 391–96.
- Feng K, Yun YX, Wang XF, et al. Analysis of CT features of 15 children with 2019 novel coronavirus infection. *Zhonghua Er Ke Za Zhi* 2020; **58**: E007.
- National Health and Health Commission of the People's Republic of China. Diagnosis and treatment guidelines for 2019 novel coronavirus pneumonia (draft version 5). Feb 4, 2020. <http://www.nhc.gov.cn/yzygj/s7653p/202002/3b09b894ac9b4204a79db5b8912d4440.shtml> (accessed March 12, 2020; in Chinese).
- Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020; published online Feb 7, 2020. DOI:10.1001/jama.2020.1585.
- National Institute for Viral Disease Control and Prevention. Novel primers and probes for detection of novel coronavirus 2019. Jan 21, 2020. http://ivdc.chinacdc.cn/kyjz/202001/t20200121_211337.html (accessed March 12, 2020; in Chinese).
- Chen Z, Fu J, Shu Q, et al. Diagnosis and treatment recommendation for pediatric coronavirus disease-19. *Zhejiang Da Xue Xue Bao Yi Xue Ban* 2020; **49**: 1–8 (in Chinese).
- Chen D, Li X, Song Q, Hu C, Su F, Dai J. Hypokalemia and clinical implications in patients with coronavirus disease 2019 (COVID-19). Feb 29, 2020. <https://www.medrxiv.org/content/10.1101/2020.02.27.20028530v1> (accessed March 12, 2020).
- Babyn PS, Chu WC, Tsou IY, et al. Severe acute respiratory syndrome (SARS): chest radiographic features in children. *Pediatr Radiol* 2004; **34**: 47–58.
- Wang Z, Li X, Li D, Li Y. Clinical features of 167 children with the novel influenza A (H1N1) virus infection in Xi'an, China. *Turk J Pediatr* 2012; **54**: 99–104.
- Tang B, Bragazzi NL, Li Q, Tang S, Xiao Y, Wu J. An updated estimation of the risk of transmission of the novel coronavirus (2019-nCoV). *Infect Dis Model* 2020; **5**: 248–55.
- Wardlaw T, Salama P, Johansson EW, Mason E. Pneumonia: the leading killer of children. *Lancet* 2006; **368**: 1048–50.
- Standage SW, Wong HR. Biomarkers for pediatric sepsis and septic shock. *Expert Rev Anti Infect Ther* 2011; **9**: 71–79.
- Ling Y, Xu S-B, Lin Y-X, et al. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. *Chin Med J* 2020; published online Feb 28, 2020. DOI:10.1097/CM9.0000000000000774.