



Comparison of hospitalized patients with pneumonia caused by COVID-19 and influenza A in children under 5 years

Ying Li^{a,1}, Haizhou Wang^{b,c,1}, Fan Wang^{b,c}, Hui Du^a, Xueru Liu^a, Peng Chen^a, Yanli Wang^a, Xiaoxia Lu^{a,*}

^a Department of Respiratory Medicine, Wuhan Children's Hospital, Wuhan, China

^b Department of Gastroenterology, Zhongnan Hospital of Wuhan University, Wuhan, China

^c Hubei Clinical Center & Key Lab of Intestinal & Colorectal Diseases, Wuhan, China



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ABSTRACT

Background: Since the outbreak of Coronavirus Disease 2019 (COVID-19) in Wuhan, considerable attention has been paid to its epidemiology and clinical characteristics in children. However, it is also crucial for clinicians to differentiate COVID-19 from other respiratory infectious diseases, such as influenza viruses.

Methods: This was a retrospective study. Two groups of COVID-19 patients ($n=57$) and influenza A patients ($n=59$) were enrolled. We analyzed and compared their clinical manifestations, imaging characteristics and treatments.

Results: The proportions of cough (70.2%), fever (54.4%) and gastrointestinal symptoms (14.1%) in COVID-19 patients were lower than those of influenza A patients (98.3%, $P<0.001$; 84.7%, $P<0.001$; and 35.6%, $P=0.007$; respectively). In addition, COVID-19 patients showed significantly lower levels of leukocytes (7.87 vs. $9.89 \times 10^9 \text{ L}^{-1}$, $P=0.027$), neutrophils (2.43 vs. $5.16 \times 10^9 \text{ L}^{-1}$, $P<0.001$), C-reactive protein (CRP; 3.7 vs. 15.1 mg/L , $P=0.001$) and procalcitonin (PCT; 0.09 vs. 0.68 mm/h , $P<0.001$), while lymphocyte levels (4.58 vs. $3.56 \times 10^9 \text{ L}^{-1}$; $P=0.006$) were significantly higher compared with influenza A patients. In terms of CT imaging, ground-glass opacification in chest CT was more common in COVID-19 patients than in influenza A patients (42.1% vs. 15%, $P=0.032$). In contrast, consolidation was more common in influenza A patients (25%) than in COVID-19 patients (5.2%, $P=0.025$).

Conclusion: The clinical manifestations and laboratory tests of COVID-19 children are milder than those of influenza A children under 5 years. Additionally, imaging results more commonly presented as ground-glass opacities in COVID-19 patients.

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Introduction

Since December 2019, a novel coronavirus has broken out in Wuhan, and spread rapidly worldwide. On February 11, 2020, the World Health Organization (WHO) officially named this novel coronavirus pneumonia as Coronavirus Disease 2019 (COVID-19), whereas the International Committee on Taxonomy of Viruses has named it as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On 11 March, WHO declared that COVID-19 should

be characterized as a pandemic. Because of the highly contagious nature of SARS-CoV-2, the entire population was generally susceptible, including young children. Data from China showed young children were vulnerable to SARS-CoV-2 infection (Dong et al., 2020). In addition, WHO estimated that more than 2 million children under 5 years of age die from pneumonia, accounting for almost one in five under-5 deaths worldwide in 2004 (Wardlaw et al., 2006). Pneumonia was the leading infectious cause of death in children younger than 5 years (Wardlaw et al., 2006). Therefore, close attention should be paid to children with pneumonia less than 5 years old during the COVID-19 pandemic.

Influenza viruses have precipitated pandemics several times over the past 100 years, specifically in 1918, 1957, 1968 and 2009. Influenza A was a common cause of pneumonia in young children (Jain et al., 2015). Recently, Kong et al. retrospectively investigated

* Corresponding author at: 100 Hongkong Road, Jiangnan District, Wuhan, Hubei, China.

E-mail address: lusi74@163.com (X. Lu).

¹ These authors contributed equally to this work.

the presence of SARS-CoV-2 among local patients with influenza like illness (ILI) from 6 October 2019 to 21 January 2020 and found SARS-CoV-2 RNA was detected in nine ILI patient specimens (Kong et al., 2020). In addition, ILI data for the 2019–2020 winter was significantly higher in comparison to previous years regarding children, suggesting that it was necessary to distinguish the difference between influenza A and COVID-19 pneumonia in young children. Therefore, the aim of this study was to compare the different clinical presentations between patients infected with COVID-19 pneumonia versus influenza A pneumonia, to provide some recommendations for their differential diagnosis.

Methods

Study design and participants

Subjects of the study were consecutive children with either confirmed COVID-19 pneumonia (admitted between 28 January and 11 March 2020) or influenza A pneumonia (admitted between 14 December 2019 and 30 February 2020) in Wuhan Children's hospital. The study was approved by the Research Ethics Board of Wuhan Children's Hospital (No. 2020003). Consent of the patients' legal guardians was obtained.

Definitions

Children were included in the study if they had evidence consistent with pneumonia as assessed by means of chest radiography or CT within 72 h before or after admission. The virus nucleic acid detection kit confirmed COVID-19 patients through detecting the RNA of SARS-CoV-2 in throat swab samples based on the manufacturer's protocol (Shanghai BioGerm Medical Biotechnology Co., Ltd.). Influenza A was detected by direct immunofluorescence assay. The diagnostic criteria for severe pneumonia caused by SARS-CoV-2 and influenza A conform to guidelines (Society of Pediatrics, 2020, Harper et al., 2009).

Data collection

A COVID-19 or influenza A case report form was designed to document primary data regarding demographic, clinical and laboratory characteristics from electronic medical records. The following information was extracted from each patient: gender, age, medical history, chief complaints, laboratory findings and computed tomography (CT) imaging on admission.

Statistical analysis

Categorical data were described as percentages, and continuous data as median with standard deviation (SD). Nonparametric comparative test for continuous data and χ^2 test for categorical data were used to compare variables between groups. The statistical analyses were performed using SPSS Statistics version 25.0 software. $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics of COVID-19 and influenza A patients

A total of 57 COVID-19 patients and 59 influenza A patients were included (Table 1). No significant differences were found in the median age between COVID-19 patients and influenza A patients (18.7 months vs. 21.8 months, $P = 0.121$). The proportion of males to females was also not significantly different between the two groups (61.4% vs. 66.1%, $P = 0.599$). The most common symptoms and signs were cough (84.5%), fever (69.8%) and gastrointestinal symptoms (25%), whereas dyspnea (6.0%) and convulsions (3.4%) were less common. Moreover, the proportions of cough (70.2%), fever (54.4%) and gastrointestinal symptoms (14.1%) in COVID-19 patients were lower than those of influenza A patients (98.3%, $P < 0.001$; 84.7%, $P < 0.001$; and 35.6%, $P = 0.007$; respectively). Additionally, the highest body temperature of influenza A patients was also significantly higher than that of COVID-19 patients (38.5 °C vs. 39.3 °C, $P < 0.001$). The proportion of severe pneumonia in COVID-19 patients was also lower than that in patients infected with influenza A (3.5% vs. 18.6%, $P = 0.016$) (Table 1).

Laboratory and imaging findings between COVID-19 and influenza A patients

For blood inflammatory indicators, lower levels of C-reactive protein (CRP) and procalcitonin (PCT) were observed in COVID-19 patients than in influenza A patients (3.7 vs. 15.1 mg/L, $P = 0.001$; 0.09 vs. 0.68 ng/ml, $P < 0.001$). For routine blood tests, COVID-19 patients showed significantly lower levels of leukocytes and neutrophils, while lymphocyte levels were significantly higher compared with influenza A patients (7.87 vs. $9.89 \times 10^9 L^{-1}$, $P = 0.027$; 2.43 vs. $5.16 \times 10^9 L^{-1}$, $P < 0.001$; 4.58 vs. $3.56 \times 10^9 L^{-1}$, $P = 0.006$). For biochemistry testing, no significant differences were found in the alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB), bilirubin, blood urea nitrogen (BUN) and blood creatinine between the two groups of patients.

Table 1
Characteristics of patients with COVID-19 or Influenza A.

Variable	No. (%) or median $\pm$ SD			P value
	Total (n = 116)	COVID-19 (n = 57)	Influenza A (n = 59)	
Male	74 (63.8)	35 (61.4)	39 (66.1)	0.599
Age (months)	20.2 $\pm$ 16.7	18.7 $\pm$ 16.7	21.8 $\pm$ 16.7	0.121
Severe pneumonia	13 (11.2)	2 (3.5)	11 (18.6)	0.016
Symptoms and signs				
Fever	81 (69.8)	31 (54.4)	50 (84.7)	<0.001
Highest temperature (°C)	38.9 $\pm$ 0.7	38.5 $\pm$ 0.7	39.3 $\pm$ 0.6	<0.001
Cough	98 (84.5)	40 (70.2)	58 (98.3)	<0.001
Dyspnea	7 (6.0)	2 (3.5)	5 (8.5)	0.439
Gastrointestinal symptoms	29 (25)	8 (14.1)	21 (35.6)	0.007
Convulsions	4 (3.4)	1 (1.7)	3 (5.1)	0.619
Hospitalized treatment				
Oxygen inhalation	8 (6.9)	1 (1.7)	7 (11.8)	0.061
ICU	6 (5.2)	2 (3.5)	4 (6.7)	0.679

COVID-19, coronavirus disease 2019; No., number; SD, standard deviation; ICU, Intensive Care Unit.

Table 2

Laboratory findings of COVID-19 and Influenza A patients.

Variable	No. (%) or median ± SD			P value
	Total (n = 116)	COVID-19 (n = 57)	Influenza A (n = 59)	
Blood routine test				
Leukocytes (×10 ⁹ L ⁻¹)	8.88 ± 4.07	7.87 ± 2.87	9.89 ± 4.84	0.027
Neutrophils (×10 ⁹ L ⁻¹)	3.81 ± 3.69	2.43 ± 1.92	5.16 ± 4.46	<0.001
Lymphocytes (×10 ⁹ L ⁻¹)	4.06 ± 2.09	4.58 ± 2.06	3.56 ± 2.01	0.006
Platelets (×10 ⁹ L ⁻¹)	304 ± 110	298 ± 107	311 ± 113	0.455
Hemoglobin((g/L))	117 ± 11	117 ± 11	117 ± 12	0.932
Coagulation function				
PT (s)	10.9 ± 0.8	10.8 ± 0.7	11.2 ± 0.8	0.014
APTT (s)	33.6 ± 5.4	33.4 ± 5.2	34.1 ± 5.9	0.650
D-Dimer (ng/ml)	0.8 ± 1.7	0.34 ± 0.29	1.94 ± 2.88	<0.001
Inflammatory indicators				
CRP (mg/dl)	9.5 ± 24.1	3.7 ± 6.85	15.1 ± 32.2	0.001
PCT (ng/ml)	0.41 ± 1.35	0.09 ± 0.09	0.68 ± 1.82	<0.001
Biochemical test				
ALT (U/L)	31 ± 57	36 ± 78	26 ± 25	0.595
AST (U/L)	54 ± 64	57 ± 86	50 ± 30	0.591
TIBL (umol/L)	7.44 ± 4.53	7.35 ± 4.58	7.51 ± 4.52	0.799
ALB (g/L)	43.1 ± 5.5	42.7 ± 6.9	43.5 ± 3.6	0.964
CK (U/L)	138 ± 106	147 ± 89	130 ± 121	0.042
LDH (U/L)	338 ± 128	319 ± 92	357 ± 154	0.340
CK-MB (U/L)	42 ± 32	38 ± 20	46 ± 41	1.000
Creatinine (umol/L)	28.6 ± 29.9	26.5 ± 24.7	30.6 ± 34.2	0.939
BUN (mmol/L)	3.3 ± 1.7	3.48 ± 2.24	3.24 ± 1.15	0.122

COVID-19, coronavirus disease 2019; No., number; SD, standard deviation; CRP, C-reactive protein; PCT, procalcitonin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TIBL Total-bilirubin; ALB, albumin; PT, prothrombin time; APTT, activated partial thromboplastin time; LDH, lactate dehydrogenase; CK, Creatinine kinase; CK-MB, MB isoenzyme of creatine kinase; BUN, blood urea nitrogen.

However, lower levels of D-dimer and prothrombin time (PT) and potassium ion were found in COVID-19 patients than influenza A patients (0.34 vs. 1.94, $P < 0.001$; 10.8 vs. 11.2 mm/h, $P = 0.014$; 5.14 vs. 7.07 mmol/L, $P = 0.001$) (Table 2).

In terms of CT imaging, ground-glass opacification in chest CT was more common in COVID-19 patients than in influenza A patients (42.1% vs. 15%, $P = 0.032$). In contrast, consolidation was more common in influenza A patients (25%) than that in COVID-19 patients (5.2%, $P = 0.025$) (Figure 1 and Table 3).

Discussion

Since December 2019, an outbreak of coronavirus disease 2019 (COVID-19) has spread globally. The outbreak of COVID-19 began in December 2019, which also corresponded with the flu season in China (Yu et al., 2013). It is important to differentiate these two respiratory infectious diseases via early clinical presentation in consideration of their different therapies, prognoses, and protective measures. In this study, we first compared the different clinical

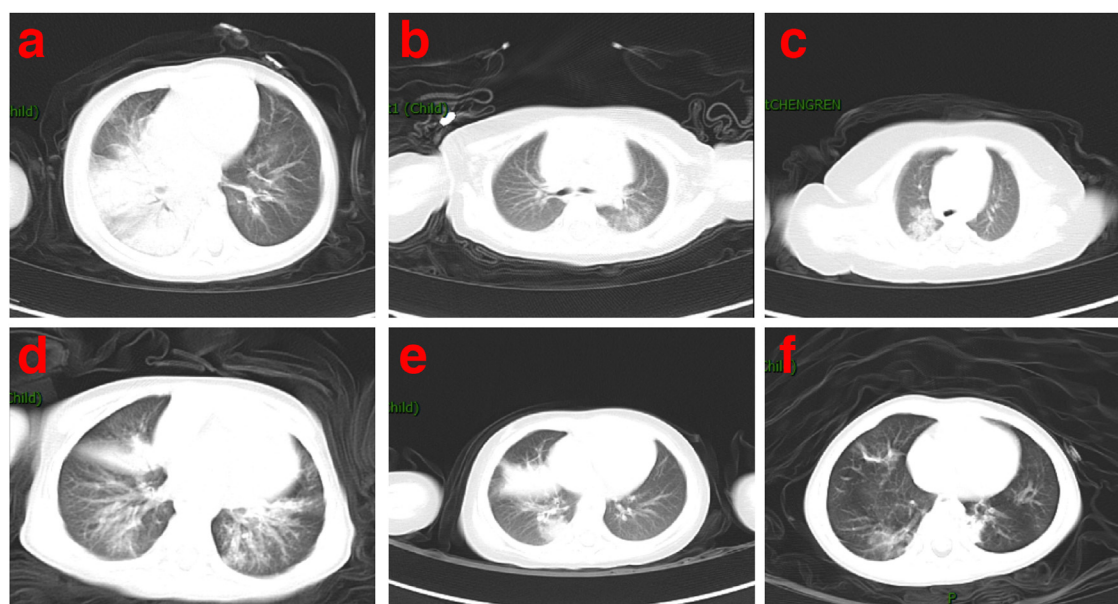


Figure 1. Imaging characteristics of chest CT from COVID-19 and influenza A patients. (a) A 1-year-old boy with COVID-19 exhibited ground-glass opacity mixed consolidation in both lungs. (b) A 7-month-old girl with COVID-19 exhibited ground-glass opacities in left lung. (c) A 1-month-old boy with COVID-19 exhibited consolidation in right lung. (d) A 1-year-old boy with influenza A exhibited exudation and consolidation distributed diffusely in both lungs. (e) A 2-year-old girl with influenza A exhibited consolidation in right lung. (f) A 2-year-old boy with influenza A exhibited consolidation in left lung and ground-glass opacity in right lung.

Table 3
CT Imaging findings of patients with COVID-19 or H1N1 at presentation

Variable	No. (%)			P value
	Total (n = 77)	COVID-19 (n = 57)	H1N1 (n = 20)	
Patterns of the lesion				
Ground glass opacification	24 (20.7)	24 (42.1)	3 (15)	0.032
Consolidation	8 (6.9)	3 (5.2)	5 (25)	0.025

COVID-19, coronavirus disease 2019; CT, computed tomography; No., number.

courses of pneumonia caused by SARS-CoV-2 and influenza A virus. We found that COVID-19 patients were mild in clinical symptoms and laboratory examinations in children under 5 years. Additionally, imaging results more commonly presented as ground-glass opacity in COVID-19 patients.

As we found before, cough and fever were common symptoms in COVID-19 (Lu et al., 2020), which is similar with influenza A. Our present study revealed that COVID-19 manifested as mild; severe pneumonia was less than influenza A patients. Some COVID-19 patients only presented as fever or cough. Meanwhile, influenza A patients were more likely to have fever with higher temperature. Gastrointestinal symptoms were common in patients with COVID-19 (Cheung et al., 2020), however, they were less than compared with influenza A. Convulsions could be found in both patients, but the reason was different, as only one in COVID-19 was secondary to pneumonia and three in influenza A were confirmed as febrile convulsion.

Lymphopenia and increase in D-dimer were common laboratory abnormalities in COVID-19 adults (Huang et al., 2020; Wang et al., 2020) and were proven as a caution for severity in COVID-19 (Ruan et al., 2020; Yang et al., 2020; Zheng et al., 2020). In our study, lymphocyte count and D-dimer were lower in influenza A patients than in COVID-19, which could further prove that COVID-19 is milder than influenza A. Similarly, CRP (C-reactive protein) and PCT (procalcitonin), which was the severity index of pneumonia, were lower in COVID-19 than influenza A.

In our study, we found that ground-glass opacity was more common in COVID-19 patients than in influenza A patients, whereas consolidation was more frequent in influenza A patients, which was consistent with previous studies. The radiological findings of children with COVID-19 pneumonia from our team and other studies showed that ground-glass opacities were the most common pattern of abnormalities in chest CT (Chang et al., 2020). Additionally, studies on influenza A-associated pneumonia showed that consolidation was common on CT (Guo et al., 2012). Therefore, these differential pathological changes may contribute to distinguish imaging characteristics during clinical assessments.

There were some limitations of our present study. First, this was a retrospective study that included data from a single-center cohort. We hope for a prospective cohort and multi-center study. Second, influenza A was diagnosed by direct immunofluorescence assay and failed to be typed.

In conclusion, COVID-19 cases were mild not only in clinical symptoms but also in laboratory examination results which included lymphocyte, CRP, PCT, and D-dimer in the children under 5 years. Additionally, imaging results more commonly presented as ground-glass opacity in COVID-19 patients.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding source

None declared.

Ethical approval

This study was approved by the Research Ethics Board of Wuhan Children's Hospital (No. WHCH 2020003).

Authors' contribution

All authors collected the clinical data. YL and HZW drafted the manuscript. XXL revised the final manuscript. FW, HD and XRL were responsible for summarizing all data related to this study.

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