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Co-infections of SARS-CoV-2 with multiple common respiratory pathogens in infected children

A retrospective study

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Abstract

Since the outbreak of coronavirus disease 2019 (COVID-19) in Wuhan, considerable attention has been paid on its epidemiology and clinical characteristics in children patients. However, it is also crucial for clinicians to summarize and investigate the co-infection of SARS-CoV-2 in children.

We retrospectively reviewed the clinical manifestations, laboratory findings, and imaging characteristics of COVID-19 patients in co-infection group (CI, n = 27) and single infection group (SI, n = 54). Samples were tested for multiple pathogens.

A high incidence (27/81, 33%) of co-infection in children with COVID-19 was revealed. The most frequent co-infected pathogen was mycoplasma pneumoniae (MP, 20/81, 25%), followed by virus (6/81, 7%), and bacteria (4/81, 5%). No significant difference in clinical characteristics, laboratory examinations, or hospital stay was observed between the patients with co-infections and those with monomicrobial, only lower in white blood cell counts (CI: 5.54 ± 0.36 vs SI: 7.38 ± 0.37, $P = .002$), neutrophil counts (CI: 2.20 ± 0.20 vs SI: 2.92 ± 0.23, $P = .024$) and lymphocyte counts (CI: 2.72 ± 0.024 vs SI: 3.87 ± 0.28, $P = .006$). Compared with the patients with monomicrobial, chest imaging of those with co-infections showed consolidation in more cases (CI: 29.6% vs SI: 11.1%, $P = .038$) and duration of positive in nucleic acid was shorter (CI: 6.69 ± 0.82 vs SI: 9.69 ± 0.74, $P = .015$).

Co-infection was relatively common in children with COVID-19, almost 1/3 had co-infection, most commonly caused by MP. Co-infection did not cause a significant exacerbation in clinical manifestations.

Abbreviations: ALB = albumin, ALT = alanine aminotransferase, APTT = activated partial thromboplastin time, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CAP = community-acquired pneumonia, CI = co-infection, CK = creatinine kinase, CK-MB = isoenzyme of creatine kinase, COVID-19 = coronavirus disease 2019, CRP = C-reactive protein, CT = computed tomography, MERS-CoV = Middle East respiratory syndrome coronavirus, MP = mycoplasma pneumoniae, PCT = procalcitonin, PT = prothrombin time, RT-PCR = real-time reverse transcription polymerase chain reaction, SARS-CoV = severe acute respiratory syndrome coronavirus, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SI = single infection.

Keywords: co-infection, coronavirus disease 2019, severe acute respiratory syndrome coronavirus 2

1. Introduction

Coronaviruses are positive-stranded, single-stranded RNA viruses with envelopes. Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) have been reported to cause serious diseases.[1,2] Since December 2019, many cases of unexplained pneumonia in Wuhan, Hubei have been confirmed as a new coronavirus infection. Since then, they have spread rapidly in the China and abroad. The virus was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Virus Classification Committee and World Health Organization named this disease caused by SARS-CoV-2 infection as coronavirus disease-19 (COVID-19).

There have been many reports of COVID-19 child cases, as we have presented in our study before, fever and cough were common symptoms in children with COVID-19, which is similar to another study in New York city.[3,4] What is more, children experience less severe COVID-19 than adults, presenting mild symptoms.[5] However, there are still few studies on co-infection in COVID-19 patients.[6] As reported by Jain et al in 2015, respiratory viruses were the most commonly detected in community-acquired pneumonia in children, such as adenovirus, human metapneumovirus, and

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mycoplasma pneumoniae.[7] Furthermore, Wu et al reported 19/34 (51.35%) COVID-19 children showed coinfection with other pathogens.[8] However, the clinical characteristics of co-infection and single infection in COVID-19 children are still unclear.

In this study, 81 cases of COVID-19 children hospitalized in Wuhan Children's Hospital were used to retrospectively summary of the co-infections in COVID-19 children. Our aim was designed to understand the co-infections in children with COVID-19 and provided a reference for clinical work.

2. Patients and methods

2.1. Study design and participants

Among the 101 children with COVID-19 who admitted to Wuhan Children's hospital from January 21, 2020 to February 16, 2020, 81 who did sputum culture, common respiratory virus (adenovirus, influenza virus A, B, parainfluenza virus 1, 2, 3, and respiratory syncytial virus) detected by direct immunofluorescence method, and mycoplasma pneumoniae specific immunoglobulin M (IgM) at the first 24 hours after admission were enrolled. This retrospective study was approved by the ethics committee of Wuhan Children' Hospital (No. 2020003).

2.2. Method of diagnosing COVID-19 patients

The virus nucleic acid detection kit was confirmed COVID-19 patients through detecting the RNA of SARS-CoV-2 in throat swab samples using based on the manufacturer's protocol (Shanghai BioGerm Medical Biotechnology Co.Ltd). Briefly, throat swabs from suspected children were obtained for detection of SAR-CoV-2 RNA. After collection, the swabs were transported to the laboratory within 2 hours in a collection tube with 150 microliter virus preservative medium. RNA from the respiratory specimens was extracted with the High Pure Viral Nucleic Acid Kit. The extracted nucleic acids were tested for SAR-CoV-2 using real-time reverse transcription polymerase chain reaction (RT-PCR) assay as described previously.

2.3. Inclusion and exclusion criteria

The inclusion criteria were children with COVID-19 who did sputum culture, common respiratory virus at the same time. The exclusion criteria were patients with recent respiratory infection or use medications, such as immunosuppressive drugs. Informed consent was obtained from each enrolled patient' parents. The definition of CI was children with COVID-19 infected another pathogen, such as bacteria (the sputum culture was positive), common respiratory virus or mycoplasma pneumoniae. The SI was patients with no evidence of infection by another pathogen.

2.4. Data collection

A COVID-19 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 and chest computed tomography (CT), and laboratory findings on admission.

2.5. 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. $P < .05$ was considered statistically significant.

Table 1

The details of co-infected pathogen.

	n (%)
Co-infection	27 (33)
Mycoplasma Pneumoniae (MP)	20 (25)
Virus	6 (7)
Influenza A + MP	1 (1)
Influenza B	2 (2)
RSV	1 (1)
Adenovirus + MP	1 (1)
Parainfluenza virus 2 + MP	1 (1)
bacteria	4 (5)
Moraxella catarrhalis	3 (4)
Streptococcus pneumoniae	1 (1)

3. Results

3.1. The details of co-infected pathogen

The most frequent co-infected pathogen was mycoplasma pneumoniae (MP, 20/81, 25%), followed by virus (6/81, 7%), and bacteria (4/81, 5%). The virus contained influenza A (1/81, 1%), influenza B (2/81, 2%), RSV (1/81, 1%), adenovirus (1/81, 1%). The bacteria contained moraxella catarrhalis (3/81, 4%), streptococcus pneumoniae (1/81, 1%) (Table 1).

3.2. Baseline characteristics

A total of 81 COVID-19 patients were divided into 27 co-infection (CI) group and 54 single infection (SI) group (Table 2). No significant differences were found in the baseline characteristics between the 2 groups. CI and SI patients showed similarly median age (CI: 76.55 months vs SI: 59.88 months, $P = .196$). The proportion of male was also not significantly different between the 2 groups (CI: 15 [55.6%] vs SI: 36 [66.7%], $P = .329$). Moreover, there was also no significant difference in the proportions of cough (CI: 18 [66.7%] vs SI: 32 [59.2%], $P = .518$) and fever (CI: 16 [59.2%] vs SI: 33 [61.1%], $P = .872$) between CI an SI patients. Children in our study did not have any underlying disease. There was no death in our study, and only 1 child who suffered from respiratory failure (the ABG was pH

Table 2

Characteristics of patients with CI and SI patients.

	CI group (n = 27)	SI group (n = 54)	*P* value
Age (month)	76.55 ± 9.64	59.88 ± 7.63	.196
Male (%)	15 (55.6)	36 (66.7)	.329
Fever (%)	18 (66.7)	32 (59.2)	.518
Fever duration (d)	3.81 ± 0.87	3.80 ± 0.73	.992
Cough (%)	16 (59.2)	33 (61.1)	.872
Vomiting	1 (3)	2 (3)	NA
Diarrhea	1 (3)	3 (5)	NA
Fatigue	0	2 (3)	NA
Tachypnea	0	1 (2)	NA

Characteristics of patients with COVID-19 or influenza A.
CI = co-infection, SI = single infection.

Table 3

Laboratory and CT Imaging findings of CI and SI patients.

	CI group (n = 27)	SI group (n = 54)	*P* value
Leukocytes ($\times 10^9$/L)	5.54 ± 0.36	7.38 ± 0.37	.002
Neutrophils ($\times 10^9$/L)	2.20 ± 0.20	2.92 ± 0.23	.024
Lymphocytes ($\times 10^9$/L)	2.72 ± 0.024	3.87 ± 0.28	.006
PT (s)	11.29 ± 0.012	10.95 ± 0.11	.081
APTT (s)	31.41 ± 0.77	31.94 ± 0.66	.631
D-Dimer (ng/ml)	0.68 ± 0.40	0.28 ± 0.02	.336
ALT (U/L)	13.00 (11.00,23.50)	16.00 (11.00,23.00)	.064
AST (U/L)	28.00 (25.00,42.00)	36.00 (24.00,51.00)	.193
CK (U/L)	125.75 ± 12.17	138.26 ± 12.44	.521
CK-MB (U/L)	24.00 (18.00,35.50)	32.00 (20.00,48.00)	.208
LDH (U/L)	284.75 ± 21.49	314.34 ± 24.83	.436
BUN (mmol/L)	4.10 (2.80,5.30)	3.86 (3.00,4.60)	.598
Creatinine (μmol/L)	33.84 ± 1.75	32.06 ± 1.69	.498
CRP (mg/dl)	2.93 (0.00,5.52)	0.00 (0.00,5.00)	.626
PCT (ng/ml)	0.06 (0.03,0.09)	0.06 (0.04,0.08)	.692
Ground glass opacification	7 (25.9)	16 (29.6)	.727
Consolidation	8 (29.6)	6 (11.1)	.038
Length of hospitalization (d)	11.53 ± 0.84	12.74 ± 0.72	.321
Negative conversion time (d)	6.69 ± 0.82	9.69 ± 0.74	.015

ALB = albumin, ALT = alanine aminotransferase, APTT = activated partial thromboplastin time, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CK = creatinine kinase, CK-MB = MB isoenzyme of creatine kinase, COVID-19 = coronavirus disease 2019, CRP = C-reactive protein, LDH = lactate dehydrogenase, PCT = procalcitonin, PT = prothrombin time, TIBL = total-bilirubin.

7.29, PCO_2 28.1 mm Hg, PO_2 52 mm Hg, HCO_3 13 mmol/L, SaO_2 83.1%) in our study need respiratory support treatment mechanical ventilation.

3.3. Comparison of laboratory and imaging findings between CI and SI groups

For blood inflammatory indictors, the level of C-reactive protein (CRP), procalcitonin (PCT), creatinine kinase (CK), and MB isoenzyme of creatine kinase (CK-MB) were similar between the 2 groups. For blood routine test, CI patients showed significantly lower levels of leukocytes, lymphocytes, and neutrophils compared with SI patients (CI: 5.54 vs SI: 7.38×10^9/L, $P = .002$; CI: 2.20 vs SI: 2.92×10^9/L, $P = .024$; CI: 2.72 vs SI: 3.87×10^9/L; $P = .006$). For biochemistry testing, no significant differences were found in the alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB), bilirubin, blood urea nitrogen (BUN), blood creatinine, prothrombin time (PT), activated partial thromboplastin time (APTT), and D-Dimer between the 2 groups of patients. Interestingly, patients in the CI group had a shorter conversion time for nucleic acid test from positive to negative than patients in the SI group (Table 2).

In terms of CT imaging, consolidation in chest CT was more common in CI patients than in SI patients (CI: 8 [29.6%] vs SI: 6 [11.1%], $P = .038$), while no significant difference in ground-glass opacification (CI: 7 [25.9%] vs SI: 16 [29.6%], $P = .727$) (Table 3).

4. Discussion

Since December 2019, an outbreak of COVID-19 has spread globally. There were many case reports of concurrent infections with other pathogens, such as influenza virus, human metapneumovirus, and seasonal coronaviruses such as CoV-HKU-1 in adults and children with SARS-CoV-2 infection.[9–11] However, details about co-infection is limit. In this study, we firstly analyzed the clinical symptoms, laboratory examinations, and imaging in the COVID-19 children with CI compared with the SI. We found that almost 33.3% of COVID-19 children had co-infection, most commonly caused by MP, and blood routine test and consolidation in CT imaging could help us to recognize co-infection. Co-infection is common in COVID-19 children, but did not make the clinical course serious.

Our present study revealed that the rate of co-infection in children was 33.3%, which was higher than data in adult,[12] but was similar to co-infection in community-acquired pneumonia (CAP).[13] Moreover, this study suggested that the proportion of mixed MP was the highest, about 25%. Wang et al analyzed the pathogens of CAP in our country, suggesting that MP played an increasingly important role in the pathogenic microorganisms of CAP in children.[14]

Recent case reports suggested that co-infection might influence morbidity and mortality.[9–11] However, no death cases were found in this study and only 1 child in our study need respiratory support treatment (mechanical ventilation). Our study further analyzed the clinical characteristics we collected and found that there was no significant difference in clinical manifestations and hospital stays between the CI and the SI group, suggesting that co-infection could not aggravate the severity of the disease. However, the levels of leukocytes, neutrophils and lymphocytes in the CI group were significantly lower than those in the SI group, while all were within the normal range. In the CI group, imaging of lung consolidation was more common than that in the SI group, which may be mainly due to the fact that the co-infections in this study were mostly mixed with MP infection. Previous studies showed that the most common changes were lung consolidation on imaging in children infected with MP.[15]

It was worth noting that the SARS-CoV-2 nucleic acid conversion time from positive to negative in the CI group was significantly shorter than that of the SI group. To analyze the reasons, the CI group was mostly mixed with MP infection, and treated with oral azithromycin. The SI group mostly was treated with interferon atomization or spray. The study of Philippe Gautreta et al showed that azithromycin could contribute to the eliminate SARS-CoV-2,[16] so it is speculated that azithromycin may accelerate the removal of SARS-CoV-2 in children with COVID-19. However, another viewpoint indicated that no evidence of rapid antiviral clearance with azithromycin was shown in patients with COVID-19.[17] Therefore, this view needs further and more rigorous research and demonstration.

There were some limitations of our present study. First, this was a retrospective study that included data from a single-center cohort, a large multi-center study was needed. Second, this study only recruited 81 COVID-19 patients. Increasing the number of cases was better for observing the clinical manifestations in co-infection COVID-19 children. Third, information about these children were limited.

In conclusion, our study found that co-infection in COVID-19 children was relatively common and was mainly caused by MP infection. Furthermore, co-infection did not cause a significant exacerbation in clinical manifestations.

Author contributions

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