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Co-infection with respiratory pathogens among COVID-2019 cases

Xiaojuan Zhu^{a,1}, Yiyue Ge^{a,1}, Tao Wu^a, Kangchen Zhao^a, Yin Chen^a, Bin Wu^a, Fengcai Zhu^a,
Baoli Zhu^{a,b,**}, Lunbiao Cui^{a,*}

^a NHC Key laboratory of Enteric Pathogenic Microbiology, Jiangsu Provincial Center for Disease Control and Prevention, Nanjing 210009, China

^b From Center for Global Health, School of Public Health, Nanjing Medical University, Nanjing 211166, China

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ABSTRACT

Accumulating evidence shows that microbial co-infection increases the risk of disease severity in humans. There have been few studies about SARS-CoV-2 co-infection with other pathogens. In this retrospective study, 257 laboratory-confirmed COVID-19 patients in Jiangsu Province were enrolled from January 22 to February 2, 2020. They were re-confirmed by real-time RT-PCR and tested for 39 respiratory pathogens. In total, 24 respiratory pathogens were found among the patients, and 242 (94.2 %) patients were co-infected with one or more pathogens. Bacterial co-infections were dominant in all COVID-19 patients, *Streptococcus pneumoniae* was the most common, followed by *Klebsiella pneumoniae* and *Haemophilus influenzae*. The highest and lowest rates of co-infections were found in patients aged 15–44 and below 15, respectively. Most co-infections occurred within 1–4 days of onset of COVID-19 disease. In addition, the proportion of viral co-infections, fungal co-infections and bacterial-fungal co-infections were the highest severe COVID-19 cases. These results will provide a helpful reference for diagnosis and clinical treatment of COVID-19 patients.

1. Introduction

Respiratory illness caused by a novel coronavirus was first noted in December of 2019 in Wuhan, Hubei Province, China (Zhu, et al. 2020). The novel coronavirus is now referred to as severe and critical acute respiratory syndrome coronavirus-2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses (ICTV). The SARS-CoV-2 was transmitted through respiratory tract and could induce pneumonia (Chen, et al. 2020; Chu, et al. 2020). By 6 April, WHO has reported of 1, 210, 956 laboratory-confirmed cases of SARS-CoV-2 infection and 67,594 deaths worldwide (WHO, 2020). The current outbreaks of coronavirus infection remind us that CoVs are still a severe and critical threats to global public health.

There are no proven antiviral therapies or vaccines till now. Thus, the best way to deal with severe and critical infections of SARS-CoV-2 is to control the source of infection, early diagnosis, quarantine and supportive treatments. It is difficult for physicians to distinguish causative agents without a laboratory diagnosis due to the similar clinical presentations of different pathogens. Therefore, the fast and accurate diagnosis of SARS-CoV-2 are particularly important for patients.

However, most studies only focused on SARS-CoV-2, while the co-infection with SARS-CoV-2 has been somewhat neglected. Co-infection with certain pathogens may also hinder accurate disease diagnosis. Wang et al. presented the latest status of the SARS-CoV-2 co-infection in China and added details on combined bacterial and fungal infections (Wang, et al. 2020). However, the types of co-infected pathogens and the proportion of co-infection in SARS-CoV-2-positive patients are unclear. In this study, the clinical features of COVID-19 patients were analyzed, then 39 respiratory pathogens in their throat swab were detected by specific real-time RT-PCR. This study will provide a reference for epidemic prevention and clinical treatment in Wuhan and other areas combating this epidemic.

2. Materials and methods

2.1. Clinical data and specimens collection

From Jan 22 to Feb 2, 2020, 257 throat swab samples with initial positive real-time RT-PCR results were collected from local hospital in Jiangsu Province. The samples were taken immediately from each

* Corresponding author.

** Corresponding author at: NHC Key laboratory of Enteric Pathogenic Microbiology, Jiangsu Provincial Center for Disease Control and Prevention, Nanjing 210009, China.

E-mail addresses: zhubl@jscdc.cn (B. Zhu), lbcui@jscdc.cn (L. Cui).

¹ These authors contributed equally to this article.

COVID-19 patient on admission. The clinical, laboratory, and outcome data were obtained from medical records. The following parameters were recorded on admission: age, sex, clinical presentation classification. All procedures conducted in this study involving human materials were approved by the Jiangsu Provincial Center for Disease Control Ethics Committee.

2.2. Detection respiratory pathogens

Firstly, SARS-CoV-2 was re-confirmed by real-time RT-PCR using the same protocol described previously (Chu, et al. 2020; Huang, et al. 2020). Other 39 respiratory pathogens including influenza A (FluA), influenza B (FluB), human respiratory syncytial virus (RSV), parainfluenza types 1, 2, 3 and 4 (PIV1, 2, 3, 4), human metapneumovirus (HMPV), coronaviruses 229E, OC43, NL63 and HKU1 (HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1), human bocavirus adenovirus (HBoV), human adenovirus (HAdV), human rhinovirus (HRV), herpes simplex virus (HSV), cytomegalovirus (CMV), EB virus (EBV), *Mycoplasma pneumoniae* (MP), *Chlamydia pneumoniae* (CP), *Legionella pneumoniarum*(LP), *Haemophilus influenzae* (Hi), *Moraxella catarrhalis* (MC), *Klebsiella pneumoniae* (KP), *Streptococcus pneumoniae* (S.pneumoniae), *Mycobacterium tuberculosis* (TB), *Escherichia coli* (E. coli), *Staphylococcus aureus* (S. aureus), *Acinetobacter baumannii* (A. baumannii), *Pseudomonas aeruginosa* (P. aeruginosa), *pneumocystis carinii* (PC), *Bordetella pertussis* and fungi (*Aspergillus*, *Cryptococcus*, *Cryptococcus neoformans* A, B, *Mucor*, *Candida*, *Histoplasma capsulatum*) were also detected using pathogen specific real-time RT-PCR as previously described (Zhu, et al. 2019).

2.3. Statistical analysis

Kruskal-Wallis H-test was used to compare continuous variables among multiple groups, and Dunnett test was used for pair-wise comparison; categorical variables were expressed as number (%) and compared by Chi-square test or Fisher's exact test among multiple groups. A value of $P < 0.05$ was considered to be significant. SPSS 19.0 software and GraphPad 7.0 were used for statistical analysis.

3. Result

3.1. Characteristics of patients

Baseline characteristics of all cases and different groups are described in Table 1. 257 patients were diagnosed with the SARS-CoV-2 infection and their clinical severity was classified according to National Health Commission of the People's Republic of China revised criteria for diagnosis and treatment of novel coronavirus infection pneumonia (trial version fifth, revised version). These patients were categorized into four clinical types, of which 22 (8.5 %) were asymptomatic cases (A total of 19 patients showed symptoms after sampling), 78 (30.4 %)

were mild cases, 140 (54.5 %) were moderate cases, and 17 (6.6 %) were severe/critical cases (including 14 severe cases and 3 critical cases). There was no death of all the cases in our study, 3 cases of critical patients were admitted to intensive care unit (ICU). The age of patients in moderate category was significantly lower than in mild category ($P < 0.01$), whereas asymptomatic and severe/critical category did not significantly differ in age from the moderate category. Totally, more men (53.7 %) than women were observed, but most of the patients were female (68.2 %) in asymptomatic category. Below 15 years of age, a total of 11 (4.3 %) were diagnosed with the SARS-CoV-2 infection and there were no case in severe/critical category.

3.2. Co-infection of SARS-CoV-2 with respiratory pathogens

A total of 243 (94.2 %) patients had viral, bacterial and fungal co-infections. As shown in Fig. 1, 9 viruses, 11 bacteria and 4 fungi were detected. 81 patients (31.5 %) had viral co-infection, 236 (91.8 %) had bacterial co-infection, and 60 (23.3 %) had fungal co-infection (Table 2). The co-infection pathogens were as follows: *S.pneumoniae* (153, 59.5 %), KP (143, 55.6 %), Hi (103, 40.1 %), *Aspergillus* (60, 23.3 %), EBV (52, 20.2 %), E. coli (24, 9.3 %), *S. aureus* (21, 8.2 %), HRV (12, 4.7 %), *P.aeruginosa* (12, 4.7 %), MC (11, 4.3 %), HAdV (10, 3.9 %), HSV (8, 3.1 %), *A. baumannii* (7, 2.8 %), CP (6, 2.5 %), *Mucor* (6, 2.5 %), influenza B (5, 1.9 %), MP (4, 1.6 %), *Bordetella pertussis* (3, 1.2 %), *Candida* (2, 0.8 %), CMV (3, 1.2 %), influenza A (2, 0.8 %), HBoV (1, 0.4 %), HMPV (1, 0.4 %) and *Cryptococcus* (1, 0.4 %). The proportion of bacterial co-infection (75, 96.2 %) was highest, followed by bacterial-viral (26, 33.3 %), viral-fungal (11, 14.1 %) and viral-bacterial-fungal (11, 14.1 %) co-infections in mild category ($P > 0.05$; Table 2). The rates of viral co-infection (6, 35.3 %), fungal co-infection (5, 29.5 %) and bacterial-fungal co-infection (5, 29.5 %) were the highest in severe/critical category ($P > 0.05$; Table 2).

3.3. Co-infections varied with age and time of onset

Of the 138 male patients, 128 (92.8 %) were co-infected, while 113 (95.0 %) females had co-infection. Below 15 years of age, there were 11 pathogens were found and HMPV only appeared in this group (Fig. 2A). The rates of KP, *Aspergillus*, E. coli, and HRV co-infection were the lowest. Between 15 and 44 years of age, 22 pathogens were discovered except for HMPV and *Cryptococcus*. Among these, influenza A and HBoV were only found in this group (Fig. 2A). The rates of *S.pneumoniae*, KP, Hi, *Aspergillus*, EBV, E. coli, *S. aureus*, *P.aeruginosa*, HAdV, *A. baumannii*, *Mucor*, influenza B and MP co-infection were the highest. Between 45 and 64 years of age, 19 pathogens were discovered and *Cryptococcus* only appeared in this group (Fig. 2A). The rates of HRV, CP and MC co-infection were highest. Above 65 years of age, there were 14 pathogens (Fig. 2A). The rates of EBV, *S. aureus*, *P.aeruginosa* and MC co-infection were the lowest. However, the co-infection rates had no statistical significant difference among different age groups

Table 1
Characteristics of patients infected with SARS-CoV-2.

Characteristic	No. (%)				
	Total (n = 257)	Asymptomatic (n = 22)	Mild (n = 78)	Moderate (n = 140)	Severe/critical (n = 17)
Median age (range)-yr	51 (2–99)	46 (14–77)	52 (4–99)	41 (2–80)	52 (32–72)
Age group					
< 15 yr	11 (4.3)	1 (4.5)	7 (9.0)	3 (2.1)	0 (0)
15–44 yr	124(48.2)	11 (50)	36 (46.2)	72 (51.4)	5 (29.4)
45–64 yr	96 (37.4)	7 (31.8)	27 (34.6)	55 (39.3)	7 (41.2)
≥ 65 yr	26 (10.1)	3 (13.6)	8 (10.3)	10 (7.1)	5 (29.4)
Gender					
Female	119 (46.3)	15 (68.2)	34 (43.6)	62 (44.3)	8 (47.1)
Male	138 (53.7)	7 (31.8)	44 (56.4)	78 (55.7)	9 (52.9)

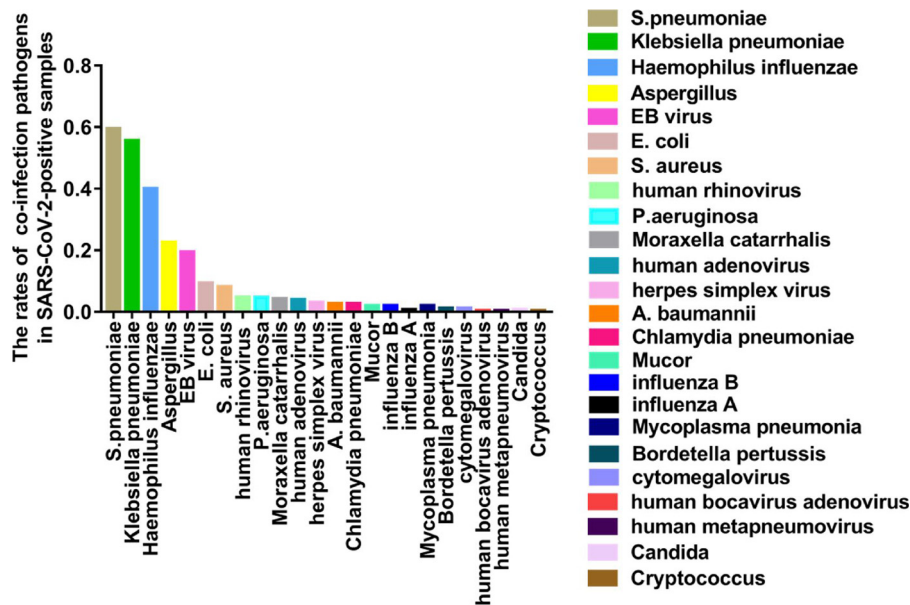


Fig. 1. Distribution of respiratory pathogens with the SARS-CoV-2 co-infection.

Table 2
Characteristics of respiratory pathogens with the SARS-CoV-2 co-infection.

Characteristic	No. (%)				
	Total (n = 257)	Asymptomatic (n = 22)	Mild (n = 78)	Moderate (n = 140)	Severe/critical (n = 17)
Co-infections any virus isolated ^a	242 (94.2)	21 (95.5)	75 (96.2)	129 (92.1)	17 (100)
any bacteria isolated ^b	81 (31.5)	4 (18.2)	26 (33.3)	45 (32.1)	6(35.3)
any fungi isolated ^c	236 (91.8)	21 (95.5)	75 (96.2)	124(88.6)	16 (94.1)
Bacteria-virus	60 (23.3)	6 (27.3)	18 (23.8)	31 (22.1)	5 (29.4)
Bacteria-fungi	77 (30.0)	4 (18.2)	26 (33.3)	42 (30)	5 (29.5)
Virus-fungi	61 (23.7)	6 (27.3)	20 (25.6)	30 (21.4)	5 (29.5)
Bacteria-virus-fungi	24 (9.3)	1 (4.5)	11 (14.1)	11 (7.9)	1 (5.9)
Bacteria-virus-fungi	23 (8.9)	1 (4.5)	11 (14.1)	10 (7.1)	1 (5.9)

The viruses in the table refer to viruses other than SARS-CoV-2.

^a included “virus only” and “virus-fungi or bacteria-virus or bacteria- virus-fungi”.

^b included “bacteria only” and “bacteria-fungi or bacterial-virus or bacteria-virus-fungi”.

^c included “fungi only” and “fungi-virus or fungi-bacterial or bacteria- virus-fungi”.

($P > 0.05$). The pathogen distribution was also analyzed along with disease course. The results showed that there were 19 pathogens in -4–0 days after onset, and CMV and HMPV co-infection only appeared in this group (Fig. 2B). The rates of *E. coli* and HRV co-infection were the highest. 21 pathogens were discovered in 1–4 days after onset. HBoV and *Candida* only appeared in this group. The rates of *S.pneumoniae*, KP, Hi, *Aspergillus*, EBV, *S. aureus*, *P.aeruginosa*, MC, HAdV, HSV, *A. baumannii* and CP co-infection were the highest. There were 18 pathogens in 5–8 days after onset, and *Cryptococcus* only appeared in this group (Fig. 2B). The rates of Influenza B co-infection were highest. Only 9 pathogens were found in 9–15 days after onset (Fig. 2B). No significant differences were found by days after onset ($P > 0.05$).

3.4. Co-infection pattern related to different clinical types

There were 10, 22, 20 and 13 pathogens were found in symptomatic, mild, moderate, and severe/critical cases, respectively (Fig. 3). *S.pneumoniae*, KP, Hi, *Aspergillus*, EBV, *E. coli*, and *S. aureus* were simultaneously found in four clinical groups. *S.pneumoniae*, KP, Hi, *Aspergillus*, EBV were most frequently found. MC and *A. baumannii* were found in asymptomatic category, mild category and moderate category. Although no statistical significance was found, the nucleic acid-positive rate of MC (3, 13.6 %) was the highest in mild category. HAdV, HRV, HSV and *P.aeruginosa* were found in mild category, moderate case, severe/critical category. The positive rates of HRV (8, 10.3 %) were highest in mild category. CMV was discovered in asymptomatic category and moderate category. influenza A, influenza B, CP, MP and *Mucor* were detected in mild case and moderate category. The positive rates of influenza A (1, 1.3 %), influenza B (2, 2.6 %), and MP (3, 3.9 %) were higher in mild category, whereas CP (4, 2.9 %) and *Mucor* (4, 2.9 %) were higher in moderate category. *Bordetella pertussis* and *Candida* were determined in moderate category, severe/critical category.

4. Discussion

Co-infection may significantly inhibit the immune system of host, increase antibacterial therapy intolerance, and be harmful to the prognosis of the disease (Li and Zhou, 2013). In our study, 94.2 % of COVID-19 patients could be co-infected with one or more other pathogens, including 9 viruses, 11 bacteria and 4 fungi. There was no death of all the cases. Only 3 patients were admitted to the ICU. The proportions of the co-infection had no statistical significant difference between ICU and non-ICU patients. The results suggested that there was no specific relationship between co-infection and ICU admission, as well as the occurrence of death. The prognosis of patients with co-infection needs to be further studied.

Bacterial co-infection in the setting of viral pneumonia is known as major cause of mortality (Guo, et al. 2019). Our results showed that bacterial co-infection were dominant in all COVID-19 patients. *S.pneumoniae*, KP, and Hi were the most common bacterial co-infection in our study. Although some of them are co-colonization, they are conditional pathogen. They might also pathogenic when the immune function of COVID-19 patients were decreased. It suggested that pneumococcal conjugate and polysaccharide vaccines would offer an

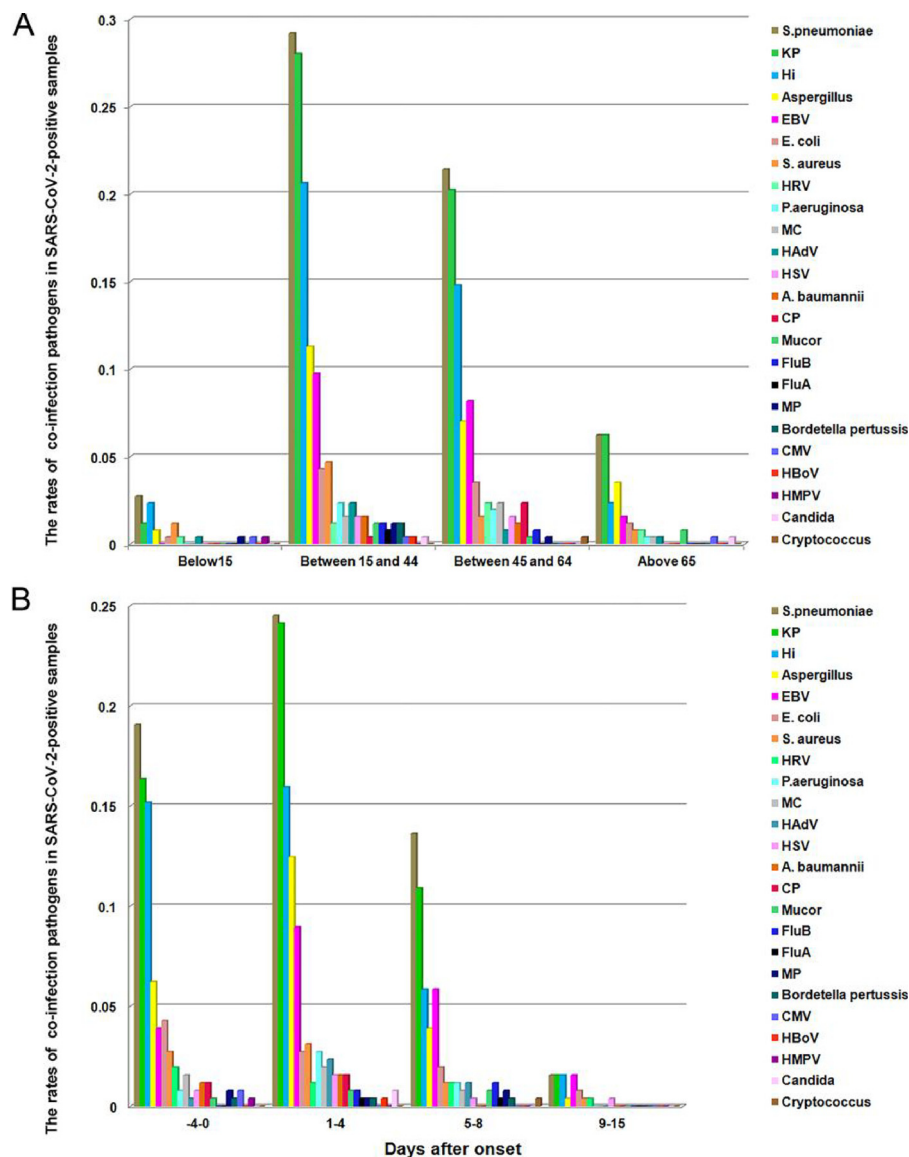


Fig. 2. Distribution proportion of respiratory pathogens with SARS-CoV-2 co-infection. A: Distribution pathogens in different ages; B: Distribution of pathogens in different time of onset.

effective approach to preventing the most common co-infection during the COVID-19 pandemic. In addition to bacteria, fungi was also a major factor of co-infection secondary to viral infections such as seen in influenza infection in which *A. baumannii*, *Aspergillus*, *Candida* and KP were discovered as common secondary infections (Gao, et al. 2013; Guo, et al. 2019). In this study, the highest rates of co-infection with bacteria and fungi were found among severe and critical category. Some of pathogens are known antibiotic resistance which may make the treatment of COVID-19 patients more difficult. Wang et al. studied 104 patients with SARS-CoV-2 infection and found that 3 (2.88 %) patients were co-infected with other coronavirus, 2 (1.94 %) were co-infected with influenza A (Wang, et al. 2020). In this study, we also found a few of influenza A, influenza B co-infections, but no coronavirus was detected. These results indicated that the co-infections with influenza A, influenza B or coronavirus were not common in COVID-19 patients, though the seasonal influenza is now prevalent. However, influenza A, influenza B co-infections may increase the risks of COVID-19 patients. Influenza vaccination is still recommended. It was notable that the positive rates of HAdV and HRV were higher than that of influenza viruses. HAdV and HRV are associated with lower mortality, but significant higher morbidity, causing a huge economic burden (Fendrick,

et al. 2003). EBV and HSV were the common pathogens carried by adults. The effects of their roles in the process of COVID-19 need to be explored. CMV, HBoV, and HMPV were important pathogens of respiratory tract infection in children. However, only a few of them were found co-infected with SARS-CoV-2. The virus co-infection could cause both upper and lower respiratory tract infections, and demonstrate overlapped clinical presentations. Thus, other viruses should also be considered while diagnosing and treating SARS-CoV-2.

Similar co-infection rate and pathogens in females was found when compared with males which mean both man and women are susceptible to other respiratory pathogens. The species of co-infected pathogens were higher between patients of 15–64 years old than that of below 15 years and above 65 years of age. We also found that the rates of influenza, HRV, and HAdV co-infection were higher among cases of 15–64 years old which was different from the previous studies in which the pathogens were found mainly affecting the young and aged people. It may be due to the decreased immunity after SARS-CoV-2 infection. The highest Co-infection rate and the most pathogen species were detected in cases of 1–4 days after onset. Along with the course of disease, both the rates and pathogen species of co-infection among COVID-19 patients were decreased significantly, which may due to the treatment

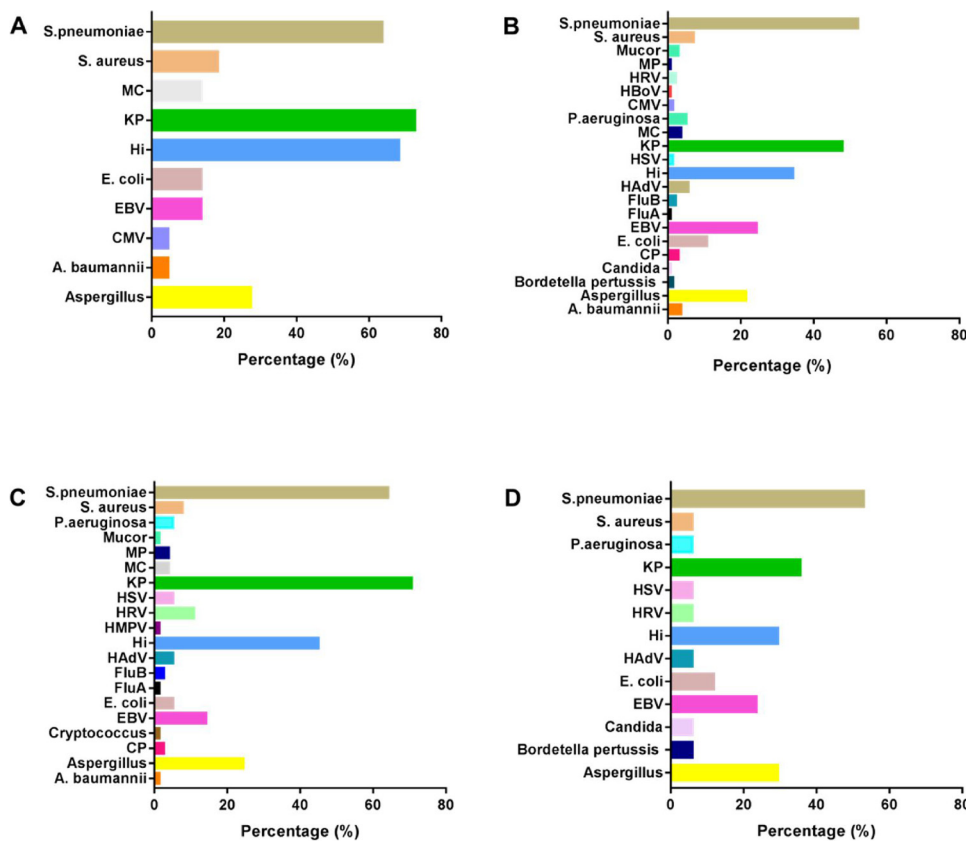


Fig. 3. Distribution and positive rates of co-infected respiratory pathogens. A: The nucleic acid-positive rates of 10 respiratory pathogens in 22 symptomatic category; B: The nucleic acid-positive rates of 20 pathogens in 78 mild category; C: The nucleic acid-positive rates of 22 pathogens in 140 moderate category; D: The nucleic acid-positive rates of 13 pathogens in 17 severe/critical category.

the patients received. We noticed that a high co-infection rate and pathogen species in patients of -4-0 days after onset, which indicated asymptomatic category also have high co-infection opportunity although the pathogen species was the lowest, and early treatment should be taken for them. Pathogen species was also not high in severe/critical category, which may attribute to all of them have been taken medical intervention.

5. Conclusions

In this study, we tested for the presence of 24 types of respiratory pathogens in 257 COVID-19 patients. At present, more and more patients of infectious diseases were characterized by an increased multipathogen co-infection, which has increased the difficulty in clinical diagnosis and treatment. Therefore, while testing SARS-CoV-2, we needed simultaneously screen other respiratory pathogens which was very important to for the appropriate treatment and diagnosis.

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CRedit authorship contribution statement

Xiaojuan Zhu: Methodology, Data curation, Formal analysis, Visualization, Writing - original draft. **Yiyue Ge:** Funding acquisition,

Visualization, Software, Writing - review & editing. **Tao Wu:** Methodology. **Kangchen Zhao:** Methodology. **Yin Chen:** Methodology. **Bin Wu:** Funding acquisition, Methodology. **Fengcai Zhu:** Project administration, Supervision. **Baoli Zhu:** Project administration, Supervision. **Lunbiao Cui:** Conceptualization, Funding acquisition, Project administration, Validation, Writing - review & editing.

Declaration of Competing Interest

The authors declare no conflict of interest.

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