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Co-infection of SARS-COV-2 and Influenza A Virus: A Case Series and Fast Review*

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Summary: Coronavirus disease 2019 (COVID-19) occurs in the influenza season and has become a global pandemic. The present study aimed to examine severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) co-infection with influenza A virus (IAV) in an attempt to provide clues for the antiviral interventions of co-infected patients. We described two patients who were co-infected with SARS-CoV-2 and IAV treated at Wuhan Union Hospital, China. In addition, we performed a review in PubMed, Web of Science and CNKI (from January 1 up to November 1, 2020) with combinations of the following key words: "COVID-19, SARS-COV-2, influenza A and co-infection". A total of 28 co-infected patients were enrolled in the analysis. Of the 28 patients, the median age was 54.5 years (IQR, 34.25–67.5) and 14 cases (50.0%) were classified as severe types. The most common symptoms were fever (85.71%), cough (82.14%) and dyspnea (60.71%). Sixteen patients had lymphocytopenia on admission and 23 patients exhibited abnormal radiological changes. The median time from symptom onset to hospital admission was 4 days (IQR, 3–6), and the median time of hospital stay was 14 days (IQR, 8.5–16.75). In conclusion, patients with SARS-COV-2 and IAV co-infection were similar to those infected with SARS-COV-2 alone in symptoms and radiological images. SARS-COV-2 co-infection with IAV could lead to more severe clinical condition but did not experience longer hospital stay compared with patients infected with SARS-COV-2 alone.
Key words: co-infection; COVID-19; influenza A; SARS-COV-2

A new acute respiratory disease occurred in the winter of 2019, and was named coronavirus disease 2019 (COVID-19). It was found to be caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 falls within the subgenus *Sarbecovirus* of the genus *Betacoronavirus*, with about 79% identity to SARS-associated coronavirus (SARS-CoV) and sharing a similar receptor-binding domain structure to that of SARS-CoV[1]. SARS-CoV-2 now has swept the world again with a stunning speed and brought tremendous pressure to the medical system. The clinical characteristics and radiological changes of COVID-19 have been well documented. The most common symptoms of COVID-19 are fever and cough[2, 3], and the most representative images of computed tomography are peripheral ground-glass opacities[4, 5].

Influenza A viruses (IAV) belong to the *Orthomyxoviridae* family and are further divided into subtypes according to the two surface glycoproteins, haemagglutinin and neuraminidase. The acute respiratory illnesses caused by IAV usually occur in winter and lead to economic loss around the world[6, 7]. Based on the features of host and virus, patients infected with IAV could present different symptoms, including fever, chills, myalgia and respiratory symptoms such as dry cough, nasal congestion, etc. The typical changes in chest radiology images of IAV patients are ground-glass opacities and consolidations[8, 9].

Viral-bacterial and viral-viral co-infection are common during the influenza season and may lead to severe clinical illness[10, 11]. There have been a number of patients infected with both SARS-CoV-2 and IAV in the COVID-19 pandemic[12–14]. Due to the sporadic cases, the characteristics and course of those co-infected patients remain unknown. In the present study, we reviewed all published studies and described a cohort of patients co-infected with SARS-CoV-2 and IAV in the COVID-19 pandemic, aiming to improve

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the management of these co-infection patients.

1 MATERIALS AND METHODS

1.1 Search Strategy and Study Selection

We retrospectively screened out two patients infected with SARS-CoV-2 and IAV in 145 confirmed COVID-19 patients in Wuhan Union Hospital, China, and oral consents were obtained from the two patients. Then we searched PubMed (National Library of Medicine, Washington, DC), Web of Science and China National Knowledge Infrastructure (CNKI) from January 1 up to November 1, 2020, using different combinations of the following key words: "COVID-19, SARS-CoV-2, influenza A and co-infection". We also reviewed the reference lists of retrieved articles to search for other proper studies. All retrievals were publications concerning human studies in English or Chinese. The flow chart of searching and selecting the studies is shown in fig. 1.

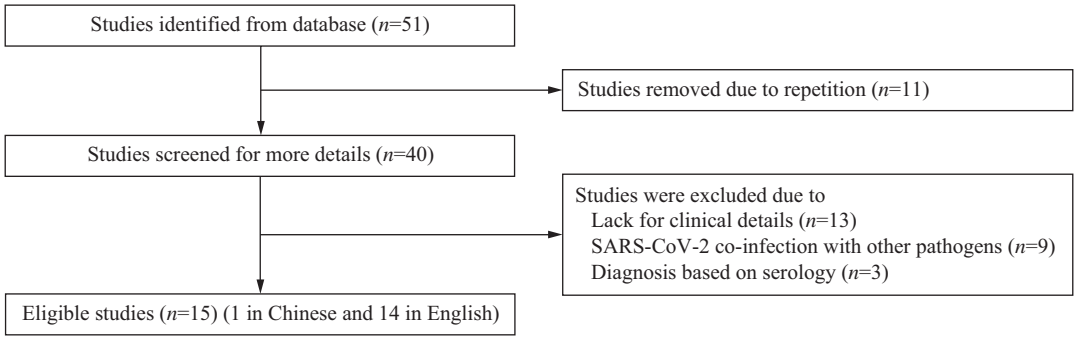

Fig. 1 The process of searching and selecting the studies

Inclusive criteria were as follows: (1) studies on SARS-CoV-2 and IAV co-infection; (2) case report on SARS-CoV-2 and IAV co-infection. Exclusion criteria were: (1) studies not containing any information on clinical course of co-infected patients; (2) studies on SARS-CoV-2 co-infection with other pathogens; (3) SARS-CoV-2 or IAV infection diagnosed based on serum antibody.

1.2 Data Extraction

For each study, the following information was extracted: the author's last name; year; country; study design; number of patents reported; number of patents co-infected with SARS-CoV-2 and IAV; selected clinical data [age; gender; comorbidities; symptoms; days from symptom onset to hospital admission; days in hospital; lymphocyte count on admission; oxygen saturation on admission; radiological images after admission; treatment; clinical events, including acute respiratory distress syndrome (ARDS), data about noninvasive ventilation, endotracheal intubation, and intensive care unit (ICU); clinical outcome (improved or death)]. Patients were divided into moderate type (showing fever and respiratory symptoms with radiological findings of pneumonia) and severe type (severe type was defined if one of the following conditions was met: 1. respiratory distress, respiratory rate ≥30 per min; 2. oxygen saturation on room air at rest ≤93%; 3. partial pressure of oxygen in arterial blood/fraction of inspired oxygen ≤300 mmHg) according to the Novel Coronavirus Pneumonia Diagnosis and Treatment Plan (trial version 7) developed by the National Health Committee of the People's Republic of China[15].

1.3 Statistical Analysis

Frequency with percentages (%) was used to describe categorical variables. Continuous variables were described using median and interquartile range (IQR) values. All statistical analyses were performed with GraphPad Prism 8.0.2.

2 RESULTS

2.1 Study Screening

After independent review, 40 publications on SARS-CoV-2 and IAV co-infection were considered eligible for inclusion in the analysis. Of these publications, 13 were excluded for not having detailed clinical information on patients co-infected with SARS-COV-2 and IAV, and 9 for SARS-CoV-2 co-infection with other pathogens. We also excluded 3 studies in which IAV diagnosis was based on serology. It is not reliable to diagnose IAV infection by only serological results[16]. The remaining 15 publications (one searched from CNKI and 14 from PubMed) provided 26 cases with clinical information. Therefor 28 patients who suffered from both SARS-CoV-2 and IAV co-infection were enrolled in the analysis[13, 14, 17–29] (table 1).

2.2 Clinical Characteristics of Patients with SARS -CoV-2 and IAV Co-infection

Table 2 summarizes the demographics and clinical characteristics of the total 28 patients. In this descriptive study, 14 patients (50.0%) were classified as severe cases and 16 (57.1%) were males. The median age was 54.5 years (IQR, 34.25–67.5). Thirteen patients had comorbidities such as hypertension,

Table 1 Study samples included in the review

Authors, year, country	Type of study	Case number	No. of SARS-COV-2 co-infection with IAV	Diagnostic method of IAV
Data from our hospital, 2020, China*	Original data	145	2	NAA
Wu *et al*, 2020, China[13]	Case report	1	1	NAA
Khodamoradi *et al*, 2020, Iran[14]	Case report	4	4	NAA
Azekawa *et al*, 2020, Japan[25]	Case report	1	1	NAA
Konala *et al*, 2020, USA[24]	Case report	1	1	NAA
Konala *et al*, 2020, USA[18]	Case report	3	3	NAA
Sha, 2020, China[17]	Case report	1	1	NAA
Cuadrado-Payán *et al*, 2020, Spain[28]	Case report	4	2	NAA
Wehl *et al*, 2020, Germany[21]	Short communication	1	1	RICAT
Ozaras *et al*, 2020, Turkey[27]	Research article	1103	2	DFA
Singh *et al*, 2020, USA[26]	Case report	3	1	RAA
Kakuya *et al*, 2020, Japan[29]	Short communication	3	1	CI
Zheng *et al*, 2020, China[22]	Letter to the Editor	1001	4	NAA
D'Abramo *et al*, 2020, Italy[19]	Case report	1	1	NAA
Pongpirul *et al*, 2020, Thailand[20]	Clinical study	11	1	NAA
Hashemi *et al*, 2020, Iran[23]	Letter to the Editor	600	2	NAA

NAA: nucleic acid amplification; DFA: direct fluorescent antigen; RAA: rapid antigen assay; CI: chromatographic immunoassay; RICAT: rapid immune chromatographic assay testing. *Data were collected from Wuhan Union Hospital.

diabetes, tumor, cerebrovascular disease, coronary artery disease, dyslipidemia, hypothyroidism, pituitary microadenoma, congestive heart failure, chronic kidney disease and chronic lung disease. The most common symptoms before admission were fever (85.7%), cough (82.1%), dyspnea (60.7%) and myalgia (46.15%).

On admission, 69.6% of the patients had decreased lymphocyte count and 23 patients (85.2%) had abnormal radiological changes in their first examination after admission. The median time from symptom onset to hospital admission was 4 days (IQR, 3–6), and the median time of hospital stay was 14 days (IQR, 8.5–16.75). 50.0% patients had lower oxygen saturation (SpO_2 ≤93%) on ambient air. 54.6% of these patients had oxygen inhalation, including five patients receiving noninvasive ventilation, and five endotracheal intubation in the ICU. 64.3% had oseltamivir treatment, and 73.9% had other antiviral treatment except oseltamivir. 79.3% received antibiotic therapy, and only 8.7% were treated with corticosteroids. Six patients suffered from ARDS and three patients failed surviving the pandemic. The clinical condition of 18 patients was improved after admission. The outcomes of the remaining seven patients, however, were not available.

3 DISCUSSION

Viruses co-infection usually occurs in the influenza epidemic and pandemic[30, 31]. Previous studies found that co-infection with IAV and other viruses significantly increased the risk of admission to a general ward, and IAV and influenza B virus co-infection increased the risk of admission to ICU or death[30]. During the COVID-19 pandemic, numerous studies have reported co-infection of SARS-CoV-2 and IAV. To better understand the clinical course of patients co-infected with SARS-CoV-2 and IAV, we performed a fast review on these patients.

In this review, we collected 28 patients co-infected with SARS-CoV-2 and IAV from China[13, 17, 22], Japan[25, 29], Iran[14, 23], America[18, 24, 26], Germany[21] and other countries[19, 20, 27, 28]. In the 28 patients, 50.0% of patients were severe type and 14.3% died, which were higher than those reported in COVID-19[32]. Moreover, a report from Iran showed 22.3% of dead cases were co-infected with SARS-CoV-2 and IAV[33], indicating co-infection with SARS-CoV-2 and IAV may result in more severe condition. IAV infection was more common in children and old people[6]. We only found three children suffering from SARS-CoV-2 and IAV co-infection in our cohort[17, 21, 29]. The clinical manifestations of patients co-infected with SARS-CoV-2 and IAV are similar to those infected with SARS-CoV-2 alone, such as fever, cough, dyspnea and myalgia, etc. However, in this review, we found 60.7% patients had dyspnea on admission, higher than that reported by Wang and Huang *et al* (31.2% and 55% respectively)[2, 3]. The median time of hospital stay in this review was 14 days (IQR, 8.5–16.75), shorter than the previous finding (median, 18 days, IQR, 14–27)[34]. These data indicate that patients co-infected with SARS-CoV-2 and IAV developed more severe clinical condition, while having shorter hospital stay. We speculate that one important reason may be attributed to the timely use of effective antiviral drugs such as oseltamivi. 64.3% of patients were treated with oseltamivi in this cohort, which could limit the propagation of IAV infection and reduce

Table 2 clinical characteristics of patents in the included studies

Variables	Our hospital	Wu [13]	Khodamoradi [14]	Azekawa [25]	Konala [24]	Konala [18]	Sha [17]	Cuadrado-Payán[28]	Wehl [21]	Ozaras [27]	Singh [26]	Kakuya [29]	Zheng [22]	D'Abramo [19]	Pongpirul [20]	Hashemi [23]	Total (n=28) n (%)
Gender																	
M	1	1	3	0	0	1	1	2	NA	1	0	1	2	1	1	1	16 (57.14)
F	1	0	1	1	1	2	0	0	NA	1	1	0	2	0	0	1	11 (39.28)
Age*	41, 34	69	74, 40, 64, 50	78	66	57, 35, 38	5	53, 78	4Δ	49, 51	61	11	33, 62, 30, 15	56	61	78, 75	–
Comorbidities#	1/2	0/1	1/4	1/1	1/1	2/3	0/1	2/2	0/1	1/2	1/1	0/1	1/4	1/1	0/1	1/2	13 (48.15)
Clinical classification																	
Severe	1	1	3	0	1	2	0	2	0	0	0	0	1	1	0	2	14 (50.00)
Moderate	1	0	1	1	0	1	1	0	1	2	1	1	3	0	1	0	14 (50.00)
Symptoms																	
Fever	1/2	1/1	4/4	1/1	1/1	3/3	1/1	2/2	1/1	0/2	0/1	1/1	4/4	1/1	1/1	2/2	24 (85.71)
Cough	2/2	1/1	4/4	1/1	1/1	2/3	1/1	2/2	1/1	2/2	0/1	1/1	3/4	0/1	1/1	1/2	23 (82.14)
Dyspnea	1/2	1/1	4/4	0/1	1/1	3/3	0/1	2/2	0/1	1/2	1/1	0/1	1/4	0/1	0/1	2/2	17 (60.71)
Myalgia	2/2	0/1	3/4	0/1	0/1	1/3	0/1	NA	0/1	2/2	1/1	0/1	1/4	0/1	0/1	2/2	12/26 (46.15)
Fatigue	2/2	0/1	2/4	0/1	0/1	0/3	0/1	NA	0/1	2/2	0/1	1/1	1/4	1/1	1/1	0/2	10/26 (38.46)
Clinical course																	
Days from symptom onset to hospital admission*	4, 11	7	5, 4, 5, 2	5	3	14, 15, NA	2	3,3	1	NA	NA	2	3, 15, 1, 3, 4	4	13	6, NA	–
Decreased lymphocyte count on admission	1/2	1/1	2/4	0/1	1/1	3/3	1/1	2/2	0/1	1/2	NA	1/1	NA	1/1	0/1	2/2	16/23 (69.56)
Abnormal radiological changes (%)	2/2	1/1	4/4	1/1	1/1	3/3	1/1	1/2	0/1	2/2	1/1	1/1	2/4	1/1	NA	2/2	23/27 (85.18)
SpO_2 ≤93% on admission	1/2	1/1	3/4	0/1	1/1Δ	2/3	0/1	2/2	0/1	NA	0/1	0/1	NA	0/1	0/1	NA	10/20 (50.00)
Days in hospital*	20, 17	NA	NA	16	NA	>7, >7, 1**	15	NA	NA	NA	NA	13	NA	NA	13	4**, 8**	–
Treatment																	
Oseltamivir	2/2	1/1	0/4	1/1	0/1	2/3	1/1	2/2	1/1	2/2	1/1	0/1	3/4	1/1	1/1	0/2	18 (64.29)
Antiviral therapy (except oseltamivir)	2/2	NA	NA	0/1	1/1	3/3	1/1	2/2	0/1	2/2	1/1	1/1	1/4	1/1	0/1	2/2	17/23 (73.91)
Antibiotic therapy	2/2	NA	NA	1/1	1/1	3/3	1/1	0/2	0/1	2/2	1/1	1/1	3/4	1/1	1/1	0/2	17/23 (73.91)
Corticosteroids therapy	0/2	NA	NA	0/1	0/1	0/3	1/1	0/2	0/1	0/2	0/1	0/1	0/4	1/1	0/1	0/2	2/23 (8.70)
Oxygen inhalation	1/2	1/1	NA	0/1	1/1	3/3	0/1	2/2	0/1	NA	0/1	0/1	1/4	1/1	0/1	2/2	12/22 (54.55)

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Variables	Our hospital	Wu [13]	Khodamoradi [14]	Azekawa [25]	Konala [24]	Konala [18]	Sha [17]	Cuadrado-Payán[28]	Wehl [21]	Ozaras [27]	Singh [26]	Kakuya [29]	Zheng [22]	D'Abramo [19]	Pongpirul [20]	Hashemi [23]	Total (n=28) n (%)
Clinical events																	
Acute respiratory distress syndrome	0/2	1/1	NA	0/1	0/1	1/3	0/1	2/2	0/1	NA	0/1	0/1	NA	1/1	0/1	1/2	6/18 (33.33)
Noninvasive ventilation	0/2	0/1	NA	0/1	0/1	1/3	0/1	2/2	0/1	NA	0/1	0/1	NA	1/1	0/1	1/2	5/18 (27.78)
Endotracheal intubation	0/2	1/1	NA	0/1	1/1	1/3	0/1	2/2	0/1	NA	0/1	0/1	NA	0/1	0/1	0/2	5/18 (27.78)
Intensive care unit	0/2	1/1	NA	0/1	1/1	1/3	0/1	NA	0/1	NA	0/1	0/1	NA	1/1	0/1	2/2	6/16 (37.5)
Clinical outcome																	
Improved	2	1T##	NA	1	NA	2	1	2	1	2	1	1	3, 1T##	1	1	0	18
Death	0	0	NA	0	NA	1	0	0	0	0	0	0	0	0	0	2	3

M: male; F: female; NA: not available. *Median and interquartile range (IQR) were used to describe the data: age, 54.5 (34.25, 67.5); days from symptom onset to hospital admission, 4 (3, 6); days in hospital, 14 (8.5, 16.75). #Comorbidities included hypertension, diabetes, tumor, cerebrovascular disease, coronary artery disease, dyslipidemia, hypothyroidism, pituitary microadenoma, congestive heart failure, chronic kidney disease, and chronic lung disease. ΔThe patient was a 4-month-old infant. **Patients died in hospital and thus were not included in the analysis of "Days in hospital (median, IQR)". ##Transferred to designated hospital

the risk of complications, especially when dealing with lower respiratory tract complications[35]. On the other hand, some interesting interference may occur in two viruses co-infection[36]. 85.2% of patients exhibited typical abnormal radiological changes and 69.56% of patients showed decreased lymphocyte count on admission, which could indicate viral infection but could not distinguish exact pathogens.

In this review, we found 18 patients (64.3%) were treated with oseltamivir, a neuraminidase inhibitor recommended to deal with influenza by the European Union and the USA[37, 38], and 73.9% patients received antibiotic therapy to prevent secondary bacterial infection[39]. However, whether oseltamivir has effect on SARS-CoV-2 viral shedding and whether co-infection with SARS-CoV-2 and IAV may cause secondary infection need further investigation. Two patients were treated with corticosteroids, while corticosteroids were not usually recommended in the COVID-19 pandemic concerning about their possible side effects on virus clearance and their association with high rates of complications[40, 41]. Eighteen patients were improved and, unfortunately, three patients lost their life in this study.

We noticed that patients co-infected with SARS-CoV-2 and IAV accounted for a small proportion in the COVID-19 pandemic[42, 43], which may be due to the interference between viruses[44]. The mechanism of SARS-CoV-2 and IAV interference remains to be further clarified.

Admittedly, this study has some limitations. First and most, the sample size is extremely small due to scanty reports on SARS-CoV-2 and IAV co-infection. Second, we could not collect detailed information about each patient since some information was not available, and, additionally, the missing information may have some influence on our results. Third, the reports did not provide SARS-CoV-2 viral shedding time, and thus whether co-infection with IAV has some influence on SARS-CoV-2 viral shedding remains unknown. Fourth, we could not identify which virus was first infected, which may help account for the co-infection course. Finally, lower respiratory tract samples were not harvested for detection of SARS-CoV-2 and IAV in these studies included, and therefore whether the two viruses were both involved in the pathological progression of pulmonary remains unclear.

In conclusion, our study found that patients with SARS-CoV-2 and IAV co-infection were similar to those infected with SARS-CoV-2 alone in symptoms and radiological images. Although patients with SARS-CoV-2 and IAV co-infection did not experience longer hospital stay than those infected with SARS-CoV-2 alone, they usually presented with more severe clinical condition. Physicians should pay more attention to the patients co-infected with two or more respiratory

pathogens.

Conflict of Interest Statement

The authors declare that there is no conflict of interest with any financial organization or corporation or individual that can inappropriately influence this work.

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