


RESEARCH ARTICLE

Co-infection of influenza A virus and SARS-CoV-2: A retrospective cohort study

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Abstract

The coronavirus 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread across the world and is responsible for over 1,686,267 deaths worldwide. Co-infection with influenza A virus (IFV-A) during the upcoming flu season may complicate diagnosis and treatment of COVID-19. Little is known about epidemiology and outcomes of co-infection. Data for 213 COVID-19 patients treated at Tongji Hospital in Wuhan from January 28, 2020 to March 24, 2020 were retrospectively analyzed. Ninety-seven of the patients (45.5%) tested positive for anti-IFV-A immunoglobulin M antibodies. The clinical characteristics were described and analyzed for patients with SARS-CoV-2 infection only and patients with SARS-CoV-2/IFV-A co-infection. Patients with co-infection showed similar patterns of symptoms and clinical outcomes to patients with SARS-CoV-2 infection only. However, an increased expression of serum cytokines (interleukin-2R [IL-2R], IL-6, IL-8, and tumor necrosis factor- α) and cardiac troponin I, and higher incidence of lymphadenopathy were observed in patients with SARS-CoV-2 infection only. Male patients and patients aged less than 60 years in the SARS-CoV-2 infection group also had significantly higher computed tomography scores than patients in co-infection group, indicating that co-infection with IFV-A had no effect on the disease outcome but alleviated inflammation in certain populations of COVID-19 patients. The study will provide a reference for diagnosing and treating IFV-A and SARS-CoV-2 co-infection cases in the upcoming flu season.

KEYWORDS

co-infection, COVID 19, cytokines, flu season, influenza A virus, SARS-CoV-2

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an ongoing public health emergency and has posed a great challenge to health care systems globally. To date (December 21, 2020), the World Health Organization has declared more than 75 million confirmed cases and 1,686,267 deaths.¹ As SARS-CoV-2 continues to spread globally, it will overlap with the flu season in the coming fall and winter.²

Both SARS-CoV-2 and influenza virus can cause respiratory illness and lead to life-threatening symptoms, especially for older adults and those with chronic conditions. So far, little is known about the interaction between SARS-CoV-2 and influenza virus.

Influenza viruses usually cause mild to severe symptoms, including fever, cough, sore throat, fatigue, and dyspnea. These symptoms are similar to those caused by SARS-CoV-2 infection. Only type A influenza virus (IFV-A) causes pandemic flu and is a leading cause of seasonal flu epidemic. According to the United States Center

for Disease Control, an estimated 30 million to 56 million people were infected with IFV-A resulting in 24,000–62,000 deaths in the 2019–2020 flu season.³ In Wuhan, China, a retrospective analysis revealed a significant rise in reported influenza-like illness during October 2019 to January 2020, in comparison to previous years.⁴ Up to July 19, 2020, the Southern hemisphere reported an inter-seasonal level of influenza activity.⁵

There are a few cases of co-infection of SARS-CoV-2 and IFV-A worldwide.^{6–10} However, information on the correlation between SARS-CoV-2 and IFV-A infection is still limited. In the present study, the clinical characteristics, diseases outcomes and laboratory testing data of patients with SARS-CoV-2 infection only (SARS-CoV-2(+) IFV-A(-)) and patients with SARS-CoV-2 who are coinfecting with IFV-A (SARS-CoV-2(+) IFV-A(+)) were described and compared.

2 | METHODS

2.1 | Patients

The retrospective cohort study was conducted on 321 confirmed COVID-19 adult inpatients (aged ≥ 18 years) from Tongji Hospital in Wuhan (which was in charge of the Peking University Medical Health Center) from January 28, 2020 to March 24, 2020. The inclusion criteria was as follows: (1) diagnosed with COVID-19; based on SARS-CoV-2 RNA reverse-transcription polymerase chain reaction (RT-PCR) tests in samples from the respiratory tract and chest CT, (2) Age ≥ 18 years. Patients without local computed tomography (CT) scan results or serum immunoglobulin M (IgM) antibody test to IFV-A, those whose symptoms from date of CT scan was greater than 60 days, and those with a history of pneumonectomy were excluded from the study. The study was approved by the Research Ethics Commission of Peking University First Hospital (2020098). The access to patient records was authorized, and all patients' information were kept confidential.

Included patients were divided into two groups: SARS-CoV-2(+) IFV-A(-) and SARS-CoV-2(+) IFV-A(+) based on serum - specific IgM antibody test for IFV-A at admission. The first chest CT scan after admission was collected for analysis.

2.2 | Data collection

Epidemiological, demographic, clinical, laboratory and outcome data were collected using standardized data collection forms. All data were independently reviewed by two physicians (CY and WX) and any discrepancies between the two primary reviewers were resolved with adjudication by a third researcher (HZW).

COVID-19 was diagnosed by RT-PCR test (C_t cut-off value of 38) of throat swabs and by chest CT. The ORF1ab and nucleocapsid (N) gene was utilized as gene target for RT-PCR assay according to recommendations of Chinese Center for Disease Control. Diagnosis of influenza virus infection was based on serological detection of IFV-A-specific IgM antibody (titer $>1:10$) (indirect immunofluorescence

assay, EUROIMMUN FI2821-17M). Bio-Plex Pro Human Cytokine Panel were used to measure plasma cytokine levels.

2.3 | Imaging evaluation

The first chest CT scans after admission were collected for analysis. The chest CT scan images were independently reviewed by one experienced pulmonologist and one experienced radiologist (CY, WH). Consensus was reached after discussion when there was a controversy. CT findings included ground glass opacity (GGO), consolidation, and fibrosis. GGO was defined as hazy increased attenuation of the lung, but with preservation of bronchial and vascular margins. Consolidation was defined as homogeneous increase in pulmonary parenchyma that obscures the margins of vessels and airway walls, and fibrosis was defined as distorted consolidation, traction bronchiectasis, and interlobular septal thickening. Lymphadenopathy was defined as a lymph node larger than 1 cm in diameter.

The CT scans were scored on the axial images as previously reported.^{11,12} Briefly, the extent of abnormality and distribution of affected lung parenchyma were independently recorded for the upper, middle, and lower zones of each side. The CT findings were graded using a three-point scale: score of 1, normal attenuation, score of 2, ground-glass attenuation, and score of 3, consolidation. According to the distribution of the affected lung parenchyma, each lung zone was scored as follows: 0 as normal, 1 as less than 25% abnormality, 2 as 25%–50% abnormality, 3 as 50%–75% abnormality, and 4 as greater than 75% abnormality. The four-point scale of the lung parenchyma distribution was then multiplied by the three-point scale of abnormality. The scores from all six zones were added for a final cumulative score that ranged from 0 to 72.

2.4 | Statistical analysis

Data are presented as numbers (percentages) for categorical variables and as medians with interquartile range for continuous variables. Laboratory data on white blood cell, lymphocyte count (LYM), C-reactive protein (CRP), interleukin-2R (IL-2R), IL-6, IL-8, tumor necrosis factor α (TNF- α), cardiac troponin I (cTNI), and D-DIMER levels were expressed as medians with interquartile range. Mann-Whitney *U* test was used for intergroup comparison of variables. χ^2 test, or Fisher's exact test were conducted to compare categorical measures. A $p < .05$ was considered to be statistically significant. GraphPad prism version 7.0, GraphPad software (La Jolla) was used for statistical analysis.

3 | RESULTS

3.1 | General information

As shown in Figure 1, during the study period (from January 28 to March 24, 2020), there were 321 patients hospitalized in Tongji Hospital and diagnosed with COVID-19. A total of 213 patients met

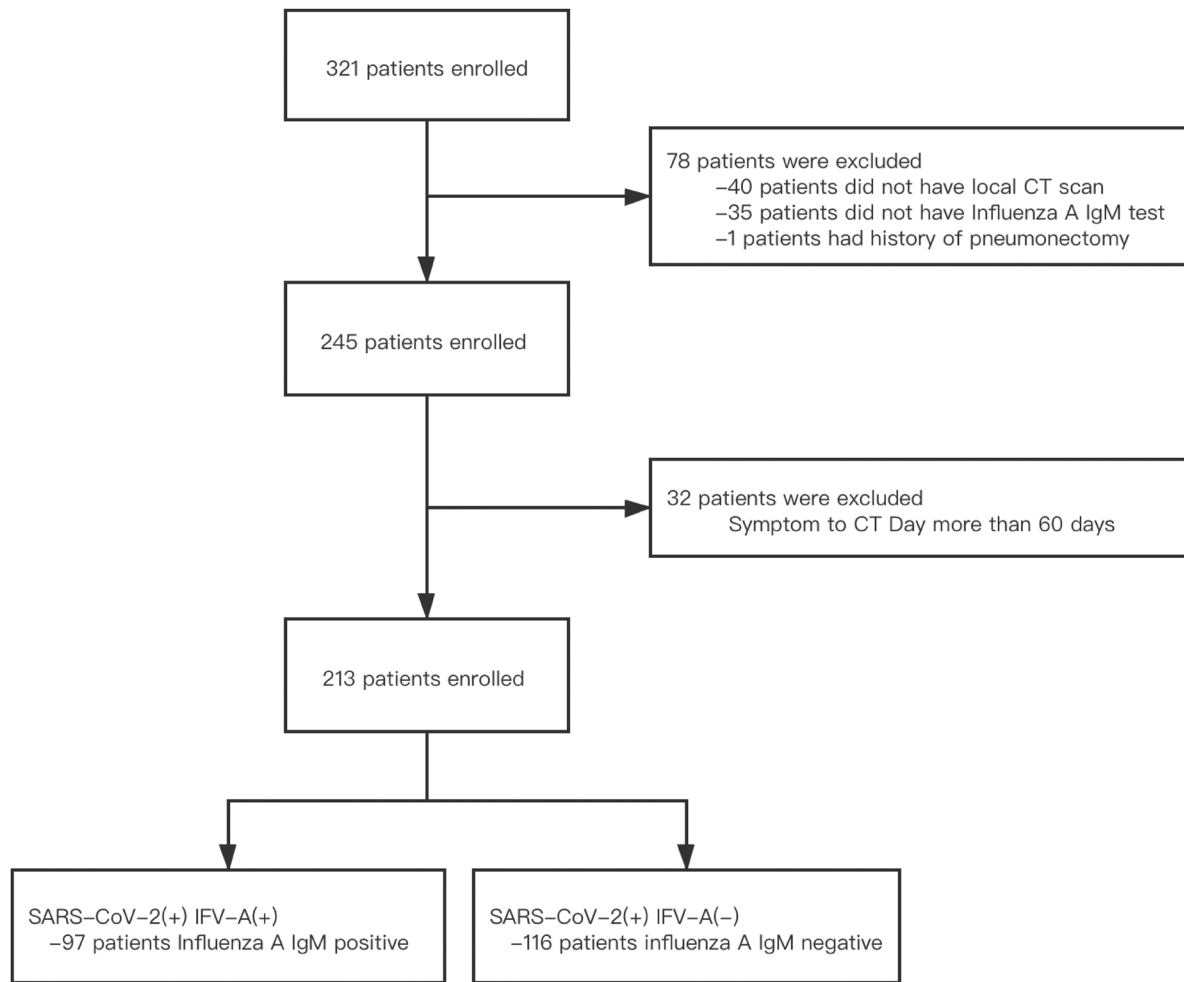


FIGURE 1 Flowchart of the participants. CT, computed tomography; IFV, influenza A virus; IgM, immunoglobulin M; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

the inclusion criteria. The median age of enrolled patients was 63 years (interquartile range, 50–69 years), with an even sex distribution (females-106 patients, males-107 patients). The overall mortality was 3.76% ($n = 8$). The median time from onset of symptoms to local CT scan was 18 (12–25) days.

3.2 | Co-infection pattern

A total of 97 patients (45.5%) were positive for anti-IFV-A IgM antibodies. The characteristics of patients at admission are presented in Table 1. The median age of patients with SARS-CoV-2 infection only (SARS-CoV-2(+) IFV-A(-)) and patients with co-infection (SARS-CoV-2(+) IFV-A(+)) were 64 (49–71) years and 61(50–68) years, respectively. Females accounted for 48.3% ($n = 56$) of patients with SARS-CoV-2 infection only and 51.5% ($n = 60$) of coinfecting patients. The most common symptoms included fever (87.9%, $n = 188$), cough (73.4%, $n = 157$), and dyspnea (56.5%, $n = 121$), regardless of co-infection. Over a third of patients had history of hypertension,

with no significant difference between the SARS-CoV-2(+) IFV-A (+) and SARS-CoV-2(+) IFV-A(-) groups (33.6% vs. 32.0%).

Of the 213 COVID-19 patients enrolled, 12 patients received noninvasive positive pressure ventilation (5 patients with SARS-CoV-2 infection only and 7 patients with co-infection, $p = .782$), and 2 patients received invasive mechanical ventilation (1 with SARS-CoV2 only and 1 with co-infection, $p = .899$). There were 8 deaths (5 patients with SARS-CoV-2 infection only and 3 patients with co-infection, $p = .899$). There was no difference in severity of illness between patients with SARS-CoV-2 infection only and patients with co-infection.

As for the serological tests (Table 2), there were no statistical differences in LYM, CRP, and D-dimer concentration between patients with SARS-CoV-2 infection only and patients with co-infection. However, patients with SARS-CoV-2 infection only had a significantly higher serum level of cytokines (IL-2 [$p = .0002$], IL-6 [$p = .032$], IL-8 [$p = .0453$], TNF- α [$p = .0024$]) and cTnl [$p = .0136$], indicating a potential alleviation in cytokine storm after co-infection with IFV-A (Figure 2).

| | All n = 213 | SARS-CoV-2(+) IFV-A(+) n = 97 | SARS-CoV-2(+) IFV-A(-) n = 116 | p Value |
|---|----------------|-------------------------------------|--------------------------------------|---------|
| Age, median, years (IQR) | 63 (50–69) | 61 (50–68) | 64 (49–71) | .349 |
| Sex, n (%) | | | | .635 |
| Female | 106 (49.8%) | 50 (51.5%) | 56 (48.3%) | |
| Male | 107 (50.2%) | 47 (48.5%) | 60 (51.7%) | |
| Coexisting medical conditions, n (%) | | | | |
| Hypertension | 70 (32.7%) | 31 (32.0%) | 39 (33.6%) | .797 |
| Diabetes | 36 (16.8%) | 19 (19.6%) | 17 (14.7%) | .339 |
| Coronary heart disease | 18 (8.4%) | 10 (10.3%) | 8 (6.9%) | .373 |
| COPD | 6 (2.8%) | 3 (3.1%) | 3 (2.6%) | .824 |
| Any | 26 (12.1%) | 9 (9.3%) | 17 (14.7%) | .233 |
| Symptoms, n (%) | | | | |
| Fever | 188 (87.9%) | 86 (88.7%) | 102 (87.9%) | .869 |
| Cough | 157 (73.4%) | 71 (73.2%) | 86 (74.1%) | .876 |
| Dyspnea | 121 (56.5%) | 53 (54.6%) | 68 (58.6%) | .559 |
| Expectoration | 95 (44.4%) | 46 (47.4%) | 49 (42.2%) | .449 |
| GI symptoms | 109 (50.9%) | 52 (53.6%) | 57 (49.1%) | .516 |
| Other | 34 (15.9%) | 13 (13.4%) | 21 (18.1%) | .351 |

Abbreviations: COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; IFV, influenza A virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

The CT features, including the location, extent and distribution of each abnormality are presented in Table 3. The median time from onset of symptoms to CT scan were 18 (12–23) days for patients with SARS-CoV-2 infection only and 20 (11–27) days for patients with co-infection ($p = .487$). Four patients (two with SARS-CoV-2

TABLE 2 Comparison of laboratory results between co-infection (SARS-CoV-2(+) IFV-A(+)) group and SARS-CoV-2 infection only (SARS-CoV-2(+) IFV-A(-)) group

| | SARS-CoV-2(+) IFV-A(+) | SARS-CoV-2(+) IFV-A(-) | p Value |
|-----------------------|------------------------|------------------------|---------|
| WBC ($10^9/L$) | 5.8 (4–7.9) | 5.44 (3.52–7.82) | .3765 |
| LYM ($10^9/L$) | 1.12 (0.78–1.77) | 1.255 (0.72–1.66) | .838 |
| CRP (mg/L) | 64.7 (26.70–112) | 67.9 (30.1–112.65) | .8389 |
| IL2R (U/ml) | 508 (396–878) | 766.5 (559–1129.75) | .0002* |
| IL6 (pg/ml) | 10.2 (2.15–27.05) | 14.43 (5.78–41.74) | .032* |
| IL8 (pg/ml) | 10.8 (5.20–22.20) | 13.2 (7.78–23.48) | .0453* |
| TNF- α (pg/ml) | 7.4 (5.00–11.55) | 9.1 (6.75–13.05) | .0024* |
| cTNI (ng/ml) | 3.2 (1.90–7.30) | 4.9 (2.75–8.60) | .0136* |
| D-Dimer (pg/ml) | 1.31 (0.40–2.43) | 1.21 (0.60–2.51) | .3379 |

Note: Data are presented as median (IQR). p Values obtained by the Mann–Whitney U test.

Abbreviation: CRP, C-reactive protein; cTNI, cardiac troponin I; IL, interleukin; IQR, interquartile range; LYM, lymphocyte count; TNF- α , tumor necrosis factor- α ; WBC, white blood cell count.

*Statistically significant ($p < .05$).

TABLE 1 Demographic and clinical characteristics of participants and comparison between co-infection (SARS-CoV-2(+) IFV-A(+)) group and SARS-CoV-2 infection only (SARS-CoV-2(+) IFV-A(-)) group

infection only and two with co-infection) had normal CT scan. The predominant CT characteristics consisted of GGO (45.8%), bilateral sides involved (88.8%), peripheral distribution (57.9%), and lower zone involved (90.2%). Lymphadenopathy and pleural effusion were only occasionally observed (10.7% for lymphadenopathy, 1.9% for unilateral pleural effusion, and 3.3% for bilateral pleural effusion). Lymphadenopathy was seen more often in SARS-CoV-2 infection only patients (14.7% vs. 6.2%, $p = .047$).

The median CT score of the influenza positive group was similar to the influenza negative group (15 vs. 19.5, $p = .052$), but in subgroup analysis, it was significant lower in patients less than 60 years (12 vs. 18, $p = .007$) and males (12 vs. 24, $p = .031$).

CT manifestation of fibrosis was observed in 21% of all patients (16% in the influenza positive group vs. 25% in the influenza negative group, $p = .130$). Linear atelectasis was observed in 45.3% of all patients and was similar in the two groups (46.4% in the influenza positive group vs. 44.8% in the influenza negative group, $p = .819$). Linear atelectasis was typically manifested as linear soft tissue opacities ranging from 1 to 3 mm in thickness and 1 to 5 cm in length, located in subpleural regions. There was no significant difference in fibrosis and linear atelectasis between the two groups.

4 | DISCUSSION

Co-infection is generally considered to worsen disease outcomes and may lead to more severe symptoms. Co-infections may however modify the virulence of the virus and cell death, therefore altering

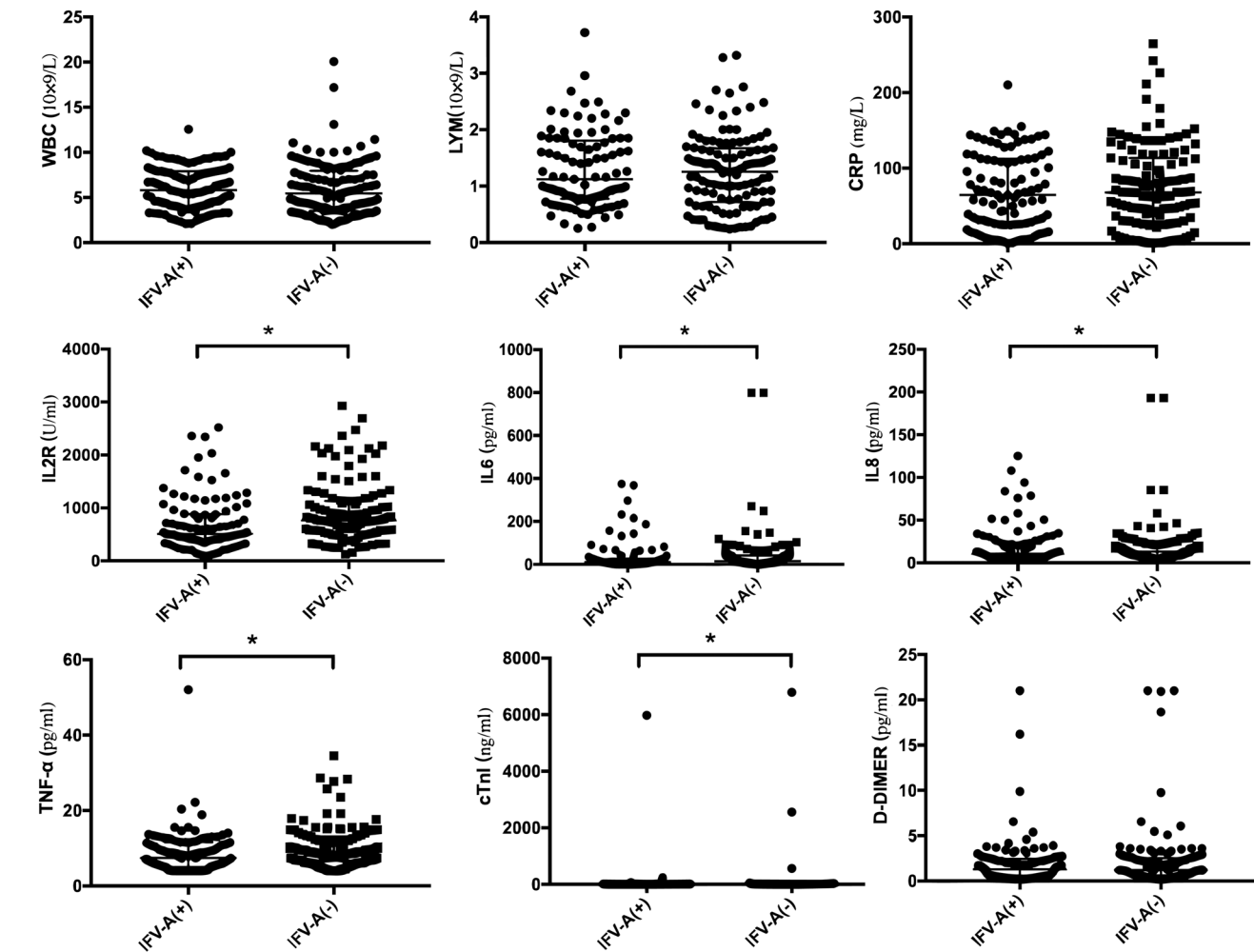


FIGURE 2 Scatterplots of WBC, LYM, CRP, IL-2R, IL-6, IL-8, TNF- α , cTnI, and D-dimer. *Statistically significant ($p < .05$). CRP, C-reactive protein; cTnI, cardiac troponin I; IL, interleukin; LYM, lymphocyte count; TNF- α , tumor necrosis factor α ; WBC, white blood cell

disease severity.¹³ Pinky¹⁴ used a mathematical model to study the dynamics of viral coinfection which showed that virus species and growth rate may affect the replication of other viruses. Some studies have suggested that viral co-infection may worsen clinical outcomes, while others have shown no effect on clinical outcomes; still, other few studies have shown improved clinical outcomes.¹⁵ These contradictory results suggest a complex mechanism on how co-infection impacts clinical outcomes. In our study, out of the 213 COVID-19 patients, 95 patients (45.5%) were coinfecting with IFV-A. This data suggested a high prevalence of co-infection of SARS-CoV-2 and IFV-A in Wuhan. There was no correlation between co-infection and sex, age, and coexisting medical conditions. All patients had similar patterns of symptoms and outcomes. However, patients with SARS-CoV-2 infection only had increased serum cytokines level and higher frequency of lymphadenopathy. In addition, in SARS-CoV-2 infected patients, males and patients younger than 60 years old had significantly higher CT scores.

In previous studies, the frequency and clinical outcomes of co-infection with influenza virus were variable.^{16,17} Co-infection was uncommon in Northern California, United States (0.9%),¹⁸ and Turkey

(0.54%).¹⁹ However, Hashemi et al.²⁰ reported a coinfection rate of 22.3% in dead patients and 19.3% in living patients in North eastern Iran. In Wuhan, the co-infection rate ranged from 0.54% to 49.5%.²¹ In other parts of China, approximately 60% (18 of 30 cases) of COVID-19 patients were coinfecting with IFV-A in Qingdao²² and only 0.8% (2 of 257 cases) in Jiangsu province, although the overall co-infection rate of respiratory pathogens was up to 94.2%.²³ The difference might be attributable to seasonality, vaccination coverage, enrolled numbers as well as regions.

Additionally, consistent with a previous report,¹⁶ our data showed that COVID-19 patients coinfecting with IFV-A presented with symptoms and clinical outcomes similar to those with single SARS-CoV-2 infection. In other studies by Ma et al.²¹ and Yue et al.,²⁴ SARS-CoV-2 co-infection with influenza, especially influenza B virus, could lead to poor outcomes. As is well known, the acute increase in secretion of cytokines, such as IL-2, IL-6, IL-8, and TNF- α , also called cytokine storm, is associated with COVID-19 disease severity.^{25,26} Additionally, increased D-dimer (a thrombosis marker) and cTnI concentration were associated with increased incidence of mortality in patients with COVID-19.²⁷⁻²⁹ Patients with co-infection showed significant reduction in cytokines and cTnI, indicating that patients

TABLE 3 Outcomes and CT manifestations

| | Total n = 213 | SARS-CoV-2(+) IFV-A(+) n = 97 | SARS-CoV-2(+) IFV-A(-) n = 116 | p Value |
|--|------------------|-------------------------------------|--------------------------------------|---------|
| Outcomes, n (%) | | | | |
| NIPPV | 12 (5.6%) | 5 (5.2%) | 7 (6.0%) | .782 |
| MV | 2 (0.9%) | 1 (1.0%) | 1 (0.9%) | .899 |
| Death | 8 (3.7%) | 3 (3.1%) | 5 (4.3%) | .642 |
| Symptom onset before CT, days (IQR) | 18 (12–25) | 20 (11–27) | 18 (12–23) | .487 |
| CT manifestations, n (%) | | | | |
| GGO | 98 (45.8%) | 44 (45.4%) | 54 (46.6%) | .584 |
| Consolidation | 26 (12.1%) | 15 (15.5%) | 11 (9.5%) | |
| Both | 85 (39.7%) | 36 (37.1%) | 49 (42.2%) | |
| None | 4 (1.9%) | 2 (2.1%) | 2 (1.7%) | |
| CT score, median (IQR), (years) | | | | |
| <60 | | 15 (10–26) | 19.5 (10–34) | .052 |
| ≥60 | | 12 (7–12) | 18 (12–34) | .007 |
| | | 22 (12–19.5) | 20 (10.5–35.5) | .796 |
| Sex (IQR) | | | | |
| Male | | 12 (9.5–26) | 24 (12–38) | .031 |
| Female | | 17 (10–26) | 20 (16–38) | .093 |
| Fibrosis, n (%) | 45 (21.0%) | 16 (16.5%) | 29 (25.0%) | .130 |
| Linear atelectasis, n (%) | 97 (45.3%) | 45 (46.4%) | 52 (44.8%) | .819 |
| Lymphadenopathy, n (%) | 23 (10.7%) | 6 (6.2%) | 17 (14.7%) | .047 |
| Pleural effusions, n (%) | | | | |
| Unilateral | 4 (1.9%) | 1 (1.0%) | 3 (2.6%) | .618 |
| Bilateral | 7 (3.3%) | 2 (2.1%) | 5 (4.3%) | |
| None | 202 (94.4%) | 94 (96.9%) | 108 (93.1%) | |
| Sides involved, n (%) | | | | |
| Unilateral | 19 (8.9%) | 11 (11.3%) | 8 (6.9%) | .513 |
| Bilateral | 190 (88.8%) | 84 (86.6%) | 106 (91.4%) | |
| None | 4 (1.9%) | 2 (2.1%) | 2 (1.7%) | |
| Predominant distribution, n (%) | | | | |
| Central | 1 (0.5%) | 1 (1.0%) | 0 | .060 |
| Peripheral | 124 (57.9%) | 62 (63.9%) | 62 (53.4%) | |
| Both central and peripheral | 83 (38.8%) | 31 (32.0%) | 52 (44.8%) | |
| None | 4 (1.9%) | 2 (2.1%) | 2 (1.7%) | |
| Assessed zone, n (%) | | | | |
| Upper | 174 (81.3%) | 76 (78.4%) | 98 (84.5%) | .964 |
| Middle | 182 (85.0%) | 81 (83.5%) | 101 (87.1%) | |
| Lower | 193 (90.2%) | 87 (89.7%) | 106 (91.4%) | |
| None | 4 (1.9%) | 2 (2.1%) | 2 (1.7%) | |

Abbreviations: CT, computed tomography; GGO, ground glass opacity; IFV, influenza A virus; IQR, interquartile range; MV, mechanical ventilation; NIPPV, noninvasive positive pressure ventilation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

with co-infection had decreased degree of hyper-inflammation. This observation was further strengthened by the lower prevalence of lymphadenopathy and lower CT scores among patients with co-infection. The mechanism of reduced inflammatory response in patients with co-infection is still unknown.

There were some limitations in the current study. First, the IFV-A IgM concentrations might be affected by vaccination, and the influence of vaccination on antibody detection needs to be considered when the influenza vaccination rate has reached 9.5% among adults in China.³⁰ In addition, antibody-based tests might produce false

negative results during the window period. Second, symptoms of influenza A virus infection are difficult to distinguish from those of COVID-19 infection. PCR-based testing is the most sensitive and specific modality for diagnosing influenza infection. In the current retrospective study, use of serology tests for diagnosis of influenza A infection might have resulted in false positive cases.

In conclusion, there was a high proportion (45.5%) of IFV-A and SARS-CoV-2 co-infection in Wuhan from January 2020 to March 2020. Patients with co-infection presented with similar symptoms and outcomes. However, increases in serum level of cytokines (IL-2R, IL-6, IL-8, and TNF- α), frequency of lymphadenopathy, and CT scores were observed in patients with SARS-CoV-2 infection only or specific population of COVID-19 patients (male or age \leq 60 years). Although a limited number of patients were enrolled, we found that co-infection with influenza A had no observable effect on disease outcomes and might alleviate cytokine storms in patients. Both viruses can cause serious illness or death, especially among vulnerable populations; thus, systematic testing for SARS-CoV-2 and influenza are necessary, and influenza vaccination is recommended not only to reduce the risk of co-infection, but also for the potential benefit to the immune system.³¹ Further studies with larger sample sizes from multiple sites are also warranted to study the prognosis and treatment of coinfecting patients.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Conceptualization: Yuan Cheng, Zhanwei Hu, He wang. Data curation: Yuan Cheng, Xi Wang, Zhanwei Hu, Jing Ma. Formal analysis: Yuan Cheng. Funding acquisition: Hong Zhang. Investigation: Haichao Li. Methodology: Yuan Cheng, He Wang. Resources: Xinmin Liu. Writing—original draft, review, and editing: Yuan Cheng, Haichao Li.

ETHICS STATEMENT

This study was approved by the Research Ethics Commission of Peking University First Hospital (2020(098)). Due to the retrospective nature of the study, requirement for informed consent was waived the by the Research Ethics Commission of Peking University First Hospital.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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