Impact of recent influenza A virus infection on clinical characteristics and outcomes in severe coronavirus disease 2019 adult inpatients

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Research Article

Keywords: coronavirus disease 2019 (COVID-19); influenza A virus; clinical outcomes

Posted Date: June 23rd, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-35441/v1>

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Abstract

Background: Coronavirus disease 2019 (COVID-19) is a current global pandemic. However, impact of recent influenza A virus infection on the clinical course and outcomes of severe COVID-19 adult inpatients needs to be further explored.

Methods: In this retrospective cohort study, severe, laboratory confirmed COVID-19 adult patients from Wuhan Tongji Hospital were included. Data were obtained from electronic medical records and compared between patients with and without recent influenza A virus infection.

Results: 200 patients were included, 51.5% with recent influenza A virus infection. Recent influenza A virus infection group presented with longer persistence of cough and sputum from illness onset (35.0 vs. 27.0 days, $P = 0.018$) and (33.0 vs. 26.0 days, $P = 0.015$), respectively. Median time of progression to critical illness from illness onset was shorter (day 11.5 vs. day 16.0, $P = 0.034$). Time to clinical improvement and length of hospital stay were longer in recent infection group (23.0 vs. 19.0 days, $P = 0.044$) and (22.0 vs. 18.0 days, $P = 0.030$), respectively.

Conclusions: Patients with recent influenza A virus infection showed a delay in time to clinical improvement and increased length of hospital stay. There is a high clinical need to improve the detection of common respiratory pathogens to identify co-infection during the epidemic of COVID-19.

Background

As of June 6, 2020, according to the report of coronavirus disease 2019 (COVID-19) outbreak situation from the World Health Organization (WHO), the COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a global pandemic that resulted in 6,663,304 infections and 392,802 deaths worldwide. The dynamic of the disease presents serious threat to global health.

Patients with SARS-CoV-2 infection presented with including among others fever, cough, sputum, fatigue; ground glass opacity, infiltration, and consolidation were the typical chest computed tomography (CT) findings [1, 2]. COVID-19 can lead to complications including acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), acute cardiac injury, and shock, which may cause fatal outcomes, especially in severe patients [2, 3]. These clinical features and ways of transmission are similar to influenza that often occurs in wintertime [4].

Recent case reports have reported that COVID-19 patients can be co-infected with other pathogens including influenza virus, human metapneumovirus and mycoplasma [5–9]. COVID-19 co-infection with a standard respiratory virus may be associated with increased morbidity and complications [6, 8]. Here, we explored the differences in clinical course and outcomes between with and without recent influenza A virus infection in severe COVID-19 adult inpatients.

Methods

Study design and participants

This was a single-center, retrospective, cohort study. 227 COVID-19 adult inpatients (≥ 18 years old) were tested for influenza serology admitted to Wuhan Tongji Hospital from 10th of February to 20th of March, 2020. Among them, 25 patients were transferred from other hospitals with missing previous hospitalization information; two patients were admitted with critical type and died on the same day. Data of 200 patients with severe COVID-19 were collected (Fig. 1). Diagnosis and clinical classification of all patients with COVID-19 included in this study accorded to WHO interim guidance and the Chinese management guideline for COVID-19 (version 7.0) [10, 11].

Adult patients with the severe form if one of the following is met: 1. Shortness of breath, respiratory rate (RR) ≥ 30 breaths/minute; 2. SaO_2 or $\text{SPO}_2 \leq 93\%$ on room air at rest; 3. $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg. Critical illness is defined as one or more of the following: 1. Respiratory failure with the requirement of mechanical ventilation; 2. Shock; 3. Combined other organs failure requiring monitoring and treatment in intensive care unit (ICU). Severe and critically ill COVID-19 patients were identified by reviewing and analyzing admission logs and histories of all available electronic medical records and patient care resources.

The laboratories of the Chinese Center for Disease Control and Prevention (CDC) and the local CDC have made a definitive diagnosis of COVID-19 through pharyngeal swab specimens from the upper respiratory tract. Using Real-time Reverse Transcription Polymerase Chain Reaction Assay to confirm SARS-CoV-2 infection [2]. The high specificity and the sensitivity of immunoglobulin M (IgM) detection method indicates that IgM is a reliable biomarker for the monitoring recent viral infection, which was used to identify recent influenza A virus infection in this study [12–14]. Indirect immunofluorescence assay (IIFA) of specific IgM antibodies (EUROIMMUN, FI 2821-17M, Germany) was used to conduct influenza A IgM antibody tests. All operations were carried out according to the provided instructions. Patients included in this study were not vaccinated against influenza A at the time of admission.

Data collection

Medical records were reviewed by trained physicians. Demographic characteristics (age and gender) and clinical characteristics (comorbidities, laboratory and radiographic findings, severity of illness scores, treatments, complications and outcomes) were collected. Clinical data collection was completed on 1st of April, 2020. For any discrepancies between the two datasets, the original medical records were checked to make sure the data accuracy.

Outcomes and definitions

Patients were followed-up from admission to hospital discharge, hospital referral or death (whichever came first). Due to the epidemic control, the number of patients in Wuhan has decreased. 27 patients in this study were transferred to other designated hospitals at the end of the data collection period. They were stable at the time but did not meet the discharge criteria. These 27 patients were followed up to 28 days hospitalization before hospital referral. The primary outcome were in-hospital mortality and clinical

improvement rate. Secondary outcomes were progressing to critical illness rate after admission, 28-day in-hospital mortality, rate of clinical improvement up to 28 days after admission, time to clinical improvement (TTCI), length of hospital stay, time from illness onset to critical illness, rate of ICU admissions, proportion of invasive mechanical ventilation (IMV) therapy, rate of conversion to negative of SARS-CoV-2 RNA from hospital admission, and duration of viral shedding after illness onset. TTCI was defined as the days from admission to clinical improvement [15]. Clinical improvement was defined as an improvement of two points (from the status on admission) on a seven-category ordinal scale or live discharge from the hospital, whichever came first [16]. The seven-category ordinal scale consisted of the following categories [15]: 1, not hospitalized with resumption of normal activities; 2, not hospitalized, but unable to resume normal activities; 3, hospitalized, not requiring supplemental oxygen; 4, hospitalized, requiring supplemental oxygen; 5, hospitalized, requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both; 6, hospitalized, requiring extracorporeal membrane oxygenation (ECMO), invasive mechanical ventilation, or both; and 7, death. The criteria for discharge were as all of follows: at least three days of absence of fever, substantial improvement in both lungs in chest CT, clinical remission of respiratory symptoms, and two throat-swab samples with SARS-CoV-2 RNA negative obtained at least 24 hours apart.

Myocardial injury was defined as serum concentration of high-sensitivity cardiac troponin I level above the 99th percentile upper reference limit [17]. Moderate-to-severe ARDS was diagnosed according to the Berlin definition [18]: $\text{PaO}_2/\text{FiO}_2$ ratio less than 200 mmHg and a positive end-expiratory pressure more than 5 cmH₂O. AKI was defined according to KDIGO clinical practice guidelines: an increase in serum creatinine values ≥ 0.3 mg/dl (≥ 26.5 $\mu\text{mol/l}$) within 48 hours, serum creatinine values ≥ 1.5 times the baseline within the previous seven days, or urine volume ≤ 0.5 ml/kg⁻¹h⁻¹ for six hours [19]. Liver injury was defined as any parameter of liver function more than the upper limit of normal value [20]. Septic shock was diagnosed according to International Guidelines for Management of Sepsis and Septic Shock: 2016 [21]. Pre-existing cardiac conditions were defined as congestive heart failure, known conduction system abnormality or ischemic heart disease [22]. Pre-existing cerebrovascular disease were defined as intracerebral hemorrhage and ischemic strokes. Corticosteroid treatment was defined as at least a dose (≥ 0.5 mg/kg⁻¹) of methylprednisolone during hospitalization [23, 24].

Statistical analysis

Continuous data with skewed distribution presented as median [interquartile range (IQR)]. Frequency data were expressed as proportions. Comparisons of continuous variables were made with Student's t test or the Mann-Whitney U test when appropriate, while differences in categorical variables were assessed using the χ^2 test, Yates's correction or Fisher's exact test, as appropriate. Survival curves were plotted using the Kaplan-Meier method and compared outcomes between patients with or without influenza A virus co-infection using the log-rank test.

Data were analyzed using SPSS 25.0 (IBM, Chicago, IL, USA). Statistical charts were performed using GraphPad Prism 7 (GraphPad Software, San Diego, CA, USA). A two-tailed P value of < 0.05 was

considered statistically significant.

Results

Patient characteristics

227 COVID-19 adult inpatients were tested for influenza serology admitted to Wuhan Tongji Hospital from the 10th of February 10 to 20th of March, 2020. 27 patients were excluded (25 were transferred from other hospitals with missing clinical data, two were admitted with critical type and died on admission day). A total of 200 adult inpatients diagnosed with severe COVID-19 were included in this study (Fig. 1). The median age was 63 years old (IQR, 52.0–72.0), 48.5% were male, 13.5% progressed to critical illness, 76.5% had clinical improvement, and 10.5% died during hospitalization (Tables 1 and 2). The most common symptoms were cough (78.5%), fever (76.5%), fatigue (48.5%), sputum (44.0%), and dyspnea (42.5%); ground glass opacity was the most common chest CT feature (67.5%) (Table 1).

Table 1
Demographic, clinical, laboratory, and radiographic findings of severe COVID-19 in-patients with and without influenza A virus recent infection.

Characteristics	All patients (n = 200)	Influenza A Recent infection (n = 103)	Influenza A Non- infection (n = 97)	p value
Age, median (IQR), yr	63.0 (52.0–72.0)	62.0 (52.0–69.0)	63.0 (52.0–74.5)	0.106
Male, n (%)	97 (48.5)	36 (35.0)	61 (62.9)	< 0.001
Current smokers, n (%)	7 (3.5)	2 (1.9)	5 (5.2)	0.268 ^c
Pre-existing condition, n (%)				
Hypertension	71 (35.5)	39 (37.9)	32 (33.0)	0.472
Cardiovascular disease ^a	22 (11.0)	7 (6.8)	15 (15.5)	0.050
Cerebrovascular disease ^b	10 (5.0)	4 (3.9)	6 (6.2)	0.673 ^d
COPD	10 (5.0)	5 (4.9)	5 (5.2)	1.000 ^d
Diabetes	32 (16.0)	20 (19.4)	12 (12.4)	0.174
Symptoms, n (%)				
Fever	153 (76.5)	73 (70.9)	80 (82.5)	0.053
Cough	157 (78.5)	80 (77.7)	77 (79.4)	0.768
Sputum	88 (44.0)	46 (44.7)	42 (43.3)	0.846
^a Cardiovascular disease were defined as congestive heart failure, known conduction system abnormality or ischemic heart disease.				
^b Cerebrovascular disease were defined as intracerebral hemorrhage and ischemic strokes.				
^c Fisher's exact test was used.				
^d Yates's correction was used.				
Abbreviations: IQR = interquartile range. COPD = chronic obstructive pulmonary disease. WBC = white blood cell. hs-CRP = high-sensitivity C-reactive protein. PCT = procalcitonin. AST = aspartate aminotransferase. ALT = alanine aminotransferase. LDH = lactate dehydrogenase. BUN = blood urea nitrogen. eGFR = estimated glomerular filtration rate. IL-6 = interleukin-6. TNF-α = tumor necrosis factor-α.				

Characteristics	All patients (n = 200)	Influenza A Recent infection (n = 103)	Influenza A Non- infection (n = 97)	p value
Dyspnea	85 (42.5)	43 (41.7)	42 (43.3)	0.824
Palpitation	32 (16.0)	17 (16.5)	15 (15.5)	0.841
Fatigue	97 (48.5)	47 (45.6)	50 (51.5)	0.403
Diarrhea	44 (22.0)	21 (20.4)	23 (23.7)	0.571
Nausea and vomiting	32 (16.0)	17 (16.5)	15 (15.5)	0.841
Laboratory findings on admission, median (IQR)				
WBC count, $\times 10^9/L$	6.4 (5.2-8.0)	6.4 (5.0-7.9)	6.6 (5.3-8.1)	0.356
Neutrophil count, $\times 10^9/L$	4.1 (3.2-5.7)	3.9 (2.9-5.5)	4.2 (3.2-6.1)	0.251
Lymphocyte count, $\times 10^9/L$	1.3 (0.9-1.8)	1.3 (0.9-1.9)	1.1 (0.8-1.7)	0.110
Platelet count, $\times 10^9/L$	235.0 (186.5- 298.0)	234.0 (187.3- 292.0)	236.5 (181.8-301.5)	0.733
hsCRP, mg/L	8.1 (1.4- 44.3)	5.3 (1.1- 32.3)	13.1 (2.2- 56.3)	0.045
PCT, ng/ml	0.07 (0.05- 0.12)	0.06 (0.05- 0.08)	0.08 (0.06- 0.15)	0.018
AST, U/L	23.0 (17.0- 35.8)	22.0 (16.0- 36.5)	24.0 (18.0- 34.0)	0.743

^a Cardiovascular disease were defined as congestive heart failure, known conduction system abnormality or ischemic heart disease.

^b Cerebrovascular disease were defined as intracerebral hemorrhage and ischemic strokes.

^c Fisher's exact test was used.

^d Yates's correction was used.

Abbreviations: IQR = interquartile range. COPD = chronic obstructive pulmonary disease. WBC = white blood cell. hs-CRP = high-sensitivity C-reactive protein. PCT = procalcitonin. AST = aspartate aminotransferase. ALT = alanine aminotransferase. LDH = lactate dehydrogenase. BUN = blood urea nitrogen. eGFR = estimated glomerular filtration rate. IL-6 = interleukin-6. TNF- α = tumor necrosis factor- α .

Characteristics	All patients (n = 200)	Influenza A Recent infection (n = 103)	Influenza A Non- infection (n = 97)	p value
ALT, U/L	22.0 (13.0-39.8)	20.0 (12.8-34.8)	25.0 (15.8-41.0)	0.120
LDH, U/L	222.5 (176.3-302.0)	221.5 (180.0-303.5)	232.5 (173.0-302.5)	0.635
BUN, mmol/L	4.5 (3.8-5.9)	4.5 (3.7-5.8)	4.7 (3.9-6.0)	0.670
Creatinine, μ mol/L	74.7 (59.0-93.6)	74.0 (60.0-90.5)	77.0 (59.0-99.0)	0.741
PaO ₂ /FiO ₂ , mmHg	227.3 (158.5-305.9)	213.8 (158.5-298.9)	234.0 (160.6-326.5)	0.549
IL-6, pg/ml	5.4 (2.4-23.9)	3.5 (1.9-10.3)	10.0 (3.6-36.7)	0.001
TNF- α , pg/ml	8.7 (6.6-11.2)	7.6 (6.2-10.4)	9.7 (7.7-12.1)	0.002
D-dimer, μ g/ml	0.7 (0.3-1.8)	0.6 (0.3-1.6)	0.8 (0.3-2.1)	0.315
Radiographic findings on admission, n (%)				
Ground glass opacity	135 (67.5)	66 (64.1)	69 (71.1)	0.287
Diffuse bilateral pulmonary infiltration	72 (36.0)	37 (35.9)	35 (36.1)	0.981
Consolidation	20 (10.0)	11 (10.7)	9 (9.3)	0.741
^a Cardiovascular disease were defined as congestive heart failure, known conduction system abnormality or ischemic heart disease.				
^b Cerebrovascular disease were defined as intracerebral hemorrhage and ischemic strokes.				
^c Fisher's exact test was used.				
^d Yates's correction was used.				
Abbreviations: IQR = interquartile range. COPD = chronic obstructive pulmonary disease. WBC = white blood cell. hs-CRP = high-sensitivity C-reactive protein. PCT = procalcitonin. AST = aspartate aminotransferase. ALT = alanine aminotransferase. LDH = lactate dehydrogenase. BUN = blood urea nitrogen. eGFR = estimated glomerular filtration rate. IL-6 = interleukin-6. TNF- α = tumor necrosis factor- α .				

Table 2

Disease severity, complications, treatments and outcomes of severe COVID-19 in-patients with and without influenza A virus recent infection.

Characteristics	All patients (n = 200)	Influenza A Recent infection (n = 103)	Influenza A Non-infection (n = 97)	p value
CURB-65 score ≥ 3 on admission, n (%)	11 (5.5)	7 (6.8)	4 (4.1)	0.407
Seven-category scale on admission, n (%)				0.925
4: Hospitalization, requiring supplemental oxygen	188 (94.0)	97 (94.2)	91 (93.8)	
5: Hospitalization, requiring HFNC or NIMV ^a	12 (6.0)	6 (5.8)	6 (6.2)	
Treatments, n (%)				
Admission to an ICU	18 (9.0)	8 (7.8)	10 (10.3)	0.530
Use of IMV	15 (7.5)	5 (4.9)	10 (10.3)	0.143
Use of CRRT	6 (3.0)	2 (1.9)	4 (4.1)	0.434 ^d
Use of oseltamivir	70 (35.0)	52 (50.5)	18 (18.6)	< 0.001
Use of arbidol	170 (85.0)	90 (87.4)	80 (82.5)	0.332
Use of lopinavir/ritonavir	22 (11.0)	10 (9.7)	12 (12.4)	0.548
Use of Lianhuaqingwen	157 (78.5)	84 (81.6)	73 (75.3)	0.279

^a HFNC was used in these 12 patients.

^b Corticosteroid treatment was defined as administration of at least a dose equivalent to ≥ 0.5 mg/kg of methylprednisolone during hospitalization.

^c Moderate-to-severe ARDS, was diagnosed according to the Berlin definition: PaO₂/FiO₂ ratio of less than or equal to 200 mmHg and a positive end-expiratory pressure of greater than or equal to 5 cmH₂O.

^d Fisher's exact test was used.

Abbreviations: HFNC = high-flow nasal cannula for oxygen therapy. NIMV = noninvasive mechanical ventilation. ICU = intensive care unit. IMV = invasive mechanical ventilation. CRRT = continuous renal replacement therapy. ARDS = acute respiratory distress syndrome. AKI = acute kidney injury. IQR = interquartile range.

Characteristics	All patients (n = 200)	Influenza A Recent infection (n = 103)	Influenza A Non-infection (n = 97)	p value
Received antibiotic treatment	136 (68.0)	65 (63.1)	71 (73.2)	0.126
Use of corticosteroid ^b	49 (24.5)	22 (21.4)	27 (27.8)	0.287
Complications during hospitalization, n (%)				
ARDS ^c	25 (12.5)	11 (10.7)	14 (14.4)	0.422
Myocardial injury	29 (14.5)	9 (8.7)	20 (20.6)	0.017
AKI	14 (7.0)	8 (7.8)	6 (6.2)	0.661
Liver injury	26 (13.0)	16 (15.5)	10 (10.3)	0.272
Septic shock	12 (6.0)	6 (5.8)	6 (6.2)	0.915
Outcomes, n (%)				
Virus clearance	173 (86.5)	91 (88.3)	82 (84.5)	0.430
Progression to critical illness	27 (13.5)	10 (9.7)	17 (17.5)	0.106
Clinical improvement	153 (76.5)	81 (78.6)	72 (74.2)	0.462
In-hospital mortality	21 (10.5)	8 (7.8)	13 (13.4)	0.194
^a HFNC was used in these 12 patients.				
^b Corticosteroid treatment was defined as administration of at least a dose equivalent to ≥ 0.5 mg/kg of methylprednisolone during hospitalization.				
^c Moderate-to-severe ARDS, was diagnosed according to the Berlin definition: PaO ₂ /FiO ₂ ratio of less than or equal to 200 mmHg and a positive end-expiratory pressure of greater than or equal to 5 cmH ₂ O.				
^d Fisher's exact test was used.				
Abbreviations: HFNC = high-flow nasal cannula for oxygen therapy. NIMV = noninvasive mechanical ventilation. ICU = intensive care unit. IMV = invasive mechanical ventilation. CRRT = continuous renal replacement therapy. ARDS = acute respiratory distress syndrome. AKI = acute kidney injury. IQR = interquartile range.				

51.5% (103/200) of the patients with recent influenza A virus infection. Recent infection group had a lower proportion of male sex than non-infection group (35.0% vs. 62.9%, $P < 0.001$). Compared with non-

infection group, patients with influenza A virus recent infection presented with a prolonged duration of cough and sputum from illness onset (35.0 vs. 27.0 days, $P = 0.018$) and (33.0 vs. 26.0 days, $P = 0.015$), respectively (Fig. 2A). Recent infection group showed lower median high-sensitive C-reactive protein (hsCRP) (5.3 vs. 13.1 mg/L, $P = 0.045$), procalcitonin (PCT) (0.06 vs. 0.08 ng/ml, $P = 0.018$), interleukin-6 (IL-6) (3.5 vs. 10.0 pg/ml, $P = 0.001$) and tumor necrosis factor- α (TNF- α) (7.6 vs. 9.7 pg/ml, $P = 0.002$) at the time of admission (Table 1). No significant difference was found between these two cohorts in age, pre-existing conditions, symptoms, other laboratory findings, radiographic findings, and length of fever and dyspnea.

Disease severity, complications, treatments and outcomes of severe COVID-19 in-patients with and without recent influenza A virus infection

Proportions of patients with CURB-65 score equal and more than 3 was higher in recent infection group than that in non-infection group, while there was no significant difference (6.8% vs. 4.1%, $P = 0.407$). All the patients in our study tolerated antiviral therapy well after illness onset. A significant higher proportion of oseltamivir therapy was shown in recent infection group (50.5% vs. 18.6%, $P < 0.001$). Among 200 patients, incidence of myocardial injury was lower in recent infection group (8.7% vs. 20.6%, $P = 0.017$). In recent infection group, proportions of moderate-to-severe ARDS (10.7% vs. 14.4%, $P = 0.422$), AKI (7.8% vs. 6.2%, $P = 0.422$), liver injury (15.5% vs. 10.3%, $P = 0.272$), and septic shock (5.8% vs. 6.2%, $P = 0.915$) during hospitalization did not significantly differ from that in non-infection group (Table 2). Between the recent infection and non-infection cohorts, the occurrence of moderate-to-severe ARDS, myocardial injury, AKI and liver injury at a median of day (10.0 vs. 18.5, $P = 0.380$), (12.0 vs. 14.0, $P = 0.555$), (12.5 vs. 23.5, $P = 0.330$), and (19.0 vs. 19.5, $P = 0.731$) from illness onset, respectively (Fig. 2B).

Progression to critical illness from illness onset in recent infection patients at a median of day 11.5, was earlier than non-infection group (11.5 vs. 16.0, $P = 0.034$). Compared with the non-infection group, duration of viral shedding was longer in recent infection group without significant statistical difference (26.0 vs. 23.5 days, $P = 0.051$) (Fig. 3A). TTCl and length of hospital stay were longer in recent infection group (23.0 vs. 19.0 days, $P = 0.044$) and (22.0 vs. 18.0 days, $P = 0.030$), respectively (Fig. 3B). No difference was found in virus clearance rate, progression to critical illness rate, clinical improvement rate and mortality during hospitalization (Table 2). The two groups showed no significant difference neither in day-28 clinical improvement rate nor in day-28 mortality (Fig. 3C and D).

Discussion

With the COVID-19 outbreak and pandemic ongoing, the number of infections and decedent continues to rise all over the world. Transmission ways of COVID-19 are similar to influenza that often occurs in wintertime [4, 25]. Previous studies found that, COVID-19 patients can be co-infected with other pathogens including influenza virus, human metapneumovirus and mycoplasma [5–8]. Our study focus on the comparison of clinical characteristics between recent infected and non-infected with influenza A virus in severe COVID-19 patients. In this study, we found that patients with influenza A virus recent

infection needed a longer time period for any clinical improvement and length of hospital stay was prolonged.

Cohort of recent infection patients in our study had fewer male patients. Sexual differences is known to play an important role in affecting the immune system function [26]. Both neutrophils from human males and peritoneal macrophages from male mice express higher levels of TNF- α after lipopolysaccharide stimulation than females [27]. Recent studies reported that, male COVID-19 patients were associated with higher mortality [28], and fatal cases showed a more severe cytokine storm [3]. These might explain that patients with recent infection had lower values of inflammation indicators in our study. In addition, cytokine storm was an important factor for myocardial injury and fatal outcome of COVID-19 patients [3, 29], which partially explained the lower incidence of myocardial injury in influenza A virus recent infection cohort.

Although there was no nucleic acid result to confirm influenza A infection, some of the patients with influenza A IgM positive in this study may have co-infection with two viruses (influenza A virus and SARS-CoV-2). Viral co-infection can affect the course of infectious diseases [30–32]. Angiotensin Converting Enzyme 2 (ACE2) was proven to be one of the major receptors that mediate the entry of SARS-CoV-2 into human cells [33, 34]. A recent study reported that, cells infected with influenza A virus significantly increase ACE2 surface expression, and the regulatory effect of influenza A virus on ACE2 expression was associated with activation of the interferon beta-induced pathway and viral RNA-activated host response [35]. In our study, even though the proportions of symptoms, complications and clinical outcomes were similar, patients with influenza A virus recent infection had significant prolonged duration of cough, sputum and viral shedding; showed shorter time of progression to critical illness from illness onset; needed more time to clinical improvement and had an increase in length of hospitalization. Although there was no statistical difference, complications occurred earlier in the recent infection patients. These findings highlight a growing need to focus on the influenza A virus recent infection especially co-infection in severe COVID-19 patients, as which may lead to earlier organ dysfunction and persistent disease progression.

This study is limited by its retrospective design, which cannot represent all the severe COVID-19 patients. Secondly, due to the epidemic situation and the limitations of the research conditions, this study used serological examination to determine whether there was influenza A virus recent infection, we cannot confirm the co-infection condition. More strict detection and diagnosis procedures for other respiratory pathogens need to be incorporated in the clinical setting during this pandemic of COVID-19. Thirdly, we cannot obtain the exact time point of influenza A virus infection, so that whether the two viruses enhance infection of each other cannot be analyzed but need future evaluation.

Conclusions

Severe COVID-19 adult inpatients, who with recent influenza A virus infection showed prolonged time to clinical improvement and an increase in length of hospital stay. For a better clinical treatment and

management strategies it is important to strengthen the detection of common respiratory pathogens, investigate the interaction between pathogens, and the impact of co-infection on the clinical process and outcomes. These steps will help to have a more comprehensive understanding of COVID-19 infection in patients.

Abbreviations

IQR

Interquartile range

COPD

Chronic obstructive pulmonary disease

WBC

White blood cell

hs-CRP

High-sensitivity C-reactive protein

PCT

Procalcitonin

AST

Aspartate aminotransferase

ALT

Alanine aminotransferase

LDH

Lactate dehydrogenase

BUN

Blood urea nitrogen

eGFR

Estimated glomerular filtration rate

IL-6

Interleukin-6

TNF- α

Tumor necrosis factor- α

HFNC

High-flow nasal cannula for oxygen therapy

NIMV

Noninvasive mechanical ventilation

ICU

Intensive care unit

IMV

Invasive mechanical ventilation

CRRT

Continuous renal replacement therapy

ARDS

Acute respiratory distress syndrome

AKI

Acute kidney injury

IQR

Interquartile range

Declarations

Ethics approval and consent to participate

This study was approved by the institutional review boards at Wuhan Tongji Hospital and The First Affiliated Hospital of Soochow University (2020-054). As an emerging infectious disease, written informed consent was exempted.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during the present study was included in this published article.

Competing interests

We declare no competing interests.

Funding

Jiangsu Province's Key Provincial Talents Program (ZDRCA2016046); Key Health Talents in Gusu (GSWS2019009).

Authors' Contributions

QG had the idea for and designed the study and had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. CG and XY drafted the paper. CG did the statistical analysis. CG, XY, LC, HX, JL, SW, HN, WY, JH, XZ, JC, LY and QZ collected the data. QG, BS, AT, JM.U contributed to critical revision of the report. All authors contributed to data acquisition, data analysis, or data interpretation, and reviewed and approved the final version.

Acknowledgments

We thank Ling Yang and Jiahao Chen at Soochow University for their help in data management, as well as all health-care workers involved in the diagnosis and treatment of patients in Wuhan.

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Figures

Figure 1

Study flow diagram

Figure 2

Comparison of Clinical courses of major symptoms and complications between with and without influenza A virus recent infection in severe COVID-19 inpatients. Shown are (A) comparison of duration of major symptoms from illness onset between recent infection and non-infection groups. Shown are (B) comparison of median time from illness onset to common complications occurrence between recent infection and non-infection groups. ARDS here meant moderate-to-severe ARDS, was diagnosed according to the Berlin definition: $\text{PaO}_2/\text{FiO}_2$ ratio of less than or equal to 200 mmHg and a positive end-expiratory pressure of greater than or equal to 5 cmH₂O. Abbreviations: ARDS = acute respiratory distress syndrome. AKI = acute kidney injury.

Figure 3

Comparison of Clinical outcomes between with and without influenza A virus recent infection in severe COVID-19 inpatients. Shown are (A) comparison of duration of viral shedding and median time of progression to critical illness from illness onset between recent infection and non-infection groups. Shown are (B) comparison of time to clinical improvement and length of hospital stay between recent infection and non-infection groups. Shown are (C) comparison of cumulative incidences of clinical improvement from admission to 28 days between recent infection and non-infection groups. Shown are (D) comparison of cumulative mortality from admission to 28 days between recent infection and non-infection groups. Clinical improvement was defined as discharge or a 2-step decrease on a 7-point ordinal scale of clinical status after admission.

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