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Clinical characteristics of critically ill patients co-infected with SARS-CoV-2 and the influenza virus in Wuhan, China

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ABSTRACT

Objective: To delineate the clinical characteristics of critically ill COVID-19 patients co-infected with influenza.
Methods: This study included adult patients with laboratory-confirmed COVID-19 form Tongji Hospital (Wuhan, China), with or without influenza, and compared their clinical characteristics.
Results: Among 93 patients, 44 died and 49 were discharged. Forty-four (47.3%) were infected with influenza virus A and two (2.2%) with influenza virus B. Twenty-two (50.0%) of the non-survivors and 24 (49.0%) of the survivors were infected with the influenza virus. Critically ill COVID-19 patients with influenza were more prone to cardiac injury than those without influenza. For the laboratory indicators at admission the following were higher in non-survivors with influenza than in those without influenza: white blood cell counts, neutrophil counts, levels of tumor necrosis factor-α, D-dimer value, and proportion of elevated creatinine.
Conclusion: The results showed that a high proportion of COVID-19 patients were co-infected with influenza in Tongji Hospital, with no significant difference in the proportion of co-infection between survivors and non-survivors. The critically ill COVID-19 patients with influenza exhibited more severe inflammation and organ injury, indicating that co-infection with the influenza virus may induce an earlier and more frequently occurring cytokine storm.

Introduction

The World Health Organization (WHO) named the coronavirus disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as 2019 novel coronavirus disease (COVID-19) and declared it as a pandemic. Similar to the influenza virus, SARS-CoV-2 is commonly transmitted through respiratory droplets and contact. The world's population is generally susceptible to SARS-CoV-2 infection. Most COVID-19 patients show mild influenza-like symptoms, such as fever, cough and fatigue. However, approximately 5% of patients rapidly progress to acute respiratory distress syndrome (ARDS), septic shock and multiple organ failure, and are admitted to intensive care units. The COVID-19-associated mortality rate in China is approximately 2.3% (Guan et al., 2020; Novel Coronavirus Pneumonia Emergency Response Epidemiology Team 2020). To date, no studies have reported on critically ill COVID-19 patients who also present with influenza. Human cases of influenza in Wuhan most often occur in winter (He and Tao 2018; Wang et al. 2018), which overlapped with the peak of COVID-19 in Wuhan. This study speculated whether co-infection with SARS-CoV-2 and the influenza virus exist. And if so, the influence of this co-infection on clinical features needs to be investigated.

The Southern hemisphere is yet to enter its flu season for the year and in many of these countries the incidence of COVID-19 is still increasing. Meanwhile, many Western hemisphere countries are still experiencing COVID-19 outbreaks. A great many countries around the world will be looking to start planning for flu season 2020/21, with many public health experts warning of the need to avoid second peaks of COVID-19 during flu season. Therefore, it is crucial to answer the above questions so as to formulate treatment strategies to manage co-infection with SARS-CoV-2 and the influenza virus.

The present study extracted the clinical data for 95 patients with laboratory-confirmed COVID-19 from Tongji Hospital

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(Wuhan) and discussed the clinical characteristics of critically ill COVID-19 patients co-infected with influenza. The results may provide new insights into the treatment and control of co-infection with SARS-CoV-2 and the influenza virus.

Materials and Methods

Study design and participants

The study was conducted among 95 adult patients with laboratory-confirmed COVID-19 (including 50 discharged cases and 45 non-survivors) who were discharged or died in Tongji Hospital (Wuhan, China) from 28 January 2020 to 29 February 2020. The discharge criteria were based on the fifth version of diagnosis and treatment guidance for COVID-19 published by the National Health Commission of People's Republic of China (2020). Patients met the discharge criteria if they had normal body temperature for 3 consecutive days, greatly improved respiratory symptoms and pulmonary imaging manifestations, and were negative for the presence of SARS-CoV-2 nucleic acid twice in succession. Owing to limited medical resources, the nucleic acid test for the presence of influenza virus in respiratory specimens was not widely carried out. Influenza virus diagnosis in this study was based on serology. None of the 95 patients had a history of influenza vaccination in the recent flu season. This study was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. The need for written informed consent was waived by the Ethics Committee of the hospital for the rapid emergence of this infectious disease.

Data collection

Data were extracted from electronic medical records, and included: age; gender; history of recent exposure; history of chronic diseases (hypertension, diabetes, coronary disease, chronic lung disease, chronic kidney disease, malignant tumors, etc.); symptoms from illness onset to admission (fever, cough, dyspnea, fatigue, myalgia, diarrhea, chest pain, headache, etc.); laboratory assessments (including complete blood count, C-reactive protein [CRP], arterial blood gas, coagulation function, D-dimer, alanine aminotransferase [ALT], aspartate aminotransferase [AST], lactate dehydrogenase [LDH], creatinine, amino-terminal pro-brain natriuretic peptide precursor [NT-proBNP], cardiac troponin I [cTnI], tumor necrosis factor-α [TNF-α], and interleukin-6 [IL-6] and respiratory virus-specific IgM antibodies); detailed medication; and tests for SARS-CoV-2 from respiratory tract specimens (including nasopharyngeal swabs, bronchoalveolar lavage fluid, sputum, or bronchial aspiration fluid). Specimen collection and lung CT scanning were completed for all patients within 24 hours of admission.

Real-time reverse-transcription polymerase chain reaction assay

A confirmed COVID-19 case was defined as a positive result in a real-time reverse-transcription polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swab specimens according to WHO guidelines. On receipt of the samples, viral RNA extraction was performed using a Magnetic Viral RNA/DNA Extraction Kit (Tianlong, Xi'an, China) following the manufacturer's instructions. This was followed by PCR screening for the specific detection of SARS-CoV-2 using a commercial kit (Tianlong). A cycle threshold value (Ct-value) $\leq$37 was defined as a positive test based on the recommendation of the National Institute for Viral Disease Control and Prevention (China).

Indirect immunofluorescence assay (IIFA) of IgM antibodies

A respiratory tract profile (IgM) kit (EUROIMMUN, Luebeck, Germany) was employed according to the manufacturer's instructions. Based on the Titerplane^{TM} technique using infected cells/cultured bacteria, this kit is designed for the *in vitro* detection of human IgM antibodies against influenza virus A, influenza virus B and six atypical respiratory pathogens: adenovirus, respiratory syncytial virus, parainfluenza virus, *Chlamydia pneumoniae*, *Legionella pneumophila*, and *Mycoplasma pneumonia* in serum/plasma samples. Fluorescence results were analyzed by experienced technicians.

Statistical analysis

Statistical analysis was performed using SPSS 20.0. Continuous variables were expressed as means ± standard deviation (SD) using the Student's *t*-test or as medians and interquartile range (IQR) using the Mann-Whitney U test. Categorical variables were expressed as numbers (%) and compared by the χ^2 test or Fisher's exact test. $P < 0.05$ was considered significant.

Results

Demographic and clinical characteristics

Of the 95 COVID-19 patients, 44 were infected with influenza virus A, two with influenza virus B, one with adenovirus, and one with parainfluenza; 47 were uninfected. A total of 93 patients were finally included, 46 (49.5%) of whom were infected with influenza virus A or B (classified as the flu group), while 47 (50.5%) were uninfected (classified as the non-flu group). Of these 93 patients, 44 were non-survivors and 49 were discharged. Twenty-two (50.0%) non-survivors and 24 (49.0%) survivors were infected with the influenza virus. There was no significant difference in the proportion of patients co-infected with SARS-CoV-2 and the influenza virus between survivors and non-survivors.

The median age of the 93 patients was 67.0 years (IQR 54.0–72.0) and females accounted for 45.2% of the total number of patients (Table 1). The median time from illness onset to admission was 12.0 days (IQR 7.0–16.0) (Table 1). Chronic diseases were found in 53.8% of the patients, with hypertension being the most common, followed by diabetes and coronary disease (Table 1). The most common symptoms on admission were fever, cough and dyspnea, followed by chest distress/chest pain and fatigue (Table 1). The most common complication was ARDS, followed by acute cardiac injury, acute kidney injury and liver dysfunction. Among the non-survivors, the incidence of acute cardiac injury was significantly higher in the flu group (86.4%) than in the non-flu group (54.5%) ($p < 0.05$) (Table 2).

Analysis of laboratory indicators

Among the 93 patients, there was a significant difference in the proportion of patients with D-dimer levels >5 μg/mL (ten times the normal D-dimer value) between the flu group (38.6%) and the non-flu group (11.4%) ($p < 0.01$), but no difference in white blood cell counts, neutrophil counts, lymphocyte counts, or levels of CRP, ALT, AST, LDH, creatinine, cTnI, NT-proBNP, TNF-α, and IL-6 ($p > 0.05$) (data not shown).

Among the non-survivors, the white blood cell count, neutrophil count, TNF-α, D-dimer value, proportion of patients with D-dimer levels >5 μg/mL, and proportion of patients with elevated creatinine levels were higher in the flu group than in the non-flu group ($p < 0.05$) (Table 3). Among the survivors, there were no significant differences in the laboratory indicators between the flu group and the non-flu group ($p > 0.05$) (data not shown).

Table 1
Clinical characteristics of the 93 COVID-19 patients.

Clinical characteristics	All patients (n = 93)	Flu (n = 46)	Non-flu (n = 47)	P-value
Female	42 (45.2)	24 (52.2)	18 (38.3)	0.18
Age (years)	67.0 (54.0, 72.0)	65.0 (57.5, 69.8)	69.0 (54.0, 74.0)	0.34
Onset to admission (days)	12.0 (7.0, 16.0)	12.0 (7.0, 17.8)	10.0 (7.0, 15.0)	0.23
Chronic diseases				
Hypertension	34 (36.6)	20 (43.5)	14 (29.8)	0.17
Diabetes	18 (19.4)	12 (26.1)	6 (12.8)	0.10
Coronary disease	12 (12.9)	7 (15.2)	5 (10.6)	0.51
Chronic pulmonary disease	8 (8.6)	5 (10.9)	3 (6.4)	0.44
Chronic kidney disease	2 (2.2)	0 (0.0)	2 (4.3)	0.16
Malignant tumor	2 (2.2)	0 (0.0)	2 (4.3)	0.16
Symptoms				
Fever	76 (81.7)	34 (73.9)	42 (89.4)	0.05
Cough	75 (80.6)	35 (76.1)	40 (85.1)	0.27
Dyspnea	60 (64.5)	28 (60.9)	32 (68.1)	0.47
Fatigue	40 (43.0)	14 (30.4)	26 (55.3)	0.02
Myalgia	20 (21.5)	9 (19.6)	11 (23.4)	0.65
Diarrhea	29 (31.2)	16 (34.8)	13 (27.7)	0.46
Chest distress/chest pain	43 (46.2)	21 (45.7)	22 (46.8)	0.91
Headache	14 (15.1)	6 (13.0)	8 (17.0)	0.59
Complications				
ARDS	39 (41.9)	19 (41.3)	20 (42.6)	0.90
Acute kidney injury	28 (30.1)	17 (37.0)	11 (23.4)	0.15
Acute cardiac injury	31 (33.3)	19 (41.3)	12 (25.5)	0.11
Liver dysfunction	17 (18.3)	8 (17.4)	9 (19.1)	0.83

Data are expressed as the median (IQR) or n (%), p-values are from the Mann-Whitney U test, χ^2 test or Fisher's exact test.
COVID-19, coronavirus disease 2019; ARDS, acute respiratory distress syndrome.

Table 2
Clinical characteristics of the non-surviving COVID-19 patients.

Clinical characteristics	Non-survivors (n = 44)	Flu (n = 22)	Non-flu (n = 22)	P-value
Female	16 (36.4)	11 (50.0)	5 (22.7)	0.06
Age (years)	70.0 (64.0, 75.5)	68.5 (64, 71.5)	72.0 (70.0, 77.8)	0.13
Onset to admission (days)	10.0 (6.0, 12.5)	9.5 (6.3, 12)	10.0 (6.3, 13.5)	0.91
Onset to death (days)	20.5 (14.8, 28.3)	17.5 (12.3, 27.8)	22.0 (18.3, 28.5)	0.16
Chronic disease				
Hypertension	17 (38.6)	10 (45.5)	7 (31.8)	0.35
Diabetes	13 (29.5)	9 (40.9)	4 (18.2)	0.10
Coronary disease	7 (15.9)	3 (13.6)	4 (18.2)	0.68
Chronic pulmonary disease	5 (11.4)	4 (18.2)	1 (4.5)	0.15
Chronic kidney disease	1 (2.3)	0 (0.0)	1 (4.5)	0.31
Malignant tumor	1 (2.3)	0 (0.0)	1 (4.5)	0.31
Symptoms				
Fever	38 (86.4)	16 (72.7)	22 (100.0)	0.008
Cough	32 (72.7)	14 (63.6)	18 (81.8)	0.18
Dyspnea	29 (65.9)	15 (68.2)	14 (63.6)	0.75
Fatigue	17 (38.6)	6 (27.3)	11 (50.0)	0.12
Myalgia	5 (11.4)	1 (4.5)	4 (18.2)	0.15
Diarrhea	13 (29.5)	6 (27.3)	7 (31.8)	0.74
Chest distress/chest pain	20 (45.5)	11 (50.0)	9 (40.9)	0.55
Headache	6 (13.6)	3 (13.6)	3 (13.6)	1.00
Complication				
ARDS	38 (86.4)	18 (81.8)	20 (90.9)	0.38
Acute kidney injury	25 (56.8)	15 (68.2)	10 (45.5)	0.13
Acute cardiac injury	31 (70.5)	19 (86.4)	12 (54.5)	0.04
Liver dysfunction	10 (22.7)	5 (22.7)	5 (22.7)	1.00

Data are expressed as the median (IQR) or n (%), p-values are from the Mann-Whitney U test, χ^2 test or Fisher's exact test.
COVID-19, coronavirus disease 2019; ARDS, acute respiratory distress syndrome.

Discussion

The COVID-19 pandemic has reached most countries throughout the world, making the global situation serious. Due to the insufficient diagnostic sensitivity of the tests used to detect SARS-CoV-2 in upper respiratory tract specimens and the similarity between COVID-19 and influenza, early diagnosis of SARS-CoV-2 and influenza virus co-infection may be more problematic (Wu et al., 2020b). Among the COVID-19 patients included in this study, approximately 50% were co-infected with

Table 3
Laboratory characteristics of the non-surviving COVID-19 patients.

Laboratory characteristics	Non-survivors (n = 44)	Flu (n = 22)	Non-flu (n = 22)	P-value
White blood cell count ($\times 10^9$/L)	9.5 (6.1, 13.6)	12.9 (8.9, 15.4)	7.4 (5.1, 11.0)	0.01
Neutrophil count ($\times 10^9$/L)	8.7 (5.1, 12.6)	11.5 (7.5, 13.6)	6.5 (4.0, 10.0)	0.01
Neutrophil >6.3 $\times$ 10^9/L	30/44 (68.2)	18/22 (81.8)	12/22 (54.5)	0.05
Lymphocyte count ($\times 10^9$/L)	0.5 (0.4, 0.8)	0.6 (0.4, 0.8)	0.5 (0.4, 0.7)	0.64
Lymphopenia <1 $\times$ 10^9/L	41/44 (93.2)	20/22 (90.9)	21/22 (95.5)	0.55
C-reactive protein (mg/L)	78.2 (47.4, 153.1)	86.4 (48.4, 146.5)	78.2 (48.9, 158.4)	0.95
C-reactive protein >10 mg/L	41/44 (93.2)	20/22 (90.9)	21/22 (95.5)	0.55
ALT (U/L)	28.5 (18.8, 40.5)	27.5 (19.5, 33.8)	35.0 (19.0, 42.3)	0.31
AST (U/L)	45.0 (29.0, 59.5)	40.0 (24.3, 52.0)	48.0 (36.8, 63.5)	0.12
ALT>45 U/L or AST>35 U/L	28/44 (63.6)	13/22 (59.1)	15/22 (68.2)	0.53
Creatinine (μmol/L)	91.0 (72.8, 118.5)	87.5 (67.3, 135.8)	92.5 (79.5, 102.8)	0.61
Creatinine >1 $\times$ 10^6 μmol/L	13/44 (29.5)	10/22 (45.5)	3/21 (14.3)	0.03
Cardiac troponin I (pg/mL)	22.5 (10.3, 111.3)	27.8 (17.8, 599)	15.6 (10.3, 59.5)	0.28
Cardiac troponin I > 130 pg/mL	10/41 (24.4)	7/20 (35.0)	3/21 (14.3)	0.12
NT-proBNP (pg/mL)	756 (246, 2566)	1319 (309, 2691.5)	663 (225, 2524)	0.42
NT-proBNP >300 pg/mL	31/41 (75.6)	16/20 (80.0)	15/21 (71.4)	0.52
D-dimer (μg/mL)	5.1 (1.7, 21.0)	16.5 (5.0, 21.0)	2.3 (1.1, 7.6)	0.01
D-dimer >5 μg/mL	20/44 (45.5)	14/22 (63.6)	6/22 (27.3)	0.02
Tumor necrosis factor –α (pg/mL)	11.4 (8.1, 16.0)	15.9 (10.3, 20.7)	8.35 (7.5, 13.0)	0.03
Interleukin-6 (pg/mL)	57.9 (36.0, 152.9)	57.9 (47.5, 345.2)	57.3 (19.2, 124.1)	0.27

Data are expressed as the median (IQR) or n/N (%), p-values are from the Mann–Whitney U test, χ^2 test or Fisher's exact test.
COVID-19, coronavirus disease 2019; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NT-proBNP, amino-terminal pro-brain natriuretic peptide precursor.

influenza virus, and most were co-infected with influenza virus A. Moreover, the similarity between the early clinical symptoms of the two diseases likely increased the false-negative rate of COVID-19 detection, thereby exacerbating the spread of SARS-CoV-2. The COVID-19 outbreak resulted in a large number of people gathering in hospitals, which intensified the spread of the influenza virus and increased the likelihood of co-infection with SARS-CoV-2.

Recent studies have reported that females accounted for approximately 33% of the critically ill/non-surviving COVID-19 patients in Wuhan (Guan et al. 2020; Yang et al. 2020). In the current study, females comprised 36.4% of the non-surviving COVID-19 patients, including 50% of those with influenza and 22.7% of those without influenza (p = 0.06). Due to insignificant statistical difference, whether the co-infection may reduce sex difference in the non-surviving COVID-19 patients requires a larger sample of research. COVID-19 patients co-infected with the influenza virus did not demonstrate different clinical symptoms, which further compounded the diagnostic difficulties.

Most patients with severe COVID-19 exhibit substantially elevated serum levels of pro-inflammatory cytokines, characterized as cytokine storm (Cao 2020; Mehta et al. 2020). Elevated cytokines also mediate extensive pulmonary pathology, leading to massive infiltration of neutrophils and macrophages (Cao 2020). Neutrophil counts are increased in both the peripheral blood (Wang et al. 2004) and lung (Nicholls et al. 2003) among critically ill patients with severe acute respiratory syndrome. Extensive pulmonary infiltration of neutrophils in patients with influenza induces lung tissue injury and worsens the disease (Kulkarni et al. 2019). In the current study, neutrophil and cytokine levels were generally elevated among the non-survivors, and the increment was more apparent among the non-survivors with influenza. Co-infection with the influenza virus may further enhance neutrophil activation, thereby contributing to an excessive immune response against the virus and also to the development of a cytokine storm.

Studies have reported that elevated D-dimer levels are a risk factor for death in COVID-19 patients (Wu et al. 2020a; Zhou et al. 2020). The current study also found that the D-dimer levels of non-survivors were substantially higher than those of survivors. Among the non-survivors, the D-dimer value was higher among patients with influenza than in those without influenza, which may have been due to local vascular injury, ischemia and thrombosis caused by a viral infection-associated cytokine storm (Davidson and Warren-Gash 2019). The current results further confirmed that co-infection with the influenza virus may induce an earlier and more severe cytokine storm in critically ill COVID-19 patients, leading to serious complications such as shock, ARDS, fulminant myocarditis, acute kidney injury or multiple organ failure (Cao 2020; Ruan et al. 2020; Wu et al. 2020a; Zhou et al. 2020).

The current research had some limitations. First, the results of serological tests may have been false-negative, especially within 1 week of infection or reinfection; or they may have been false-positive due to long-term infections or carrier states. Second, the study was unable to determine the strains of influenza, and the infecting strain might have affected the clinical characteristics. Third, the included cases originated from Wuhan, but differences in races and influenza strains among different countries may cause COVID-19 patients with influenza to present different clinical characteristics. In addition, the number of included cases was small, and other factors such as gender, age, chronic disease, and time from illness onset to admission may have affected the results of this study.

Under the background of the COVID-19 global pandemic, the number of patients co-infected with SARS-CoV-2 and the influenza virus in some countries may increase as the flu season approaches. The clinical research of this co-infection, especially in critically ill patients, will benefit global control efforts for 2020–2021. Research on different regions, races, age brackets, and influenza strains can more accurately reveal the epidemiological and clinical characteristics of co-infected patients, which requires larger sample sizes from multiple countries. Furthermore, research from larger sample could contribute to unveiling whether this co-infection is a higher risk for severe disease or death associated with COVID-19.

It is believed that this is the first study of co-infection with SARS-CoV-2 and the influenza virus among critically ill COVID-19 patients. The results showed that a high proportion of COVID-19 patients were co-infected with influenza in Tongji Hospital. Co-infection with SARS-CoV-2 and the influenza virus may lead to a much earlier occurrence of cytokine storm and organ damage in critically ill COVID-19 patients. The results suggest that detection of the influenza virus should be considered in patients with COVID-19, and that treatment strategies for anti-influenza virus and dampening inflammatory responses may be helpful for critically ill patients co-infected with SARS-CoV-2 and the influenza virus.

Author contributions

KQ and SMM contributed to the conception and design of the study, had full access to all data in the study and take responsibility for the integrity and accuracy of data analysis. SMM and XQL contributed to data acquisition. ZC, SHT and KQ contributed to the analysis and interpretation of the data. All authors participated in manuscript writing and revision and approved the final version of the manuscript.

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Conflicts of interest

The authors declare no conflict of interest.

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