Clinical characteristics and outcome of influenza virus infection among adults hospitalized with severe COVID-19: a retrospective cohort study from Wuhan, China

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Abstract

Background: Coronavirus disease 2019 (COVID-19) is an emerging infectious disease that rapidly spreads worldwide and co-infection of COVID-19 and influenza may occur in some cases. We aimed to describe clinical features and outcomes of severe COVID-19 patients with co-infection of influenza virus.

Methods: Retrospective cohort study was performed and a total of 140 patients with severe COVID-19 were enrolled in designated wards of Sino-French New City Branch of Tongji Hospital between Feb 8th and March 15th in Wuhan city, Hubei province, China. The demographic, clinical features, laboratory indices, treatment and outcomes of these patients were collected.

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Results: Of 140 severe COVID-19 hospitalized patients, including 73 patients (52.14%) with median age 62 years were influenza virus IgM-positive and 67 patients (47.86%) with median age 66 years were influenza virus IgM-negative. 76 (54.4%) of severe COVID-19 patients were males. Chronic comorbidities consisting mainly of hypertension (45.3%), diabetes (15.8%), chronic respiratory disease (7.2%), cardiovascular disease (5.8%), malignancy (4.3%) and chronic kidney disease (2.2%). Clinical features, including fever (≥38°C), chill, cough, chest pain, dyspnea, diarrhea and fatigue or myalgia were collected. Fatigue or myalgia was less found in COVID-19 patients with IgM-positive (33.3% vs 50/7%, P = 0.0375). Higher proportion of prolonged activated partial thromboplastin time (APTT) > 42 s was observed in COVID-19 patients with influenza virus IgM-negative (43.8% vs 23.6%, P = 0.0127). Severe COVID-19 Patients with influenza virus IgM positive have a higher cumulative survivor rate than that of patients with influenza virus IgM negative (Log-rank P = 0.0308). Considering age is a potential confounding variable, difference in age was adjusted between different influenza virus IgM status groups, the HR was 0.29 (95% CI, 0.081–1.100). Similarly, difference in gender was adjusted as above, the HR was 0.262 (95% CI, 0.072–0.952) in the COX regression model.

Conclusions: Influenza virus IgM positive may be associated with decreasing in-hospital death.

Keywords: COVID-19, Influenza virus IgM, SARS-CoV-2
virus-specific antibody IgM which responses following influenza infection and detected by indirect immunofluorescence assay (Respiratory tract 8 joint detection kit; EUROIMMUN, Inc., Germany) [11, 15, 16].

Statistical analysis
Descriptive analyses of the variables were expressed as median (interquartile range [IQR]) or number (%) and compared using Mann-Whitney test. Categorical data were compared using $X^2$ test or the Fisher exact test, where appropriate. The patients’ characteristics of deaths verses discharged and death/discharge & influenza IgM positive/negative were also described and shown in Supplementary Table 1 and 2. Kaplan-Meier curve was portrayed by influenza virus IgM positive/negative to describe the cumulative survival rate of COVID-19 patients. COX regression model was fitted to investigate the association between influenza virus IgM positive and the in-hospital death. To avoid overfitting, at most two covariates were allowed to the model and we adjusted for age and gender respectively in the model. Adjusted hazard ratios (aHRs) and 95% confidence intervals (95% CIs) were then estimated. All tests were 2-sides, and a $P$ value less than .05 was considered statistically significant. All analyses were performed with SPSS, version 23.0 (IBM inc.).

Results
Baseline characteristics
A total of 140 adult patients confirmed with COVID-19 from designated hospital was enrolled in this study, with 73 patients (52.14%) were identified as influenza virus IgM-positive. 76 (54.4%) of the COVID-19 patients were males. The median age of patients with influenza virus IgM-negative was 66 years (IQR, 55 to 70 years), older than patients with influenza virus IgM-positive (median age 62, IQR, 47 to 70 years, $P = 0.1118$). Chronic comorbidities consisting mainly of hypertension (45.3%), diabetes (15.8%), chronic respiratory disease (7.2%), cardiovascular disease (5.8%), malignancy (4.3%) and chronic kidney disease (2.2%). Clinical features, including fever ($\geq 38^\circ C$), chill, cough, chest pain, dyspnea, diarrhea and fatigue or myalgia were collected. Fatigue or myalgia was less found in COVID-19 patients with IgM-positive (33.3% vs 50/7%, $P = 0.0375$). (Table 1).

Laboratory findings
Higher proportion of prolonged activated partial thromboplastin time (APTT) > 42s was observed in COVID-19 patients with influenza virus IgM-negative (43.8% vs 23.6%, $P = 0.0127$). (Table 1) Counts of lymphocytes and platelets were significantly lower, while aspartate aminotransferase (AST), creatinine, lactate dehydrogenase (LDH), troponin, NT-proBNP, C-reactive protein (CRP), interleukin-6 (IL-6), ferritin, prothrombin time (PT), APTT and D-Dimer were significantly higher in dead cases (all $P < 0.05$). (Supplementary Table 1).

Treatment and outcomes
43.6% of the patients received nasal cannula, 2.1% oxygen mask, 49.3% non-invasive mechanical ventilation (NMV)/high-flow nasal cannula (HFNC) and 8.6% invasive mechanical ventilation (IMV)/extracorporeal membrane oxygenation (ECMO). Compound Methoxamine capsule were used in more patients with influenza IgM positive than the other group (23.3% vs 9.0%, $P = 0.0222$). (Table 2) higher levels of respiratory support were more seen in dead patients, especially those with influenza IgM positive. (supplementary Table 1 and supplementary Table 2)

According to the score of CURB-65, more COVID-19 patients with influenza IgM positive group were in low
Table 1 Clinical Characteristics of COVID-19 Patients with and Without Influenza IgM positive

| Study Population | With Influenza IgM positive (n = 73) | Without Influenza IgM positive (n = 67) | Total (n = 140) | P value |
|------------------|-------------------------------------|----------------------------------------|-----------------|---------|
| **Demographic**  |                                     |                                        |                 |         |
| Gender, Male     | 39 (53.4)                           | 37 (55.2)                              | 76 (54.3)       | 0.8310  |
| Age, media (IQR), yrs | 62.0 (47.0, 70.0)                  | 66.0 (55.0, 70.0)                      | 65.0 (48.5, 70.0)| 0.1118  |
| **Comorbidities**|                                     |                                        |                 |         |
| Hypertension     | 32/70 (45.7)                        | 30/67 (44.8)                           | 62/137 (45.3)   | 0.9122  |
| Diabetes         | 12/72 (16.7)                        | 10/67 (14.9)                           | 22/139 (15.8)   | 0.7787  |
| Chronic respiratory disease | 5/72 (6.9)                  | 5/67 (7.5)                             | 10/139 (7.2)    | 0.9060  |
| Cardiovascular disease | 5/72 (6.9)                  | 3/67 (4.5)                             | 8/139 (5.8)     | 0.5301  |
| Malignancy       | 3/72 (4.2)                          | 3/67 (4.5)                             | 6/139 (4.3)     | 0.9282  |
| Chronic kidney disease | 2/72 (2.8)                  | 1/67 (1.5)                             | 3/139 (2.2)     | 0.5983  |
| **Signs and symptoms** |                                   |                                        |                 |         |
| Fever            | 55 (75.3)                           | 53 (79.1)                              | 108 (77.1)      | 0.5964  |
| Highest temperature, °C | 38.5 (38.0, 39.0)   | 38.7 (38.2, 39.0)                      | 38.5 (38.0, 39.0)| 0.1274  |
| Chills           | 13 (17.8)                           | 19 (28.4)                              | 32 (22.9)       | 0.1375  |
| Cough            | 41/72 (56.9)                        | 44/67 (65.7)                           | 85/139 (61.2)   | 0.2915  |
| Productive cough | 20/72 (27.8)                        | 25/67 (37.3)                           | 45/139 (32.4)   | 0.2299  |
| Chest pain/Chest congestion | 19/72 (26.4) | 13/67 (19.4)                           | 32/139 (23.0)   | 0.3283  |
| Dyspnea          | 21/72 (29.2)                        | 29/67 (43.3)                           | 50/139 (36.0)   | 0.0831  |
| Diarrhea         | 18 (24.7)                           | 25 (37.3)                              | 43 (30.7)       | 0.1049  |
| Fatigue or myalgia | 24/72 (33.3)                      | 34/67 (50.7)                           | 58/139 (41.7)   | 0.0375  |
| **Laboratory findings, median (IQR)** |                             |                                        |                 |         |
| White blood cells, × 10^9/mL | 5.7 (4.2, 6.8)                  | 5.7 (4.6, 7.9)                         | 5.7 (4.4, 7.2)  | 0.3226  |
| Neutrophils, × 10^9/mL | 3.9 (2.5, 4.8)                  | 4.0 (2.6, 5.9)                         | 3.9 (2.5, 5.3)  | 0.3600  |
| Lymphocytes, ×10^9/mL | 1.2 (0.9, 1.6)                  | 1.1 (0.8, 1.5)                         | 1.1 (0.8, 1.5)  | 0.3826  |
| Lymphocytes< 0.8 × 10^9/mL | 18/73 (24.7)                  | 18/66 (27.3)                           | 36/139 (25.9)   | 0.7252  |
| Red blood cells, ×10^{12}/mL | 4.1 (3.6, 4.6)                | 4.0 (3.7, 4.4)                         | 4.0 (3.7, 4.5)  | 0.4502  |
| Platelets, ×10^9/mL | 230.0 (173.0, 292.0)           | 253.0 (169.0, 340.0)                   | 235.0 (169.0, 312.0)| 0.3622  |
| Platelets< 100 ×10^9/mL | 5/73 (6.8)                    | 6/66 (9.1)                             | 11/139 (7.9)    | 0.6249  |
| Hemoglobin, g/L   | 122.0 (114.0, 137.0)             | 125.5 (113.0, 137.0)                   | 123.0 (113.0, 137.0) | 0.9143  |
| ALT, U/L          | 23.0 (17.0, 40.0)                | 22.5 (15.0, 41.0)                      | 23.0 (16.0, 41.0)| 0.7373  |
| AST, U/L          | 26.0 (19.0, 37.0)                | 30.0 (19.0, 41.0)                      | 28.0 (19.0, 39.0)| 0.3370  |
| Albumin, g/L      | 36.1 (32.2, 38.3)                | 35.0 (31.4, 37.1)                      | 35.2 (31.7, 38.1)| 0.2945  |
| Creatinine, μmol/L | 70.0 (60.0, 89.5)               | 70.0 (59.0, 87.0)                      | 70.0 (59.0, 89.0)| 0.8596  |
| LDH, U/L          | 268.5 (204.0, 329.5)             | 287.0 (235.0, 351.0)                   | 281.0 (212.0, 334.0)| 0.2419  |
| LDH > 245 U/L     | 44/72 (61.1)                     | 47/65 (72.3)                           | 91/137 (66.4)   | 0.1658  |
| Troponin> 15.6 pg/ml, No (%) | 7/51 (13.7)                  | 12/56 (21.4)                           | 19/107 (17.8)   | 0.2977  |
| NT-proBNP, pg/mL  | 140.0 (60.0, 334.0)             | 157.0 (640.0, 459.0)                   | 151.0 (630.0, 411.0)| 0.2883  |
| NT-proBNP≥247 pg/ml, No (%) | 29/57 (50.9)                | 35/58 (60.3)                           | 64/115 (55.7)   | 0.3069  |
| CRP, mg/L         | 21.3 (4.1, 49.2)                 | 34.7 (9.1, 73.4)                       | 27.2 (6.1, 69.8) | 0.1281  |
| CRP ≥ 1 mg/L, No (%) | 57/61 (93.4)                  | 47/49 (95.9)                           | 104/110 (94.5)  | 0.5551  |
| IL-6, pg/mL       | 9.8 (4.2, 21.1)                  | 6.8 (3.6, 23.2)                        | 9.4 (3.9, 23.2) | 0.5603  |
| IL-6 ≥ 7 pg/mL, No (%) | 25/42 (59.5)                 | 15/35 (42.9)                           | 40/77 (51.9)    | 0.1450  |
| Ferritin, μg/L    | 522.1 (320.5, 729.0)            | 630.5 (310.2, 1519.9)                  | 562.6 (320.5, 986.5)| 0.0964  |
| Ferritin> 150 μg/L, No (%) | 39/43 (90.7)                  | 33/35 (94.3)                           | 72/78 (92.3)    | 0.5495  |
to moderate risk level \((P = 0.0397)\). No differences were observed in the duration of viral shedding, the length of hospital stay and time from illness onset to discharge between groups. 9.3% of the patients died in hospital and the rate of death was significantly lower in patients with IgM positive than those with IgM negative \((4.1\% \text{ vs } 14.9\%, P = 0.0276)\). (Table 2).

Severe COVID-19 Patients with influenza virus IgM positive have a higher cumulative survivor rate than that of patients with influenza virus IgM negative \((\text{Log-rank } P = 0.0308)\). Considering age is a potential confounding variable, difference in age was adjusted between different influenza virus IgM status groups, the HR was 0.29 (95% CI, 0.081–1.100). Similarly, difference in gender was adjusted as above, the HR was 0.262 (95% CI, 0.072–0.952) in the COX regression model. (Fig. 2).

### Discussion

In this retrospective cohort study, we described the clinical features and outcomes of hospitalized COVID-19 patients. Clinical characteristics and outcomes of patients infected with influenza virus IgM positive and negative are presented in Tables 1 and 2, respectively. The differences in clinical presentation and outcomes between the two groups were analyzed using appropriate statistical tests. The results indicate that patients with influenza virus IgM positive had a higher cumulative survivor rate compared to those with IgM negative. Age and gender were found to be potential confounding variables, and their effects were adjusted in the analyses. The findings suggest that influenza coinfection may have a significant impact on the clinical course and outcomes of COVID-19 patients.
patients with different influenza virus IgM status. We found that influenza virus IgM positive may be associated with decreasing in-hospital death. Fatigue and myalgia were less presented in COVID-19 patients with influenza virus IgM positive. It is the first time for influenza virus IgM to be a prognostic factor of COVID-19.

Previous studies reported cases with co-infection of SARS-CoV-2 and influenza showed the implications of co-infection during the pandemic area [17–20]. It was necessary to assess the effect of the SARS-CoV-2 and influenza co-infection in clinical outcomes. Previous studies demonstrated that influenza virus-specific IgM antibody responses follow primary influenza virus infection in adults [11, 21]. Serological confirmation of a clinical diagnosis is by demonstration of greater rise in functional strain specific antibody titer. Specific neutralizing antibody can be detected from about 10 to 14 days post infection, reaches a plateau at around 28 days and decreased to normal level around a month and a half. This test uses nucleocapsid antigens that are type-specific and can distinguish A from B and C infections. Due to the huge task of rapid tests for SARS-CoV-2 and the absence of widely available testing methods, thousands of patients were diagnosed of COVID-19 without identification of co-infection pathogens at the initial period. During the epidemic of seasonal influenza and other respiratory illness, our concern is on the possibility of the co-infection of virus. Therefore, influenza virus IgM antibody may help us review these cases. The outbreak of COVID-19 may occur during influenza season, which brings difficulty in prevention, diagnosis and treatment. Increasing number of literatures has been demonstrating that influenza virus infection may trigger non-neutralizing antibodies responses which also binds to pathogens as diverse as HIV-1, herpes simplex virus and Ebola [22–28]. Some other researches showed that influenza vaccination could reduce cardiovascular morbidity and mortality in patients with COVID-19 [29]. Therefore, some potential mechanisms including active immunity or passive immunity may involve in the virus immunity for exhibition its protective effects. In this study, influenza virus IgM positive showed as a protective effector in severe COVID-19 patients associated with better prognosis and higher cumulative survivor rate. Considering the potential confounding variables, age and gender were adjusted between different influenza virus IgM status groups, respectively. After that, the potential protective effects influenza virus IgM positive in severe COVID-19 patients were observed if patients are suspected ILI, especially suffering from virus infection, a prompt test, like a one-time diagnostic panel for the respiratory virus nucleic acid, antigen or serological...

Fig. 2 Kaplan-Meier curve for portraying the cumulative survival rate of COVID-19 patients
detection of virus specific IgM/ IgG, should be the first step with an expanded detectable range towards confirming diagnosis, which help in making early and effective prevention and treatment strategy.

The strengths of this study include adults hospitalized with diagnosis of COVID-19, the retrospective cohort design, standardized patient screening in the participating, and centralized confirmation of respiratory viruses and other laboratory indices. Our study has several limitations. Firstly, a large number of patients were continually being admitted to hospital, but the sample size of our study is still limited. Secondly, our study was conducted in a local hospital in Wuhan, which may result in biases. Especially consideration of influenza season, it may become epidemic of different type in different regions. Thirdly, this cohort study did not last for a long time. Missing information of death status at discharge and initial influenza virus IgM status may influence the demographics and available clinical characteristics between included and excluded patients. Thus, the results may partly help us recognize co-infection of influenza and SARS-CoV-2. Further studies focused on the co-infectious pathogens, the treatment and prevention will be needed.

Conclusions
Influenza virus IgM positive may be associated with decreasing in-hospital death. The co-infection of SARS-CoV-2 and influenza virus may occur by causing a crisis and we need to improve our understanding for confronting it in the future.

Abbreviations
APTT: Activated partial thromboplastin time; CDC: Centers for disease control and prevention; COVID-19: Coronavirus disease 2019; ECMO: Extracorporeal membrane oxygenation; eGFR: Estimated glomerular filtration rate; ELISA: Enzyme-linked immunosorbent assay; FiO2: Fraction of inspired oxygen; HAI: Hemagglutinin inhibition; HFNCl: High-flow nasal cannula; IL: Influenza like illness; IQR: Interquartile range; LDH: Lactate dehydrogenase; MV: Mechanical ventilation; N:M: Noninvasive methods of mechanical ventilation; NT-proBNP: N-terminal pro brain natriuretic peptide; PaO2: Partial pressure of oxygen; PT: Prothrombin time; RT-PCR: Reverse-transcriptase–polymerase chain-reaction; SARS-CoV: Severe acute respiratory syndrome-coronavirus; SARS-CoV-2: Severe acute respiratory syndrome-coronavirus – 2; WHO: World Health Organization; ALT: Alanine transaminase; AST: Aspartate aminotransferase; CRP: C-reactive protein; IL-6: Interleukin-6; FIB: Fibrinogen; NMV: Non-invasive mechanical ventilation; IMV: Invasive mechanical ventilation

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12879-021-05975-2.

Additional file 1: Supplementary Table 1 Clinical Characteristics of COVID-19 Patients by death or discharge

Additional file 2: Supplementary Table 2 Clinical Characteristics, treatment and prognosis of COVID-19 Patients by death and influenza IgM+/-

Acknowledgments
The authors thank Academician Chen Wang for his guidance and assistance with this work.

Authors’ contributions
YL and XT contributed to the conception and design of the study and interpretation of the results and drafted the manuscript. XT, XX, GL and HW contributed to the acquisition of the data and revision of the manuscript for important intellectual content. AC, YZ, GF and DW performed the statistical analysis and revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Funding
This project was supported by project grant 81870013 from the National Natural Science Foundation of China; and grant 7202178 from the National Science Foundation of Beijing.

Availability of data and materials
The data used for the current study will be available based on a reasonable request from the lead author Dr. Yanning Li (lyynli@263.net).

Declarations

Ethics approval and consent to participate
The study was approved by Ethics Committee of Beijing Hospital (2020BYJYCC-046-01).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Received: 7 January 2021 Accepted: 9 March 2021

Published online: 12 April 2021

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