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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Research

Keywords: COVID-19, influenza virus, SARS-CoV-2

Posted Date: May 14th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-27484/v1

Abstract

Background

Coronavirus disease 2019 (COVID-19) is an emerging infection disease that rapidly spreads worldwide. Clinical features and outcomes of severe COVID-19 patients with influenza virus IgM positive during the influenza season need to be described.

Methods

Retrospective cohort study of 140 patients with severe COVID-19 hospitalized in designated wards of Sino-French New City Branch of Tongji Hospital between Feb 8th and March 15th in Wuhan, Hubei province, China. The demographic, clinical feature, laboratory, treatment and outcome were collected and analyzed.

Results

Of 140 severe COVID-19 hospitalized patients, 73 patients were with median age of 66 years old with identification of influenza virus IgM-positive and 67 patients were with median age of 62 years old in influenza virus IgM-negative group. Nearly half of severe COVID-19 patients in this research are male. Majority of the severe COVID-19 patients had chronic underlying conditions. Wheeze was the clinical feature of severe COVID-19 patients with influenza IgM-positive (26.4% vs 9.0%, $P = 0.008$). On contrary, fatigue or myalgia was the feature of the COVID-19 patients without IgM-positive (38.4% vs 58.2%, $P = 0.019$). In laboratory examination, increased levels of ferritin and prolonging APTT were showed in severe COVID-19 patients without influenza IgM-positive compared with patients in the other group with significant differences. Death rate in the group of severe COVID-19 patients with influenza IgM-positive is higher than it is in other group with significant differences (14.9% vs 4.1%, $P = 0.040$). In univariate regression analysis, several factors were associated with higher risk of death, which included LDH, troponin, NT-proBNP, D-dimer, PT, APTT, lymphocytes, platelet and eGFR. However, influenza virus IgM positive was associated with lower risk of death. Multivariate Regression analysis showed that troponin and lymphocyte were independently associated with higher risk of death.

Conclusion

The characteristics of patients hospitalized with severe COVID-19 with identification of influenza virus IgM-positive were described. It hints proof of seasonal influenza which may overlap with COVID-19 and may cause a crisis we could confront in the future.

Background

In December 2019, unknown reason cases of pneumonia appeared in Wuhan, China. The etiology of this infectious disease was identified as novel coronavirus, which showed high similarity to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV), so renamed SARS-CoV-2[1–3]. After that, the World Health Organization (WHO) announced that the pandemic of Coronavirus disease 2019 (COVID-19) have constituted a public health emergency of international concern[4].

Review the outbreak of COVID-19 in Wuhan at beginning of February, 2020, initial surveillance has focused primarily on patients with fever accompanied with or without respiratory symptoms, gastrointestinal symptoms and so on[5, 6]. According to its screening criteria, the clinical manifestation of influenza like illness (ILI) may occur in population which overlap co-infection with SARS-CoV-2 and influenza virus during this special period. Influenza A and B viruses account for the majority of influenza in influenza season in China[7, 8]. Sustained surveillance has been implemented by CDC during the influenza season in 2020 in national wide[9]. Although continuing challenges include the emergence of pandemic COVID-19 in 2020, influenza viruses comes to the possibility of co-infection with SARS-CoV-2 due to the influenza season[2, 10]. Previous studies demonstrated that influenza virus-specific antibody responses following influenza infection and have risen in HA-specific serum IgM (86 to 94%) antibodies following primary influenza virus infection in adults[11]. The aims of this study were to describe the clinical features and the outcomes of patients hospitalized with COVID-19, who were also with positive in influenza virus IgM.

Methods

Study design

This is a retrospective cohort study which performed during Feb 8th to March 15th at wards designated for patients with COVID-19 in the Sino-French New City Branch of Tongji Hospital in Wuhan, Hubei province, China. Total of 140 patients diagnosed of COVID-19 pneumonia were enrolled from two wards managed by multidisciplinary team from Beijing hospital and First Hospital attached to Jilin University (Fig. 1). The study was approved by Ethics Committee of Beijing Hospital (2020BJYYEC-046-01).

Procedures

All the data from electronic medical records were reviewed by experienced physicians separately and checked by 2 physicians independently.

The inclusive criteria: Throat-swab specimen from upper respiratory tract that were obtained and tested by RT-PCR for confirmation of SARS-CoV-2 as the same protocol described previously[1, 12]; pneumonia confirmed by CT scan[13], an oxygen saturation (SaO2) of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen (PaO2) to the fraction of inspired oxygen (FiO2) at or below 300 mmHg[14]; The enzyme-linked immunosorbent assay (ELISA) has been used to detect influenza virus-specific antibody IgM responses following influenza infection[11, 15, 16].

Exclusive criteria included without examined influenza virus IgM in the first 24 hours, sudden death within 24 hours. The baseline of clinical data was recorded in the first 24 hours after administration. The treatments during hospitalization and the most intense level of oxygen support during hospitalization were recorded.

Outcomes

Outcome measures were evaluated when clinical improvement or death occurred. Clinical improvement was defined as the time from hospitalization to an improvement of two points on a six-category ordinal scale or live discharge from the hospital[14]. The other clinical outcome was death with recording the time from hospitalization to death. Virology measures include the duration of viral RNA shedding by detection of RT-PCR.

Statistical analysis

Descriptive analyses of the variables were expressed as median (interquartile range [IQR]) or number (%). Differences in distributions of patient characteristics by outcome subgroups are reported using differences with 95% Cis. Categorical data were compared using $X2$ test or the Fisher exact test. Nonnormal distributed continuous data were compared using Mann-Whitney-Wilcoxon test.

Univiable logistic regression was used to determine HRs and 95% Cis between individual factors on the death. Step-wise multivariable logistic regression was used to identify independent factors associated with outcomes of the patients. Sample size varied because of missing data. 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 SPSS).

Results

Demographic information of COVID-19 hospitalized patients

Total of 140 adult patients confirmed severe COVID-19 in wards from designated hospital were enrolled in this research, 73 patients were with identification of influenza virus IgM-positive and 67 patients were in influenza virus IgM-negative group. Nearly half of severe COVID-19 patients in this research are male. The median age of patients with influenza virus-IgM negative was 66 years (interquartile range [IQR], 55 to 70 years), a litter older than the median age of patients with influenza virus IgM-positive (median age 62, interquartile range [IQR], 47 to 70 years), with an equal gender distribution. Majority of the severe COVID-19 patients had chronic underlying conditions consisting mainly of hypertension, diabetes, chronic respiratory disease, malignancy and chronic kidney disease. The demographic information showed in Table 1.

Table 1
Clinical Characteristics of COVID-19 Patients with and Without Influenza IgM positive.

Study Population	With Influenza IgM positive No. (%) (n = 73)	Without Influenza IgM positive No. (%) (n = 67)	P value
Demophrafic			
Gender, Male	39(53.4%)	37(55.2%)	0.831
Age, median (IQR), yrs	62(47,70)	66(55,70)	0.112
Comorbidities			
Chronic respiratory disease	5(6.9%)	5(7.5%)	1.000
Malignancy	3(4.2%)	3(4.5%)	1.000
Hypertension	34(45.7%)	30(44.8%)	0.912
Diabetes	12(16.7%)	10(14.9%)	0.779
Cardiovascular disease	5(6.9%)	3(4.5%)	0.720
Chronic kidney disease	2(2.8%)	1(1.5%)	1.000
Signs and symptoms			
Fever	55(75.3%)	53(79.1%)	0.596
Highest temperature, °C	38.5(38.0,39.0)	38.7(38.2–39.0)	0.127
Chills	13(17.8%)	19(28.4%)	0.161
Cough	41(56.9%)	44(65.7%)	0.292
Productive cough	20(27.8%)	25(37.3%)	0.230
Chest pain/Chest congestion	19(26.4%)	13(19.4%)	0.328
Wheeze	19(26.4%)	6(9.0%)	0.008*
Dyspnea	21(29.2%)	29(43.3%)	0.083
Diarrhea	18(24.7%)	25(37.3%)	0.105
Fatigue or myalgia	28(38.4%)	39(58.2%)	0.019*
Laboratory findings, median (IQR)			
White blood cells, $\times 10^9$/mL	5.65(4.23–6.88)	5.67(4.54–7.95)	0.323
Neutrophils, $\times 10^9$/mL	3.86(2.47–4.82)	3.98(2.54–5.93)	0.360
Lymphocytes, $\times 10^9$/mL	1.21(0.82–1.61)	1.08(0.77–1.53)	0.383
Lymphocytes < 0.8×10^9/mL	18 (24.7%)	18 (27.3%)	0.847
Red blood cells, $\times 10^{12}$/mL	4.10(3.62–4.58)	4.04(3.67–4.43)	0.450
Platelets, $\times 10^9$/ mL	230(169–299)	253(166–343)	0.362
PLT < 100×10^9/ mL	5 (6.8%)	6 (9.1%)	0.756
Hemoglobin, g/L	122(114–138)	126(113–138)	0.914
ALT, U/L	23(17–41)	23(15–41)	0.737
AST, U/L	26(19–38)	30(19–41)	0.337
Albumin, g/L	36(32–38)	35(31–37)	0.295
Creatinine, μmol/L	70(60–90)	70(59–88)	0.860

Study Population	With Influenza IgM positive No. (%) (n = 73)	Without Influenza IgM positive No. (%) (n = 67)	P value
eGFR	93.06 (75.8-106.8)	90.28 (70.6–98.9)	0.338
eGFR < 60	8 (11.1%)	9 (13.6%)	0.797
LDH, U/L	269(203–330)	287(235–352)	0.242
LDH > 245 U/L	44 (61.1%)	47 (72.3%)	0.206
Troponin↑ (No. (%))	7(13.7%)	12(21.4%)	0.298
NT-proBNP, pg/mL	159(67–411)	157(63–470)	0.832
NT-proBNP↑ (No. (%))	29(50.9%)	35(60.3%)	0.307
CRP, mg/L	220(4.2–50.8)	34.7(8.6–76.5)	0.153
CRP↑ (No. (%))	57(93.4%)	47(95.9%)	0.690
IL-6, pg/mL	12.3(5.2–25.5)	11.7(4.2–26.6)	0.672
IL-6↑ (No. (%))	26(59.5%)	15(42.9%)	0.145
Ferritin, μg/L	522.1(320.5–729.0)	729.5(367.8-1542.9)	0.055*
Ferritin↑ (No. (%))	39(90.7%)	34(97.1%)	0.372
PT, s	13.7(13.2–14.3)	13.8(13.4–14.2)	0.976
APTT, s	39.6(35.7–42.0)	39.5(37.7–45.9)	0.024*
APTT↑ (No. (%))	17(23.6%)	28(43.8%)	0.013*
FIB, g/L	4.86(3.85–6.05)	5.31(4.26–6.19)	0.237
D-Dimer, μg/mL	0.71(0.48–1.76)	1.17(0.51–2.07)	0.196
D-Dimer↑ (No. (%))	53(72.6%)	45(70.3%)	0.767
Treatment in hospital			
Oxygen Therapy			0.485
Nasal Cannula	30(41.1%)	27(40.3%)	
Oxygen Mask	1(1.4%)	2(3.0%)	
NMV + High-flow nasal cannula	39(53.4%)	35(52.2%)	
IMV	1(1.4%)	3(4.5%)	
ECMO	2(2.7%)	0	
Drugs			
Oseltamivir	33(45.2%)	23(34.3%)	0.189
Arbidol	53(72.6%)	47(70.1%)	0.748
Compound Methoxamine capsule	19(23.3%)	6(9.0%)	0.022*
Clinical outcomes			
CURB-65			0.040*
Low risk	65(89.0%)	50(74.6%)	
Medium risk	6(8.2%)	8(11.9%)	
High risk	2(2.7%)	9(13.4%)	
Duration of viral shedding, days	26(20–32)	25(21,32)	0.969

Study Population	With Influenza IgM positive No. (%) (n = 73)	Without Influenza IgM positive No. (%) (n = 67)	P value
Hospital length of stay, days	13(11–18)	14(12,19)	0.411
Time from illness onset to discharge, days	28(22–35)	27(23–33)	0.867
Death (No. (%))	3(4.1%)	10(14.9%)	0.040*
Discharge (No. (%))	70(95.9%)	57(85.1%)	

Clinical features, laboratory indices and treatment of severe COVID-19 hospitalized patients.

The characteristics of the current episode were collected, including fever (≥ 38 °C), chill, cough, chest pain, dyspnea, diarrhea and fatigue or myalgia. Each of the above symptoms showed a different proportion of manifestations. Wheeze was the clinical feature of COVID-19 patients with influenza IgM-positive (26.4% vs 9.0%, $P = 0.008$). On contrary, fatigue or myalgia was the feature of the COVID-19 patients without IgM-positive and showed significant difference between groups (38.4% vs 58.2%, $P = 0.019$). In laboratory examination, increased levels of ferritin and prolonging APTT were showed in COVID-19 patients without influenza IgM-positive compared with patients in the other group with significant differences. According to the score of CURB-65, the severity of COVID-19 patients were much higher than the other group. Considering severity of the medical status, majority of the patients under oxygen therapy, including nasal cannula, oxygen mask, NMV or HFNC and MV or ECMO, and other supportive treatment. Comparison of the two groups, the treatments in hospital, including oxygen therapy and drugs, were similar due to lack of the effective drugs coding with COVID-19[14].

Outcomes and related risk factors

The duration of viral shedding and the length of hospital stay were without differences between-groups. Death rate in the group of COVID-19 patients with influenza IgM-positive is higher than it in other group with significant differences (14.9% vs 4.1%, $P = 0.040$). The rest patients are matched the discharge criteria and fully recover within 28 days of observation period.

Univariate Regression analysis showed that several factors were associated with higher risk of death, which included LDH, troponin, NT-proBNP, D-dimer, PT, APTT, lymphocytes, platelet and eGFR. However, influenza virus IgM positive was associated with lower risk of death (Table 2). Multivariate Regression analysis showed that troponin and lymphocyte were independently associated with higher risk of death (Table 3).

Table 2
Univariable Regression of Factors Associated with Death

	Death	
Patient characteristics and findings	OR, 95%CI	P value
Influenza	0.244(0.064,0.930)	0.039
LDH, U/L	1.006(1.003,1.010)	0.001
Troponin↑	18.90(4.91,72.76)	0.000
NT-proBNP↑	10.377(1.292,83.337)	0.028
PT, s	1.755(1.169,2.637)	0.007
APTT↑	3.719(1.141,12.126)	0.029
D-Dimer, μg/mL	1.180(1.029,1.354)	0.018
Lymphocytes < 0.8×10^9/mL	8.25(2.238,28.862)	0.001
PLT < 100×10^9/ mL	7.556 (1.858,30.730)	0.005
eGFR < 60 ml/min/1.73 m^2	3.829(1.033,14.196)	0.045

Table 3
Multivariable Regression of Factors Associated with Death

	Death	
Patient characteristics and findings	OR, 95%CI	P value
Lymphocytes < 0.8×10^9/mL	7.762(1.647,35.593)	0.010
Troponin↑	18.491(3.933,86.933)	< 0.001

Discussion

In this cohort study, we described the characteristics of patients hospitalized with COVID-19 with or without identification of influenza virus IgM-positive. Then, univariate analysis showed influenza IgM-positive was lower the likelihood of death. Influenza data in this research was detected based on enzyme-linked immunosorbent assay (ELISA). Previous studies demonstrated that influenza virus-specific IgM antibody responses following primary influenza virus infection in adults[11, 17]. 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, which is concerned of the coincidence with trend of influenza and other respiratory illnesses. In consequence, influenza virus IgM antibody may help us review these cases. Although influenza infection identified in COVID-19 patients do not affect its prognosis, seasonal influenza accounts for a very important percentage of all adult respiratory viral infections and it can be prevented and treated effectively. Therefore, influenza infection should not be regarded. If patients are suspected of suffering from virus infection, a prompt test for the respiratory virus should be the first step with an expanded detectable rang towards confirming diagnosis, which help in making early and effective treatment strategy.

SARS-CoV-2 is a new virus without well understanding of its virological characteristics. After this particular virus infection, clinical processes, virus replication kinetics, and host-host interactions have not been fully established. It is not clear that the virus epidemic trend in the future. The breakout of COVID-19 may happen in the same peak season that influenza comes, which bring the difficulty in prevention, diagnosis and treatment, may bring huge disease burden.

The strengths of this study include adults hospitalized with diagnosis of COVID-19, the retro-prospective design, standardized patient screening in the participating, centralized confirmation of respiratory viruses and identification of co-infectious influenza virus. It hints proof of seasonal influenza which may overlap with COVID-19 and may cause a crisis we could confront in the future.

Our study has several limitations. Firstly, only 146 patients were included. Until now, a large number of patients are continually being admitted to hospital as data, but not all still is a time limited mission. Secondly, as the patients were only in a hospital in Wuhan, the clinical features related to COVID-19, just could reflect the local information of influenza epidemic, which may result in biases. Especially consideration of influenza season, it may become epidemic of different type in different regions. Thus, the results may help us recognize co-infection of influenza and SARS-CoV-2 at crisis. However, it was unlikely to affect the prognosis of disease by the estimation following this study. Further studies focused on the co-infectious pathogens, the treatment and prevention will be needed.

Conclusion

Characteristics of patients hospitalized with COVID-19 with identification of influenza virus IgM-positive were described in this retrospective cohort study. It hints proof of seasonal influenza which may overlap with COVID-19 and may cause a crisis we could confront 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; HA: hemagglutinin; HFNC: high-flow nasal cannula; ILI: influenza like illness; IQR: interquartile range; LDH: lactate dehydrogenase; MV: mechanical ventilation; NMV: 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;

Declarations

Ethics approval and consent to participate

The study was approved by Ethics Committee of Beijing Hospital (2020BJYYEC-046-01).

Consent for publication

Not applicable.

Availability of data and material

All the data from electronic medical records in Tongjing Hospital were reviewed by experienced physicians separately and checked by 2 physicians independently.

Funding

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

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Yanming Li and Xunliang Tong contributed to the conception and design of the study and interpretation of the results and drafted the manuscript. Xunliang Tong, Xiaomao Xu, Guoyue Lv and He Wang contributed to the acquisition of the data and revision of the manuscript for important intellectual content. Anqi Cheng and Dingyi Wang performed the statistical analysis and revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Acknowledgments

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

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Figures

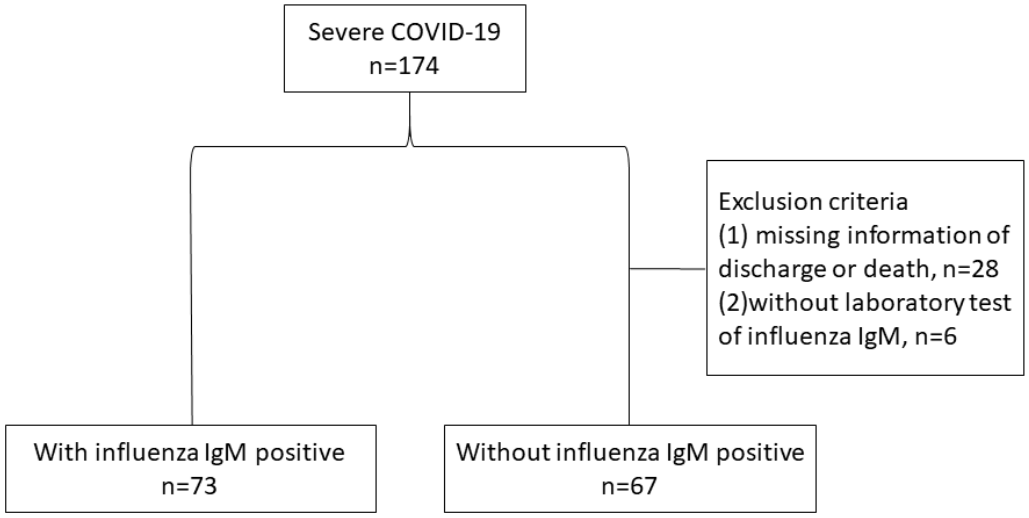

Figure 1

Flowchart