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Characteristics, Outcomes and Long-Term Sequelae of Patients with SARS-CoV-2 and Hepatitis Virus Infection

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Abstract

Background & aims: Since December 2019, a new type of coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged in Wuhan. And viral hepatitis is a major global health threat that affects the world. The purpose of our study is to reveal the clinical characteristics and outcomes of COVID-19 patients with pre-existing hepatitis virus infection.

Methods: We enrolled all COVID-19 patients with or without hepatitis virus co-infection admitted to Zhongnan Hospital from February 1 to March 30, 2020. Then we performed a comprehensive analysis of the difference in the COVID-19 patients with or without virus hepatitis in multiple aspects including demographic, laboratory parameters, treatment, prognosis and follow-up.

Results: Among non-severe patients, there were significant differences in absolute lymphocyte count, coagulation function and inflammatory biomarkers between co-infection group and mono-infection group, similar trend were not observed in the severe patients. The levels of several inflammatory markers are significantly correlated with the absolute count of T and B lymphocytes and values of hepatic and renal function-related parameters. The level of NLR (which means serial neutrophil-to-lymphocyte ratio), CK-MB (creatine-kinase-MB) and DBIL (direct bilirubin) were independently associated with the risk of in-hospital mortality. Combined with hepatitis virus infection will not increase the mortality and risk of long-term sequelae of COVID-19 patients.

Conclusions: Although chronic viral hepatitis does not affect the prognosis and sequelae of COVID-19 patients, our results prove that hepatitis virus infection causes a greater degree of dysfunction of non-severe COVID-19 patients. Regular follow-up health evaluation and treatment of COVID-19 patients are required when the patients were cured and discharged.

Keywords

SARS-CoV-2, Hepatitis virus, Risk factors, Sequelae

Introduction

Since December 2019, a new type of coronavirus disease (COVID-19) has emerged in Wuhan [1], which was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. It has been confirmed that SARS-CoV-2 is an enveloped single-stranded RNA-type beta-coronavirus [1,3]. The full-length genomic sequence shared 79.6% sequence identity with severe acute respiratory syndrome coronavirus (SARS) [3,4]. In addition, the current studies have proved that SARS-CoV-2 appears to use a receptor recognition mechanism similar to SARS to invade various organs. As a functional receptor, the binding of angiotensin-converting enzyme 2 (ACE2) to the spike protein of SARS-CoV-2 is essential for entry into target cells [5,6].

The latest emerging researches suggest that

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COVID-19 is a high mortality infectious disease with multi-system involvement [7]. Like most respiratory viruses, the SARS-CoV-2 invades bronchial epithelial cells and causes bronchiolitis and inflammation around the bronchi. SARS-CoV-2 could also cause a variety of extra pulmonary damage, which may be inseparable from the expression of ACE2 on the cells of multiple extra pulmonary organs [8-10]. ACE2 also has specific expression in the biliary tract [7,11,12], it is no doubt that SARS-CoV-2 will pose a threat to the liver function of the body. Many published clinical studies revealed that abnormal liver function is a vital manifestation of COVID-19 [13-15].

Viral hepatitis is a major global health threat that affects the world, the number of deaths due to viral hepatitis has been increasing since 2000 [16]. It is estimated that 1.34 million people die from viral hepatitis every year, 96% of which are contributed to hepatitis B virus and hepatitis C virus [17]. Acute or chronic viral hepatitis is main manifested by varying degrees of liver damage, accompanied with the abnormality of multi-system function [18]. Therefore, the primary purpose of our study is to reveal whether COVID-19 patients with pre-existing hepatitis virus infection are more vulnerable by analyzing serologic markers and clinical features, and get the most meaningful indicators for predicting the prognosis of co-infected patients, in order to provide treatment guidance for these special group and strive for the best prognosis.

Patients and methods

Study design and participants

A total of 250 confirmed patients with COVID-19 in Zhongnan hospital affiliated to Wuhan University from February 1 to March 30, 2020 were recruited in this single-center retrospective study. The clinical characteristics, laboratory test results, and treatment of all enrolled patients were recorded. Informed consent for the retrospective research was obtained from all patients.

Definitions

All patients with SRAS-CoV-2 infection were divided into two groups including COVID-19 with viral hepatitis or without viral hepatitis. Viral hepatitis was defined as who had previous hepatitis virus infection, and the laboratory examination showed positive hepatitis B surface antigen (HBs Ag) or positive hepatitis C virus antibody (HCV-Ab) at admission. COVID-19 with viral hepatitis group means the SARS-CoV-2 and hepatitis B or hepatitis C co-infection. COVID-19 without viral hepatitis group was described as having SARS-CoV-2 infection and no hepatitis virus infection. Confirmation of the COVID 19 requires real-time quantitative polymerase chain reaction (RT-PCR) to detect the RNA of SARS-CoV-2 in nasopharyngeal swabs of the patients using based on the protocol of manufacturer (Shanghai Bio Germ Medical Biotechnology Co., Ltd).

All patients with COVID-19 were divided into 4 clinical subtypes based on clinical symptoms and imaging findings. Mild types referred to the patients' clinical symptoms are mild, and no pneumonia manifestation in radiography. Moderate type was defined as patients with fever or respiratory symptoms, and radiography showed the manifestation of pneumonia, such as small patchy shadows, ground-glass shadows or infiltration shadows. Severe type was determined if it meets any of the followings: 1) Respiratory distress and respiratory rate ≥ 30 breaths per minute; 2) Peripheral blood oxidation saturation <93% at rest; 3) Arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2)<300 mmHg. Critical type was diagnosed by any respiratory failure and mechanical ventilation is required, shock, or combined with other organ failures requiring ICU monitoring and treatment.

Data collection

Data extraction was implemented by a team of professional physicians. The specific data included basic information of the patients, the symptoms at admission, the severity of the patients with COVID-19, laboratory data, and treatment measures.

Statistical analysis

Continuous data were displayed using median ± interquartile range (IQR), while frequency (%) were used to describe categorical variables. For continuous data, Mann-Whitney test was used for comparison between two groups, and for categorical variables, X^2 or Fisher exact test were performed to analysis. All analyses were performed using SPSS (version 26.0). The importance of variables was ranked by random forest model, and the ranked variables were further analyzed by binary logistic regression model to analyze the strongest predictors of death in patients with COVID-19.P less than 0.05 was considered significant.

Results

Clinical characteristics

A total 250 confirmed patients with COVID-19 were recruited in this study, of which the COVID-19 with viral hepatitis group containing 61 patients (SARS-CoV-2 + HBV/HCV group) and the COVID-19 without viral hepatitis group (SARS-CoV-2 group) including 189 patients. As showed in Table 1, the median age of all patients was 57 and there are 124 male patients. The most common clinical manifestation including cough (129[51.6%]), fever (104[41.6%]) and fatigue (70[28.0%]). The severity

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Table 1: Characteristics of COVID-19 patients with or without hepatitis virus infection.

Variable	Total (n = 250)	With hepatitis virus infection (n = 61)	without hepatitis virus infection (n = 189)	*P* value
Male, No. (%)	124(49.6%)	36(59%)	88(46.6%)	0.106
Age, median(IQR)	57.0(47.75~67.0)	54(48~65)	58(47~68)	0.191
Temperature, median (IQR)	36.5(36.3~36.8)	36.5(36.4~37)	36.5(36.3~36.8)	0.306
Heart rate, median (IQR)	82(78~96)	80(73.5~93)	84(80~96)	0.029
Symptoms and signs, No. (%)				
Fever	104(41.6%)	23(37.7%)	81(42.9%)	0.289
Fatigue	70(28.0%)	19(31.1%)	51(27.0%)	0.317
Headache	12(4.8%)	3(4.9%)	9(4.8%)	0.595
Cough	129(51.6%)	21(34.4%)	108(57.1%)	0.002
Expectoration	32(12.8%)	8(13.1%)	24(12.7%)	0.543
Chest distress/breath shortness	33(13.2%)	8(13.1%)	25(13.2%)	0.587
Diarrhea	15(7%)	4(6.6%)	11(5.8%)	0.281
Nausea and vomiting	10(4.0%)	3(4.9%)	7(3.7%)	0.458
Severity assessment on admission, No. (%)				
Moderate	192(76.8%)	29(47.5%)	163(86.2%)	
Serious	46(18.4%)	27(44.3%)	19(10.1%)	
Critical	12(4.8%)	5(8.2%)	7(3.7%)	
Treatment, No. (%)				
Arbidol	145(60%)	33(54.1%)	112(59.2%)	0.743
Lopinavir/Ritonavir	66(26.4%)	17(27.9%)	49(25.9%)	0.802
Interferon	70(28.0%)	20(32.8%)	50(26.4%)	0.616
Antibiotic	135(54.0%)	41(67.2%)	94(49.7%)	0.027
Traditional Chinese medicine	209(83.6%)	40(65.6%)	169(89.4%)	0.00
Glucocorticoid	53(21.2%)	23(37.7%)	30(15.9%)	0.00
Invasive mechanical ventilation	13(5.2%)	3(4.9%)	10(5.3%)	0.605
Anti-HBV/HCV treatment				
Entecavir	6(2.4%)	6(9.8%)	0(0%)	

Abbreviation: COVID-19: Coronavirus Disease 2019; No.: Number; IQR: Interquartile Range.

assessment at admission showed there were 192 (76.8%), 46 (18.4%) and 12(4.8%) for moderate, severe and critical type, respectively. Collectively, apart from the symptoms of cough and heart rate, there were no significant differences in other clinical features between two groups.

Laboratory parameters at admission

At admission, there were several significant differences in the results of laboratory tests between two groups. First of all, for blood cytology, the absolute lymphocyte count of the SARS-CoV-2 + HBV/HCV group was significantly lower than that of the SARS-CoV-2 group, as indicated in Table 2. In order to further analyze the differences in lymphocyte subsets count between the two groups, the lymphocyte subset measurement was performed, and the results manifested that the absolute count of $CD3^+$ T cells, $CD3^+CD4^+$ T cells and $CD19^+$ B cells in the SARS-CoV-2 with HBV/HCV co-infection group were lower compared to the SARS-CoV-2 group. In terms of coagulation indicators, the value of pro thromb in time (PT) and international normalized ratio (INR) of the SARS-CoV-2 + HBV/HCV group were longer than those of the SARS-CoV-2 group. Additionally, we compared the differences in liver function of the patients, the co-infected group had higher levels of DBIL and CK-MB, while there was no significant difference in the level of alanine amino transferase (ALT) and aspartate amino transferase (AST), which was different from the results of several reported studies. As for inflammatory cytokines, the result revealed that the patients co-infected with SARS-CoV-2 and HBV/HCV had higher interleukin-6 (IL-6) concentrations, while C-reactive protein (CRP), procalcitonin (PCT), lactate dehydrogenase (LDH) and NLR (which means serial neutrophil-to-lymphocyte ratio) sharing the similar trends (Table 2).

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Table 2: Laboratory findings of COVID-19 patients with or without hepatitis virus infection.

Variable (unit)	Total (n = 250)	With hepatitis virus infection (n = 61)	without hepatitis virus infection (n = 189)	*P* value
Blood cytology				
RBC (10^9/L)	4.0(3.73~4.34)	4.06(3.71~4.34)	3.99(3.73~4.34)	0.682
Hemoglobin (g/L)	129.2(118.85~138.88)	131.9(119.95~145.2)	128.7(118.7~137.6)	0.164
Leukocytes (10^9/L)	5.28(4.41~6.36)	5.28(4.16~6.20)	5.28(4.5~6.4)	0.332
Neutrophils (10^9/L)	3.15(2.53~4.09)	3.23(2.44~4.41)	3.14(2.54~4.05)	0.949
Platelets (10^9/L)	204.0(170.0~254.75)	186.0(142.5~237)	207(176~267)	0.016
Monocytes (10^9/L)	0.46(0.37~0.6)	0.46(0.34~0.58)	0.46(0.38~0.62)	0.637
Lymphocytes (10^9/L)	1.37(1.02~1.76)	1.2(0.63~1.61)	1.43(1.12~1.79)	0.002
CD3+ T cells (count/uL)	1063.5(731.0~1499.75)	839(458~1387)	1133(900~1508)	0.04
CD3+CD4+ T cells (count/uL)	657.0(423.0~877.25)	477(288~771)	694(508~918)	0.039
CD3+CD8+ T cells (count/uL)	374.0(276.25~544.25)	317(162~489)	383(310~590)	0.08
NK cells (count/uL)	231.5(141.0~413.75)	203(126~420)	242(156~412)	0.571
CD19+ B cells (count/uL)	198.0(97.25~273.75)	128(66~260)	216(116~303)	0.009
Coagulation function				
APTT (s)	30.7(29.15~32.9)	30.65(29.4~33.22)	30.7(29.0~32.7)	0.733
TT (s)	15.2(14.45~15.9)	15.2(14.47~16.2)	15.2(14.4~15.9)	0.611
PT (s)	11.8(11.2~12.45)	12.15(11.5~13.075)	11.7(11.1~12.3)	0.001
PT-INR	1.08(1.03~1.15)	1.115(1.06~1.20)	1.07(1.02~1.13)	0.001
Fibrinogen (mg/dL)	384(327~433.5)	393(333~429)	380(325~435)	0.793
D-Dimer (ng/ml)	193(121~352)	210(123.5~762)	184(118.75~294.75)	0.115
Blood inflammatory indicators				
CRP (mg/L)	2.6(1.3~10.55)	5.7(1.8~33.83)	2.4(1.3~8.3)	0.012
ESR (mm/h)	14.0(7.0~30.0)	18.0(6.0~34.25)	14.0(7.0~27.0)	0.343
PCT(ng/ml)	0.05(0.04~0.06)	0.05(0.05~0.06)	0.05(0.04~0.05)	0.016
LDH (U/L)	174.0(149.5~214.0)	187(151.75~247.5)	170.0(148.0~204.0)	0.041
NLR	2.22(1.69~3.27)	2.52(1.77~5.04)	2.15(1.63~3.14)	0.035
Blood biochemistry				
TBIL (umol/L)	11.65(9.3~15.1)	13.5(9.5~17.4)	11.4(9.3~14.3)	0.059
DBIL (umol/L)	2.1(1.6~3.0)	2.7(1.85~3.7)	2.0(1.55~2.7)	0.001
ALT (U/L)	26.5(17.0~43.0)	28(18~43.5)	26.0(16.0~43.0)	0.835
AST (U/L)	23.0(18.0~34.25)	26(19~39.5)	22.0(17.0~33.0)	0.089
ALB (g/L)	39.5(36.35~42.7)	39.1(34.1~42.45)	39.7(36.75~42.85)	0.187
GLB (g/L)	29.0(26.5~31.6)	29.7(26.9~32.05)	28.6(26.45~31.5)	0.203
A/G	1.37(1.20~1.56)	1.35(1.12~1.5)	1.37(1.21~1.58)	0.137
GGT (U/L)	26.0(17.5~45.5)	27(16~42.5)	26.0(18.0~47.0)	0.386
ALP (U/L)	84.0(67.0~104.0)	85(65~101.5)	84.0(68.0~106.0)	0.504
CK (U/L)	68.0(49.5~99.5)	71(51~110.25)	67.0(49.0~94.0)	0.424
CKMB (U/L)	10.0(7.0~14.0)	11.5(8.0~17.0)	10.0(7.0~13.0)	0.013
BUN (mmol/L)	4.58(3.8~5.50)	4.72(3.91~6.02)	4.58(3.80~5.44)	0.281
CREA (umol/L)	63.75(53.0~73.98)	65.1(53.25~80.25)	63.7(52.9~72.9)	0.185
CYSC (mg/L)	0.93(0.82~1.12)	0.97(0.82~1.09)	0.93(0.82~1.12)	0.685

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Cytokine				
IL-2 (ng/mL)	0.85(0.28~1.7)	0.95(0.1~1.73)	0.85(0.42~1.7)	0.793
IL-4 (ng/mL)	0.3(0.1~1.27)	0.21(0.1~0.90)	0.37(0.1~1.41)	0.456
IL-6 (ng/mL)	2.78(0.70~7.24)	5.98(1.93~19.51)	2.34(0.42~5.99)	0.002
IL-10 (ng/mL)	1.63(0.81~4.06)	2.54(1.12~7.09)	1.42(0.75~3.88)	0.071
IFN-γ (ng/mL)	0.52(0.11~1.87)	0.86(0.11~4.17)	0.395(0.11~1.33)	0.162
TNF-α(ng/mL)	0.1(0.1~0.31)	0.1(0.1~1.23)	0.1(0.1~0.24)	0.405
C3 (ng/mL)	1.1(1.0……~1.29)	1.1(0.9~1.23)	1.1(1.0~1.32)	0.420
C4 (ng/mL)	0.241(0.194~0.267)	0.22(0.17~0.25)	0.24(0.20~0.27)	0.154

Abbreviation: COVID-19: Coronavirus Disease 2019; No.: Number; SD: Standard Deviation; IQR: Interquartile Range; RBC: Red Blood Cell; APTT: Activated Partial Thromboplastin Time; TT: Thrombin Time; PT: Prothrombin Time; PT-INR: International Normalized Ratio of Prothrombin Time; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; PCT: Procalcitonin; LDH: Lactate Dehydrogenase; NLR: Neutrophil to Lymphocyte Ratio; TBIL: Total Bilirubin; DBIL: Direct Bilirubin; AST: Aspartate Amino Transferase; ALT: Alanine Aminotransferase; ALB: Albumin; GLB: Globulin; A/G: ALB To BLB Ratio; GGT: Glutamyltranspetidase; ALP: Alkaline Phosphatase; CK: Creatine Kinase; BUN: Blood Urea Nitrogen; CREA: Creatinine; CYSC: Cystatin C; IL: Interleukin; IFN-Γ: Interferon-Γ; TNF-A: Tumor Necrosis Factor-A.

Table 3: Laboratory parameters of non-severe COVID-19 patients with or without hepatitis virus infection.

Variable (unit)	Total (n = 200)	With hepatitis virus infection (n = 37)	without hepatitis virus infection (n = 163)	*P* value
Platelets (10^9/L)	207.5(176.0~256.25)	205.0(168.0~246.5)	209.0(180.0~262.0)	0.288
Lymphocytes (10^9/L)	1.49(1.21~1.84)	1.39(1.13~1.87)	1.50(1.22~1.84)	0.308
CD3+ T cells (count/uL)	1198.0(941.5~1571.0)	1036.0(715.0~1590.5)	1228.5(1015.0~1562.8)	0.048
CD3+CD4+ T cells (count/uL)	710.0(533.5~924.0)	655.0(411.5~855.5)	741.0(589.8~930.0)	0.045
CD3+CD8+ T cells (count/uL)	430.0(323.5~594.0)	421.0(290.5~509.5)	443.5(338.3~599.5)	0.181
CD19+ B cells (count/uL)	218.0(116.5~304.5)	198.0(97.0~271.0)	234.5(124.5~322.8)	0.131
PT (s)	11.6(11.1~12.2)	11.9(11.5~12.3)	11.5(11.1~12.2)	0.032
PT-INR	1.06(1.02~1.12)	1.09(1.06~1.13)	1.06(1.02~1.12)	0.029
CRP (mg/L)	2.25(1.2~5.3)	2.6(1.2~7.55)	2.1(1.2~4.9)	0.369
PCT (0~15 mm/h)	0.05(0.05~0.05)	0.05(0.05~0.06)	0.05(0.05~0.05)	0.021
LDH (U/L)	163.0(142.0~190.0)	163.0(143.5~193.5)	163.5(141.75~190.25)	0.829
NLR	2.05(1.59~2.74)	2.0(1.65~2.57)	2.06(1.59~2.74)	0.892
ALT (U/L)	26.0(16.25~43)	30.0(19.5~42.0)	26.0(16.0~43.0)	0.368
AST (U/L)	22.0(17.0~29.0)	26.0(19.0~104.0)	21.0(17.0~29.0)	0.156
DBIL (umol/L)	2.0(1.53~2.7)	2.3(1.65~3.2)	2.0(1.5~2.6)	0.097
CKMB (U/L)	9.0(7.0~13.0)	9.0(7.0~15.0)	9.0(7.0~12.0)	0.230
IL-6 (ng/mL)	2.08(0.42~4.6)	3.1(0.86~7.29)	1.89(0.42~4.39)	0.272
IL-10 (ng/mL)	1.42(0.81~3.88)	2.36(1.17~7.21)	1.34(0.75~2.77)	0.079

Abbreviation: COVID-19: Coronavirus Disease 2019; IQR: Interquartile Range; PT: Prothrombin Time; PT-INR: International Normalized Ratio of Prothrombin Time; CRP: C-Reactive Protein; PCT: Procalcitonin; LDH: Lactate Dehydrogenase; NLR: Neutrophil to Lymphocyte Ratio; DBIL: Direct Bilirubin; AST: Aspartate Aminotransferase; ALT: Alanine Amino Transferase; CK: Creatine Kinase; IL: Interleukin.

Subgroup analysis in severe and non-severe patients

Laboratory parameters of COVID-19 patients with different severity also showed significant differences, in view of this, we conducted a subgroup analysis based on the severity of the COVID-19 disease. We classified all mild and moderate patients as non-severe patients, and all severe and critical patients as severe patients. And then comparing the differences in laboratory parameters between patients with co-infection and mono-infection in the two sub groups of severe and non-severe group, respectively. The results showed that among non-severe patients, there were significant differences in absolute lymphocyte count, coagulation

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function and inflammatory biomarkers between co-infection group and mono-infection group, which were consistent with the trend of the entire cohort (Table 3). Notably, in the severe patients, the two groups of patients did not realize significant differences in laboratory parameters (Table 4).

Correlation between inflammatory factors and multiple biochemical indicators

In order to explore the mechanism of the differences in laboratory parameters between the two groups of patients, we analyzed the correlation between inflammatory factors with lymphocyte count, liver and kidney function, and coagulation function. The results suggest that the levels of inflammatory markers, including LDH, CRP, IL-6 and NLR were inversely correlated with absolute count of T and B lymphocytes (Figure 1). Therefore, we speculate that the increase of inflammatory markers caused by viral infection plays an important role in the process of lymphocytopenia. Meanwhile, the levels of these inflammatory markers are positively correlated with the levels of hepatic and renal function-related parameters. When the degree of inflammation markers increases, it is always accompanied by the deterioration of hepatic and renal function.

Risk factors for mortality of patients with COVID-19

In order to avoid the influence of confounding factors, the random forest model was selected to screen out the biochemical indicators that can accurately predict the survival status of patients, and the variables were sorted according to their importance (Figure 2). When seven variables are included, the error of the model is minimum. Therefore, the seven most important variables selected by the random forest model were incorporated into the binary logistic regression model. Multivariate logistic regression analysis showed that the level of NLR, CK-MB and DBIL at admission were independently associated with the risk of in-hospital mortality (Table 5). We drew the Kaplan-Meier curves of co-infection group and mono-infection group to evaluate the effect of hepatitis virus infection on the survival rate of patients with COVID-19 (Figure 3). The similar survival rates and Kaplan-Meier curves demonstrated that co-infection with hepatitis virus did not affect the mortality of COVID-19 patients.

Post-acute manifestations of COVID-19

Of the remaining 210 patients who completed the telephone survey in our study, excluding the patients who died because of COVID-19 in hospital, and those who lost to follow-up or died due to diseases other than COVID-19, 25.71% experienced persistent discomfort at a mean follow-up of 1 year from recovery and discharge from hospital (Table 6). Fatigue and muscle weakness (14.8%) was the most common symptom, followed by chest tightness (8.6%) and insomnia (8.6%), with 12.4%

Table 4: Laboratory parameters of severe COVID-19 patients with or without hepatitis virus infection.

Variable (unit, normal range)	Total (n = 50)	With hepatitis virus infection (n = 24)	without hepatitis virus infection (n = 26)	*P* value
Platelets (10^9/L)	177.5(124.75~249.0)	173.5(117.75~211.25)	200.0(124.75~282.75)	0.248
Lymphocytes (10^9/L)	0.84(0.415~1.18)	0.59(0.43~1.06)	0.95(0.41~1.22)	0.252
CD3+ T cells (count/uL)	451(311.5~731.5)	384.5(258.0~746.75)	594.0(343.0~732.0)	0.403
CD3+CD4+ T cells (count/uL)	316.0(116.0~420.0)	249.0(103.0~427.25)	354.0(129.0~420.0)	0.687
CD3+CD8+ T cells (count/uL)	223.0(94.5~301.5)	127.5(78.25~314.0)	266.0(145.0~290.0)	0.267
CD19+ B cells (count/uL)	84(44~191.5)	75.0(40.50~148.0)	90.0(71.0~197.0)	0.373
PT (s)	12.4(11.8~13.56)	13.0(11.9~13.9)	12.3(11.75~13.05)	0.173
PT-INR	1.14(1.08~1.24)	1.19(1.09~1.27)	1.13(1.075~1.195)	0.166
CRP ((mg/L))	32.7(8.05~95.44)	29.47(6.81~97.79)	32.7(8.5~97.5)	0.803
PCT(ng/ml)	0.05(0.05~0.14)	0.05(0.05~0.07)	0.095(0.05~0.81)	0.078
LDH (U/L)	282(199.5~449.75)	292.0(200.5~456.5)	269.0(191.5~442.0)	0.831
NLR	4.84(2.57~13.7)	4.8(3.07~14.6)	5.2(2.39~11.99)	0.669
ALT (U/L)	26.0(16.25~43)	21.5(14.5~44.0)	35.5(22.0~43.5)	0.200
AST (U/L)	22.0(17.0~29.0)	37.0(19.75~56.5)	37.5(23.5~54.25)	0.497
DBIL (umol/L)	2.1(1.6~3.0)	3.7(2.2~6.25)	2.8(1.7~4.5)	0.137
CKMB (U/L)	10.0(7.0~14.0)	15.0(10.0~23.0)	12.0(9.5~22.25)	0.519
IL-6 (ng/mL)	2.78(0.70~7.24)	15.1(6.9~82.3)	8.87(4.4~36.58)	0.279

Abbreviation: COVID-19: Coronavirus Disease 2019; IQR: Interquartile Range; PT: Prothrombin Time; PT-INR: International Normalized Ratio Of Prothrombin Time; CRP: C-Reactive Protein; PCT: Procalcitonin; LDH: Lactate Dehydrogenase; NLR: Neutrophil To Lymphocyte Ratio; DBIL: Direct Bilirubin; AST: Aspartate Amino Transferase; ALT: Alanine Aminotransferase; CK: Creatine Kinase; IL: Interleukin.

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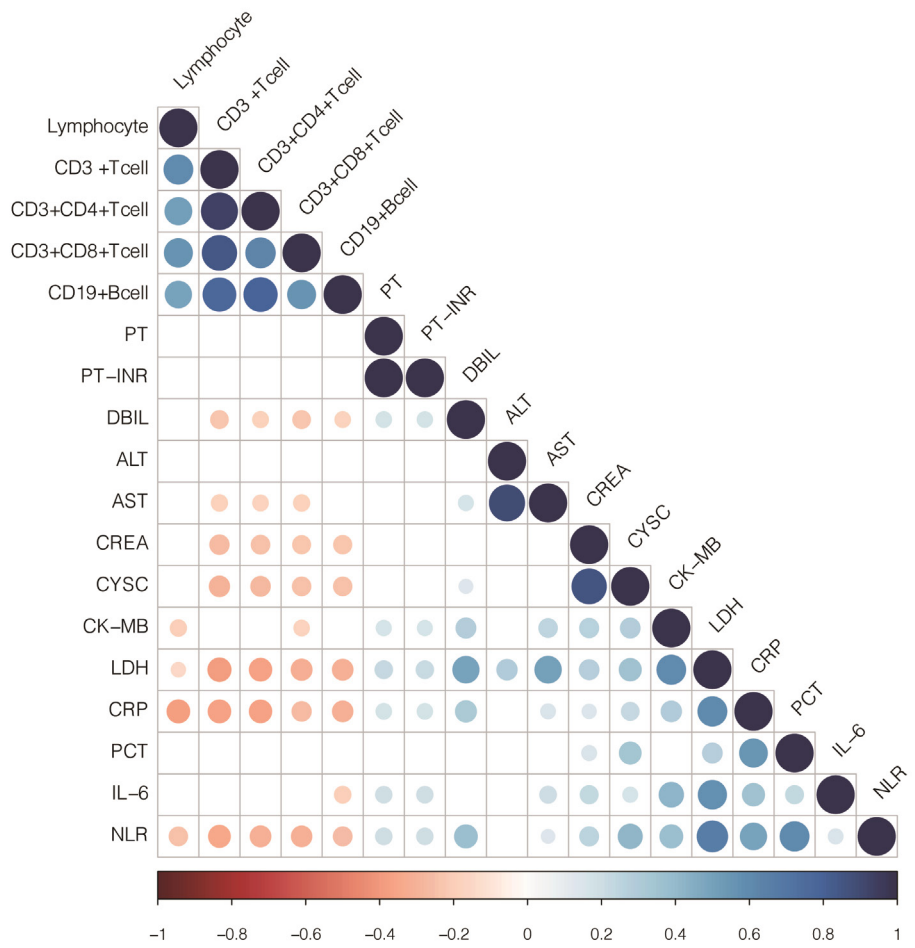

Figure 1: Correlation between inflammatory factors and multiple biochemical indicators.

Color of the circle in each grid represents the correlation between rows and columns, the bluer the color is, the stronger the positive correlation is, and the redder the color is, the stronger the negative correlation is. The size of the circle represents the P value. The larger the diameter of the circle, the smaller the P value. If there is no circle in the grid, it means that the P value is greater than 0.05.

Table 5: Logistic regression analysis of risk factors with mortality of COVID-19 patients.

Variables	Multivariate analysis	
	OR (95%CI)	P
DBIL	1.243(1.018~1.519)	0.033
CK-MB	1.136 (1.038~1.242)	0.005
NLR	1.084(1.014~1.159)	0.018

Abbreviation: COVID-19: Coronavirus Disease 2019; OR: Odds Ratio; CI: Confidence Interval; NLR: Neutrophil to Lymphocyte Ratio; DBIL: Direct Bilirubin; CK: Creatine Kinase-MB.

of the patients continuing to experience two or more symptoms. Our results of 1 year follow-up showed that fewer patients have persistent symptoms than reported articles [19,20], perhaps because we have enrolled more moderate patients, and our follow-up period is long enough, most of the patients recovered well after returning to normal life. Notably, there was no significant difference in clinical symptoms at one-year follow-up between the two groups. Results from univariate and multivariate logistic regression revealed that patients with low levels of hemoglobin and high levels of globulin at admission tend to have sequelae within one year after being cured and discharged from the hospital (Table 7).

Discussion

As a relatively common communicable disease, hepatitis virus is likely to infect with other viruses [21]. According to the documented literature, the co-infection with other viruses could accelerate the progression of the disease, the incidence of liver cirrhosis and mortality are significantly increased [22,23]. The focus of this article is to reveal the differences in multiple systems between patients with hepatitis virus and SARS-CoV-2 co-infection compared to mono-coronavirus infection, so as to better guide treatment and improve the prognosis of these special population.

A large number of clinical studies have proved

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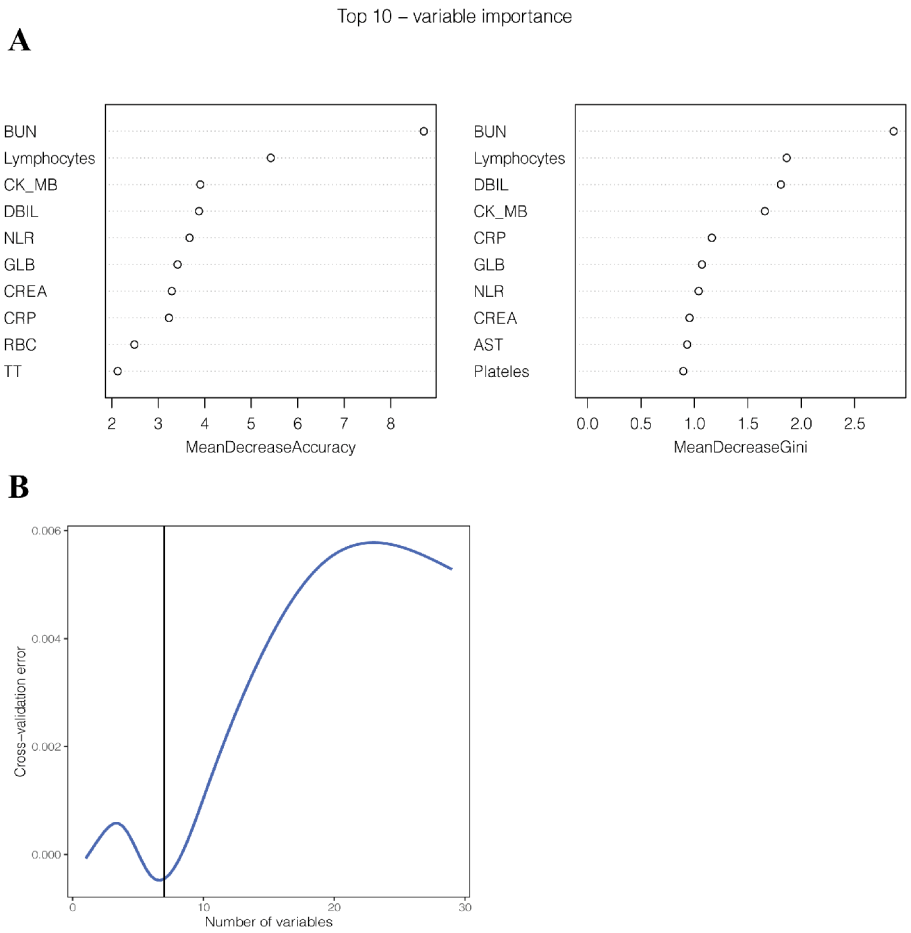

Figure 2: Clinical variables selected by random forest model (A) The mean decrease accuracy indicates the degree of decrease in the prediction accuracy of the random forest model. The larger the value, the greater the importance of the clinical variable. Mean decrease gini calculates the influence of each variable on the heterogeneity of observations at each node of the classification tree, thus comparing the importance of the variables. Similarly, the higher the value, the greater the importance of the variables; (B) The cross-validation curve shows the relationship between model error and the number of clinical features included for fitting.

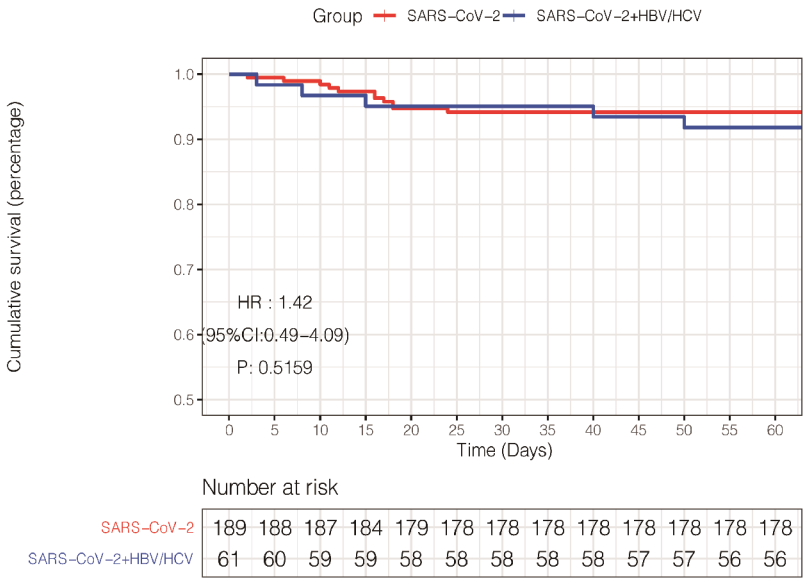

Figure 3: Kaplan-Meier survival curve for in-hospital mortality of COVID-19 patients. HR-Hazard Ratio; CI-Confidence Interval

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Table 6: Symptoms of COVID-19 patients at one year follow-up.

Symptoms and signs, No. (%)	Total (n=210)	With hepatitis virus infection (n=53)	without hepatitis virus infection (n=157)	*P* value
Fatigue or muscle weakness	31(14.8%)	10(18.9%)	21(13.4%)	0.223
Dizziness	11(5.2%)	5(9.4%)	6(3.8%)	0.150
Headache	5(2.4%)	2(3.8%)	3(1.9%)	0.602
Cough	12(5.7%)	5(9.4%)	7(4.5%)	0.184
Insomnia	18(8.6%)	6(11.3%)	12(7.6%)	0.404
Chest distress	18(8.6%)	5(9.4%)	13(8.3%)	0.780
Chest pain	6(2.9%)	3(5.7%)	3(1.9%)	0.170
Joint pain	4(1.9%)	1(0.5%)	3(1.9%)	1
Dyspnea	3(1.4%)	1(1.9%)	2(1.3%)	0.584

Abbreviation: COVID-19: Coronavirus Disease 2019; No.: Number.

Table 7: Logistic regression analysis of risk factors for sequelae of COVID-19 patients.

Variables	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P	OR (95%CI)	P
Hemoglobin	0.972(0.951~0.993)	0.01	0.973(0.953~0.995)	0.015
Globulin	1.083(1.007~1.166)	0.032	1.078(1.000~1.162)	0.049
NLR	1.094(0.994~1.203)	0.066		
A/G	0.278(0.083~0.936)	0.039		

Abbreviation: COVID-19: Coronavirus Disease 2019; OR: Odds Ratio; CI: Confidence Interval; NLR: Neutrophil to Lymphocyte Ratio; A/G: ALB to BLB Ratio.

that abnormal liver function is an epidemic feature of COVID-19 patients, mainly manifested by elevated levels of ALT and AST [13,14,24,25]. Wu, et al. reported that the average values of serum ALT and AST in group of SARS-CoV-2 and concomitant hepatitis virus are significantly higher than these of SARS-CoV-2 group [26]. Nevertheless, our data revealed that the significant difference does exit either at the time of admission or during hospitalization. Liver function in patients with COVID-19 has always been a controversial issue. Previous studies have shown that ACE2, as a prerequisite for the invasion of SARS-CoV-2 into target cells, is expressed in bile ducts dozens of times higher than that in hepatocytes [9]. However, our clinical data does not suggest co-infection of HBV/HCV and SARS-CoV-2 will aggravate liver damage. The impaired liver function of COVID-19 patients was the result of a combination of multiple factors. Direct virus damage, hypoxia-associated metabolic disorders, inflammation, and drug-induced liver injury (DILI) are potential pathological mechanisms. In particular, it is worth noting that there is a difference in the proportion of the therapeutic drugs used between the two groups in our cohort. As there were more mild patients in the SARS-CoV-2 group, 95.1% of the patients were reconciled with traditional Chinese medicine (TCM), and 47.8% of the patients used antibiotic therapy. In contrast, there were more severe cases in the co-infection group and a relatively higher proportion of patients treated with glucocorticoid, lopinavir or ritonavir. Previous studies have shown that both lopinavir, ritonavir and glucocorticoid could increase the risk of liver injury [27,28]. DILI usually occurs in the first few weeks of long-term drug treatment, typically characterized by a significantly increase in liver enzymes and may be accompanied by other allergic symptoms such as rash, vomiting, jaundice and so on. However, this obvious adverse reaction was not found in our cohort. Therefore, we can basically rule out the effect of drugs on the liver function. Liver biopsies from more and more patients with COVID-19 show steatosis and mild lobular and portal vein activity [29,30], which suggest that liver injury of COVID-19 patients is more likely to be caused by direct virus damage. To sum up, on the basis of being infected with SARS-CoV-2, chronic viral hepatitis will not aggravate the liver function of the patients significantly.

Interestingly, the levels of PT and INR at admission in the co-infection group were significantly higher than these in the SARS-CoV-2 group. Since the epidemic of SARS-CoV-2, the disorder of blood coagulation system is also a prominent manifestation of virus infection [31]. Virus-mediated endothelial injury could trigger excessive production of thrombin, which in turn leads to the imbalance of blood coagulation and anticoagulation pathway [32,33]. Disseminated intravascular coagulation (DIC) is a common phenomenon in COVID-19 patients [34]. We speculate that the

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endothelial injury caused by SARS-CoV-2 prompted the body to be in a state of hyper coagulability, so the body tends to appear microthrombus, and then due to the massive consumption of coagulation factors, the body enters into hypocoagulable state, which is characterized by an increase in the levels of PT and INR. Obviously, according to our clinical results, the co-infection group is more likely to be adversely affected in this process. Therefore, for patients with COVID-19 with pre-exiting virus hepatitis, timely evaluation of thrombus conditions and bleeding issue caused by secondary hypocoagulable state are vital medical measure.

Understanding the mechanism of lymphopenia in patients with co-infection is of great significance for clinical treatment. Several studies have reported that patients with COVID-19 will suffer from lymphopenia [31,35,36], which was consistent with the performance of the coronavirus infection in 2002 [37]. In our clinical study, co-infection will aggravate the degree of lymphopenia. We speculate that patients with co-infection are more likely to affect lymphocytes, inducing cytokine storms in the body, and then causing damage to target organs. Like the Middle East Respiratory Syndrome Coronavirus that broke out in 2013, we suspect that SARS-CoV-2 may induce apoptosis of a large number of T lymphocytes by directly infecting T lymphocytes. Other potential mechanisms include inhibition of T lymphocytes by viral infection and cytokine-mediated T cell death. Of course, these are just our guesses, which need to be verified by further experiments. T lymphocytes are of vital significance for virus clearance and limitation of further damage to the host, if we can inhibit the death of T lymphocytes, whether it can relatively improve the prognosis of co-infected patients, this is a problem worthy of further exploration.

The level of interleukin-6 (IL-6) in the co-infection group was higher than that in the mono-infection group. Huang, et al. also proved that the elevated level of inflammatory cytokines, such as IL-6, was positively correlated with the mortality of patients with COVID-19 [35]. Our results show that in addition to IL-6, the levels of other inflammatory factors in the co-infection group, such as CRP, LDH, PCT, NLR, etc., are also significantly higher than those in the single infection group. Therefore, we analyzed the correlation between inflammatory factors and other laboratory parameters. The results revealed that the increase of inflammatory markers were indeed important factors leading to lymphocytopenia and damage of liver and renal function. Therefore, in the treatment of patients with COVID-19 combined with other viral infections, antibiotic treatment actively using blood purification to remove IL-6 and other inflammatory cytokines, thereby blocking the cytokine storm and inhibiting the systemic inflammatory response syndrome, should be a reliable treatment plan to reduce mortality.

Then we conducted subgroup analysis based on the severity of the patients with COVID-19 at admission. We observed that there were significant differences in several laboratory parameters consistent with these of the entire cohort only in non-severe group. To our knowledge, such subgroup analysis in the special population has never been done before. We speculate that there may be a greater degree of deterioration of laboratory parameters in severe group, thus concealing the differences of biochemical indicators between the co-infection group and mono-infection group. At the same time, the number of severe patients included is relatively small. So as to assess the differences more precisely, larger population was expected in future investigation.

Previous studies have shown that NLR was a significant biomarker for predicting the mortality of COVID-19 patients [38]. It was well known that lymphocytes and neutrophils are important cellular components of the innate immune response. In critical patients with viral infection, over activated innate immune response could lead to dysregulated immune response and cytokine storm, while laboratory parameters show a significant increase in neutrophil levels and a decrease in lymphocyte levels [7]. In our study, NLR, as an effective indicator of inflammatory response, can also be used as a biomarker to predict the mortality of COVID-19 patients with viral hepatitis. At the same time, because NLR can be easily calculated from blood routine results, it can be widely used as a simple and practical biomarker for the disease progression and outcome in patients with SARS-CoV-2 and hepatitis virus.

In this study, we reported the first long-term follow-up data of COVID-19 patients co-infected with virus hepatitis. Follow-up results revealed that although the patient had been cured, there are still residual effects of SARS-CoV-2 infection even at 1 year after discharge from hospital. There was no significant different in symptoms between the two groups. Obviously, the co-infection with hepatitis virus has no significant impact on the residual effects of patients with SARS-CoV-2. The potential mechanisms leading to sequelae of COVID-19 may be multi factorial, including the direct effect of the virus, immune abnormalities caused by viral infection, inflammatory injury [39], psychological factors and so on. This also suggests that the treatment and care of COVID-19 patients should not end when the patients were cured and discharged. Instead, regular follow-up health evaluation and treatment are required. And our analysis suggests that the levels of hemoglobin and globulin at admission can predict if patients are going to show clinical residual effect or not. Special patients with

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low levels of hemoglobin and high levels of globulin at admission should pay more attention to periodic reexaminations and follow-up care.

We performed a comprehensive analysis of the difference in the COVID-19 patients with or without virus hepatitis in multiple aspects including demography, laboratory parameters, treatment, prognosis and follow-up, no study before us has done such a comprehensive analysis. To sum up, there are significant differences in immune function, clotting function and inflammatory response between the co-infection group and the mono-infection group. The increased level of inflammatory factors is potential mechanism leading to abnormal physiological state of the body. The levels of NLR, DBIL and CK-MB can be considered as the strongest prognostic factors in patients with COVID-19. Combined with hepatitis virus infection will not increase the mortality and risk of long-term sequelae of COVID-19 patients. Hemoglobin and globulin are effective biomarkers for predicting sequelae of COVID-19 patients. At present, COVID-19 has not been completely eliminated, and several countries are still suffering from the virus infection. I wish that we can provide more reliable assessment of the condition and clinical treatment guidance for patients with SARS-CoV-2 and hepatitis virus co-infection through our research, and strive for the best prognosis.

None the less, our current research has several limitations. A small number of patients have not been quantitatively tested for HBV DNA or HCV RNA, so the disease activity of viral hepatitis cannot be analyzed. Secondly, this single-center retrospective study still needs to be verified by a larger population or prospective study. Finally, the lone-term effects of virus co-infection on human subject have not been studied.

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Conflicts of Interest

The authors declare that they have no potential conflicts of interest that could to affect the research reported in this paper.

Ethical Approval

This retrospective study received approval of the ethics committee of Zhongnan Hospital of Wuhan University (No. 2021097K).

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