The characteristics of laboratory tests at admission and the risk factors for adverse clinical outcomes of severe and critical COVID-19 patients

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Abstract

Background Coronavirus disease 2019(COVID-19) is a worldwide pandemic.In this study, we aimed to evaluate the risk factors of death from severe and critical COVID-19 patients.

Method A retrospective study of patients diagnosed with severe and critical COVID-19 from four hospitals in Wuhan, China, describing the clinical characteristics and laboratory results, and using Cox regression to study the risk factors was conducted.

Results Four hundred and forty-six patients with COVID-19 showed a high case fatality rate(CFR)(20.2%). All patients required oxygen therapy, and 52(12%) patients required invasive mechanical ventilation,of which 50(96%) patients died.The univariate Cox proportional hazard model showed a white blood cell count of more than $10 \times 10^9/L$ (HR3.903,95%CI 2.413 to 6.313),patients' risk of death significantly increased.The multivariate Cox proportional hazard model demonstrated that older age (HR 1.074, 95% CI 1.050 to 1.098) was an independent risk factor and high white blood cell count(HR 1.119, 95% CI 1.056 to 1.186)was a predictive factor for COVID-19 on admission.

Conclusions COVID-19 is a new disease entity that carries significant risk of morbidity and CFR.Older age was an independent risk factor and high white blood cell was a predictive factor for COVID-19.

Background

In December 2019, an unidentified pneumonia appeared in Wuhan City, Hubei Province.By isolating and sequencing airway epithelial cells from patients with pneumonia, an unknown beta coronavirus infection[1],officially named COVID-19 on February 12, 2020[2]was found.The virus spread internationally within 1 month after the first identification, and it can be spread through closecontact between people[3]. Severe acute respiratory syndrome (caused by SARS-CoV) [4-6],which occurred in 2003, and Middle East respiratory syndrome coronavirus (MERS),which occurred in 2013,were previously known to belong to the beta coronavirus genus[7,8].They were highly pathogenic and the infection manifests as a severe acute respiratory disease[9].The virus was introduced into host cells through the human angiotensin-converting enzyme 2(ACE2) receptor according to bioinformatics prediction methods and in vitro testing[10,11].

As of April 18,2020,more than 2 million cases of COVID-19 patients hadbeen reported to WHO,and more than 135,000 people had lost their lives.The virus had established itself in many countries.The threat of a pandemic had became very real[12].

To explore the onset characteristics of the disease and assess the prognostic risk factors for patients,we conducted laboratory tests for 446 patients,described the short-term results,and tried to identify possible clinical consequences and final performance factors of 446 patients.

Methods

Study Design and Participants

This study was approved by the Ethics Commission of Hubei Provincial Hospital of Traditional Chinese Medicine(HBZY2020-C14-01).The requirement for informed consent was waived by the Ethics Commission.All cases came from Hubei Provincial Hospital of Traditional Chinese Medicine,Renmin Hospital of Wuhan University, Hubei Provincial Hospital of Integrated Chinese & Western Medicine,and Wuhan Jinyintan Hospital. The follow-up deadline was March 1, 2020.

All patients who were enrolled in this study were diagnosed with COVID-19 according to the guidance provided by the Chinese National Health Commission.They were either severe or critical.The clinical classification was based on the fifth trial version of the Diagnosis and Treatment Scheme for Pneumonitis with COVID-19 Infection,released by China's National Health Commission.Based on this scheme,one of the following conditions must be met for a patient to be classified as severe:①shortness of breath, respiratory rate ≥ 30 beats/min;②resting state,oxygen saturation $\leq 93\%$ ③arterial blood oxygen partial pressure (PaO₂)/oxygen concentration(FiO₂) ≤ 300 mmHg or ④pulmonary imaging of blood showing significant progression of lesions > 50%;critical patients must show either:①respiratory failure,requiring mechanical ventilation;②shock;or③combined failure of other organs requiring ICU monitoring and treatment(Table1).

Table 1 Criteria for diagnosis of severe and critical illness

Severe	Critical
①shortness of breath, respiratory rate ≥ 30 beats / min	①Respiratory failure, requiring mechanical ventilation
②resting state, oxygen saturation $\leq 93\%$	②Shock
③arterial blood oxygen partial pressure(PaO ₂)/oxygen concentration(FiO ₂) ≤ 300 mm Hg	③Combined failure of other organs requiring ICU monitoring and treatment
④pulmonary imaging of blood showing significant progression of lesions > 50%	

Severe and critical illness meet any of the above

Outcome indicators included discharge after treatment (survival) and death.The patient was discharged based on meeting the following four criterias :①no fever for at least three days;②significant improvement in both lungs on chest computed tomography(CT);③clinical relief of respiratory symptoms;④two SARS-CoV-2 RNA negative throat swab samples obtained at least 24 h apart(Table2).

Table 2 Discharge diagnosis criteria

①No fever for at least three days
②Significant improvement in both lungs on chest computed tomography(CT)
③Clinical relief of respiratory symptoms
④Two SARS-CoV-2 RNA negative throat swab samples obtained at least 24 h apart

The above four conditions must be met at the same time

Data collection

All data were collected by specialists with extensive clinical experience. Electronic medical records were used to collect data on general vital signs, clinical symptoms, underlying diseases (diabetes, hypertension, and coronary heart disease), laboratory tests, and treatment outcomes of patients at the time of admission. The collected data were collated and reviewed by a team of professionally trained doctors. The collated experimental data included blood analysis (white blood cell count, lymphocyte count, and lymphocyte percentage), liver function (glutamate transferase and aspartate transferase), renal function (blood urea nitrogen, creatinine, uric acid), and the levels of glucose, triglycerides, cholesterol, high-sensitivity cardiac troponin I, interleukin-6 (IL-6), procalcitonin, and hyper-sensitive C-reactive protein (hs-Crp).

Statistical analysis

Statistical analysis was performed using the Social Science Statistics Package version 21.0 (SPSS. Inc, Chicago, IL, USA). Categorical variables were described by frequency and percentage, and continuous variables were described by median and interquartile range (IQR) values. Continuous variables were compared using independent group tests when the data were normally distributed; otherwise, the Mann-Whitney test was used.

The Cox proportional hazard model was used to analyze baseline variables related to CFR. Variables found to be statistically significant ($p < 0.05$) in univariate analysis were further analyzed using multivariate analysis. The Kaplan-Meier method was used to analyze the patients' survival rate, and the log-rank test was used to compare these survival rates. All statistical tests were mutual. Statistical significance was set at $p < 0.05$.

Results

General characteristics

The median age of the 446 patients included in the study was 55 years (IQR 42-66); 213 (47.76%) patients were male, 90 (20.2%) patients died during hospitalization, and 356 (79.8%) patients were discharged. The median length of hospital stay was 10 days (IQR 8-14) (Table 3). There were 104 (23.3%) patients that were diagnosed with one or more chronic diseases; 84 (18.83%) patients were diabetic, 104 (23.3%) were hypertensive, and 35 (7.8%) exhibited coronary heart disease. On admission, hypoxemia was a common symptom, so all patients received oxygen therapy, 394 (88%) patients required high-flow nasal cannula oxygen therapy or non-invasive mechanical ventilation, while 52 (17%) patients required invasive mechanical ventilation. Of the 52 patients, 50 (96%) patients died. (Table 3).

Table 3 Demographic, clinical, and laboratory of patients on admission

	Total(N=446)	Alive (N=356)	Dead(N=90)	P value
	213/446(48%)	161/356(45%)	52/90(58%)	
	233/446(52%)	195/356(55%)	38/90(42%)	
)	55/446(42-66)	50(40-61)	69(62-78)	0.001
	179/446(40%)	104/356(29%)	75/90(83%)	
erapy				
P	394/446(88%)	354/356(99%)	40/90(44%)	
	52/446(12%)	2/356(1%)	50/90(56%)	
	84/446(19%)	57/356(16%)	27/90(30%)	0.002
ion	104/446(23%)	73/356(21%)	31/90(34%)	0.005
heart disease	35/446(7.8%)	22/356(6.18%)	13/90(14.44%)	0.009
ength of stay(days)	10(8-14)	10(8-13)	9(5-12)	0.001
od cell count ($\times 10^9$ per L)	5.50(4.10-7.62)	5.18(3.95-7.05)	7.56(5.34-10.95)	0.001
	105/446(23%)	92/356(26%)	13/90(14%)	
	289/446(65%)	239/356(67%)	50/90(56%)	
	52/446(12%)	25/356(7%)	27/90(30%)	
tes($\times 10^9$ per L)	1.01(0.68-1.41)	1.12(0.77-1.58)	0.66(0.44-0.89)	0.001
	218/446(49%)	145/356(41%)	73/90(81%)	
	228/446(51%)	211/356(59%)	17/90(19%)	
te percentage%	16.7(3.95-27.60)	20.75(6.83-29.80)	5.10(0.31-11.50)	0.001
	253/446(57%)	173/356(49%)	80/90(89%)	
	193/446(43%)	183/356(51%)	10/90(11%)	
/L)	25 (16-42)	24(16-40)	26(16-50)	0.157
	121/446(27%)	84/356(24%)	37/90(41%)	
/L)	27(19-40)	25(18-37)	26(16-50)	0.001
	111/446(25%)	65/356(18%)	46/90(51%)	
nmol/L)	4.5(3.5-6.0)	4.2(3.3-5.5)	6.97(4.8-10.1)	0.001
	32/446(7%)	7/356(2%)	25/90(28%)	
, (μ mol/L)	63.7(52.1-80.0)	4.2(3.3-5.5)	73.1(56.1-99.4)	0.001
	15/446(3%)	6/356(2%)	9/90(10%)	
/L)	245 (187-305)	247(194-315)	242.00(153-293)	0.065
nmol/L)	5.8(4.9-7.3)	5.6 (4.9-6.7)	7.2 (5.9-9.7)	0.001
	200/446(45%)	136/356(38%)	64/90(71%)	
1	235/446(53%)	210/356(59%)	25/90(28%)	
	11/446(2%)	10/356(3%)	1/90(1%)	
le(mmol/L)	1.3(1.0-1.7)	1.3(1.0-1.7)	1.3(1.1-1.6)	0.864
ol (mmol/L)	3.9(3.4-4.4)	3.9(3.4-4.5)	3.8(3.2-4.3)	0.061
itivity cardiac troponin I,ng/mL	0.006(0.02-0.18)	0.006(0.002-0.008)	0.02(0.007-0.038)	0.169
L	9.5(6.1-22.0)	7.8(5.7-15.5)	12.1(8.9-25.4)	0.166
nin, ng/mL	0.05(0.05-0.13)	0.05(0.04-0.09)	0.14(0.06-0.34)	0.001
r/L	26.8(5.0-78.5)	18.2(5.0-49.0)	84.3(28.8-155.5)	0.001
	327/380(86%)	254/314(81%)	82/88(93%)	

P values indicate differences between alive and dead patients.P <0.05 was considered statistically significant

Laboratory test results

At the time of admission, 105 (23%) patients presented with leukocyte count below the normal range (white blood cell count less than 4×10^9 /L), 52 (12%) with a leukocyte count above the normal range (white blood cell count more than 10×10^9 /L), and about half of the patients had a decreased

lymphocyte count(lymphocyte count less than $1.0 \times 10^9/L$). 121 (27%) patients exhibited varying degrees of liver dysfunction, with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels above the normal range. Renal dysfunction occurred in 36(7.2%) patients, who showed elevated blood urea nitrogen or serum creatinine. There were 211 (47.3%) patients with abnormal blood glucose levels, and among them, 200 (44.8%) patients showed glucose levels above the normal range (glucose count more than 6.1 mmol/L), while 11(2%) patients showed levels below the normal range (glucose count less than 3.9 mmol/L). Hyper-sensitive C-reactive protein was increased in 86% of the patients (hs-CRP ≥ 3 mg/L) (Table 3). The results of other laboratory tests were shown in Table 3.

Factors affecting mortality rate

We included 380 patients with complete data for Cox regression. The univariate Cox proportional hazard model showed that the risk of death increased 1.074-fold with an increase in age (95% CI 1.054 to 1.087; $p < 0.001$). Patients were divided into two groups based on age with a cut-off point of 60 years. The Kaplan-Meier survival curves were shown in Figure 1. The risk of death also increased with the presence of chronic diseases, such as diabetes [HR 1.886; 95% CI 1.200 to 2.963; $p = 0.006$], hypertension [HR 1.926; 95% CI 1.245 to 2.979; $p = 0.003$], and coronary heart disease [HR 2.479; 95% CI (1.372 to 4.479); $p = 0.003$]. The risk of death increased 1.182-fold in patients with an increased leukocyte count. The leukocyte count cut-off was at the upper limit of the normal value range. The Kaplan-Meier survival curves were shown in Figure 2. Other risk factors affecting death included lymphocyte count, and levels of creatinine, AST, hs-Crp, and so on, as shown in Table 4.

Table 4 Analysis of factors affecting CFR using the univariate Cox proportional hazards model

	Hazards ratio (95% CI)	p value
Gender male	1.711(1.124-2.605)	0.012
Age [#]	1.071(1.054-1.087)	≤ 0.001
≥ 60 years*	7.701(4.250-13.953)	≤ 0.001
Diabetes	1.886(1.200-2.963)	0.006
Hypertension	1.926(1.245-2.979)	0.003
Coronary heart disease	2.479(1.372-4.479)	0.003
White blood cell count [#]	1.182(1.133-1.233)	≤ 0.001
$\geq 10 \times 10^9$ per L ^{&}	3.903(2.413-6.313)	≤ 0.001
Lymphocytes percentage [#]	0.939(0.918-0.960)	≤ 0.001
Lymphocytes [#]	0.275(0.158-0.480)	≤ 0.001
AST [#]	1.016(1.011-1.021)	≤ 0.001
hs-Crp [#]	1.013(1.010-1.015)	≤ 0.001
Creatinine [#]	1.007(1.004-1.010)	≤ 0.001
Glucose [#]	1.112(1.065-1.160)	≤ 0.001

$P < 0.05$ was considered statistically significant.

[#] Per unit increase of the variable; * Reference group is patients age ≥ 60 years; & Reference group is patients White blood cell count $\leq 10 \times 10^9$ per L.

The multivariate Cox proportional hazard model was used to identify independent risk factors for CFR. We found that older age (HR 1.074, 95% CI 1.050 to 1.098) was an independent risk factor, and high white blood cell count (HR 1.119, 95% CI 1.056 to 1.186) was a predictive factor for adverse clinical outcomes (Table 5).

Table 5 Multivariate analysis showing the independent risk factors for CFR using the Cox proportional hazards model

	Hazards ratio (95% CI)	p value
Age (per 1-y increase)	1.074(1.050-1.098)	0.001
White blood cell count (per $1 \times 10^9/L$ increase)	1.119(1.056-1.186)	0.001

P < 0.05 was considered statistically significant

Discussion

We included 446 patients with COVID-19 in this study, and they showed a high CFR (20.2%). Contrary to some previous studies, which considered the disease to still be in the epidemic period and not reflective of the overall CFR, our study demonstrated that older age was an independent risk factor and high white blood cell count could predict patients' death. Among patients more than 60 years, the death rate was significantly increased, probably due to lower body tolerance, and the presence of co-morbidities. Zhou et al [13] also reported that older age was an important independent risk factor of CFR.

Results of laboratory tests demonstrated that a high white blood cell count could predict patients' death. An elevated white blood cell count often indicated inflammatory responses by bacterial infection. Thus, COVID-19 patients were prone to secondary bacterial infections due to low immune functions, the initial white blood cell count could also indicate disease progression. Previous study reported that neutrophil-to-lymphocyte ratio is an independent risk factor of the in-hospital mortality for COVID-19 [14]. Therefore, we should pay attention to the indicators of inflammatory response early. White blood cell counts could be quickly obtained based on a blood routine test on admission, clinicians may identify high risk COVID-19 patients at an early stage. This is why most patients were given combined antibacterial and antiviral therapy.

Some studies on the characteristics of patients [13, 15-16], showed a similar median age at onset. Some showed that men were more susceptible to COVID-19 [15-17]. Our study didn't demonstrate significant gender differences, but in terms of patients' CFR, men were more at risk than women, possibly because females may have stronger innate and adaptive immunity, leading to relatively stronger resistance to viral infections [18-21].

Although it was clinically found that the lymphocyte count of most patients was reduced [22-24], it was not found as an independent predictive factor in this study. The median number of lymphocytes in patients who later died was significantly lower than that in surviving patients. Hence, lymphopenia might be related to viral invasion of the immune system that leads to immune damage.

Prior to the first outbreak of SARS, a limited number of coronaviruses, causing only mild illnesses such as the common cold, were known to spread in humans[25]. Given the high prevalence, widespread distribution of coronaviruses, the extensive genetic diversity, and frequent genome recombination of coronaviruses, new coronaviruses were likely to be regularly discovered owing to frequent cross-species infections and occasional spillover events that occur in the body[26]. In the past two decades, major infectious diseases caused by coronaviruses included SARS, MERS, and COVID-19. Therefore, it is necessary to follow-up on these cases for a long time.

Our study has several limitations. First, there was insufficient information on demographic characteristics, clinical symptoms, history of exposure, and personal history of the patient in this study. Second, it was a retrospective study design and relied on data collected from case records. The included patients didn't complete all laboratory tests, including neutrophil counts, lactate dehydrogenase and serum ferritin. Therefore, their role might be underestimated in predicting death in hospital. Third, we studied a short-term prognosis of patients during hospitalization, however, SARS-CoV-2 is a newly discovered virus, and its onset, characteristics and prognosis are still being researched. Whether some patients relapsed, even die after the clinical cure need to be further investigated. So the validity of the predictive factors for CFR derived from our cohort remains tentative, we need larger sample size and longer follow-up period. In the later stages, follow-up of surviving patients survived must be continued to understand the disease better.

Conclusions

COVID-19 is currently a global pandemic. In this study, we found that older age was an independent risk factor and high white blood cell was a predictive factor for COVID-19. We hope to inform clinicians about this information to aid them in the treatment of patients.

Abbreviations

COVID-19: Coronavirus disease 2019

CFR: Case fatality rate

ICU: Intensive care unit

CT: Computed tomography

RNA: Ribonucleic acid

IQR: Interquartile range

ALT: Alanine transferase

AST: Aspartate aminotransferase

BUN:Blood urea nitrogen

UA: Uric Acid

IL-6:Interleukin-6

hs-Crp:Hyper-sensitive C-reactive protein

HFNC: High-flow nasal cannula

NVP:Noninvasive ventilation

IVP:Invasive mechanical ventilation

Declarations

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Author Contributions

Conceived and designed the study:LLW,XBC and QFD.Colleced the data:LLW,XBC,QFD,CLZ,YMW,BS,WNL,MW,RQ,QL,JL,JL,DL.Analyzed the data: LLW,GL and YMB.Wrote the paper:LLW.Interpreted the results:LLW,XBC,QFD,GL andYMB.These authors contributed equally to this work and should be considered as co-first authors:LLW,XBC and QFD.All authors have read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Ethics Commission of Hubei Provincial Hospital of Traditional Chinese Medicine(HBZY2020-C14-01).The requirement for informed consent was waived by the Ethics Commission.Informed consent about study participation was officially announced by mail and poster.All patient data were anonymized prior to the analysis.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

Fig.1

Figure 1

Survival of viral pneumonia patients by Survival analysis showing time from admission to death by different age group.

Fig.2

Time from admission to death by different levels of white blood cell count. ($P < 0.001$)

Figure 2

Survival of viral pneumonia patients by Survival analysis showing time from admission to death by different levels of white blood cell count.