Analysis of Risk Factors of Severe COVID-19 Patients

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Abstract

Objective: To explore relevant risk factors for severity of patients with novel coronavirus pneumonia (COVID-19).

Methods: The clinical data of 292 patients with COVID-19 admitted to Hubei Provincial Hospital of Integrated Chinese & Western Medicine from January 1, 2020 to February 29, 2020 were analyzed retrospectively. Patients were divided into mild or severe group according to the Guidance for Corona Virus Disease 2019 (7th version) released by the Chinese National Health Committee. The clinical data were collected at the time of admission, including demographics, clinicalcharacteristics, laboratory test results, imaging characteristics and outcome of treatment. We applied univariable and multivariable logistic regression methods to explore the risk factorsassociated with severity of the disease.

Results: The median age of patients in the severe group((68.19 ± 12.51)years) was significantly older than mild group((54.14 ± 13.62)years). The male sex was more predominant in severe group (63.45%) than that of mild group (38.1%). There were more smokers (8.97% vs 1.36%) and drinkers (4.14% vs 0%) in severe group than that of mild group. Patients in the severe group had more underlying diseases. Hypertension(48.97% vs 23.81%),coronary heart disease (22.07% vs 1.36%, $P < 0.0001$), chronic obstructive pulmonary disease (6.21% vs 1.36%), malignant tumor (7.59% vs 2.04%) and chronic kidney disease (3.45% vs 0%) were more frequent in severe group than in mild group.The dyspnea, chest tightness and dry cough were more common in severe group (43.45%, 66.9% and 66.21%) than in mild group (23.13%, 44.22% and 53.74%). Abnormality of chest radiography were more frequent in the severe group, there were more ground glass opacities, consolidation of lung and white lung in the severe cases (88.97%, 44.07% and 46.21%) than in mild cases (78.91%, 19.05% and 2.04%). Patients in the severe group were more likely to receive methylprednisolone, oxygen therapy and mechanical ventilation. Lasso algorithm showed that age, C-reactive protein (CRP), creatine kinase (CK) and α-hydroxybutyrate dehydrogenase (α-HBDB) were the independent risk factors for severeCOVID-19, and CD_4^+T lymphocyte count was the protective factor.

Conclusion: This large-scale retrospective study of 292 COVID-19 patients revealed that age, CRP, CK,α-HBDB and CD_4^+T lymphocyte were independent risk factors for severity of COVID-19. Identifying patients with risk factors at an early stage of the disease are helpful for outcome prediction and clinical management.

Introduction

Coronavirus, a single strand positive strand RNA virus, widely exists in nature[1]. Coronavirus includedhighly pathogenic acute respiratory syndrome coronavirus and Middle East respiratory syndrome (MERS) coronavirus, as well as four other coronaviruses (HCoV-229E,HCoV-0C43, HCoV-NL63,HCoV-HKU1) that cause upper respiratory tract infection [2, 3]. The newly discovered 2019 novel coronavirus (2019-nCoV) is the seventh coronavirus [4, 5] known to infect humans. 2019-nCoVwas officially named as

severe acute respiratory syndromecoronavirus 2 (SARS-Cov-2) by the international virus classification committee[6].Most of the patients withCOVID-19 were mild to moderate. However, patients with severe COVID-19 can progress to critical severe cases, which are acute respiratory failure, ARDS, septic shock, multiple organ failure, with a high risk of death. The early reported mortality rate is 11% -15% [5].

The world health organization declared that the outbreak of SARS-Cov-2 constituted a public health emergency of international concern On 30 January 2020. the global situation is very grave. Some research has suggested that the SARS-Cov-2 infection causes severe pneumonia, which clinical manifestations are similar to sars-cov infection, associated with admissions to intensive care units and high mortality rates[7]. The other study published in the lancet shows that older age, d-dimer greater than 1 μg/mL and higher Sequential Organ Failure Assessment (SOFA) score can redict severe COVID-19 in the early stage[8].

The purpose of this study is to compare the clinical and laboratory characteristics of patients with different clinical types of COVID-19 who admitted to the isolation ward of Hubei Provincial Hospital of Integrated Chinese & Western Medicine, which is one of the designated hospitals assigned by Chinese government. We aimed to explore the risk factors of severe patients, and to provide scientific basis for reducing the incidence and mortality of severe COVID-19.

Methods

Study Design and Participants

292 patients diagnosed with COVID-19 in our hospital from January 1, 2020 to February 29, 2020 were selected as the study objects. Diagnostic criteria and clinical typing criteria in according to the Guidance for Corona Virus Disease 2019 (7th version) released by the Chinese National Health Committee [9]. Exclusion criteria: (1) patients with psychiatric diseases who did not cooperate with the treatment. (2) patients with incomplete data or transferred to other hospitals. (3) patients with pneumonia caused by other pathogens. This study has been approved by the ethics committee of our hospital. This case series was approved by the institutional ethics board of Hubei Provincial Hospital of Integrated Chinese & Western Medicine (No. 2020011). Written informed consent was waived because of the rapid emergence of this serious epidemic.

Data collection

The following data was collected and recorded: (1)The basic dataincluded epidemiological history, demographic characteristics, signs and symptoms. (2) The results of laboratory examination included blood routine, C-reactive protein, SAA (Serum amyloidA protein), biochemistry, immunity, inflammation, coagulation function and other indicators. (3) The chest radiography characteristics. (4) Treatments. (5) Outcomes. The data collection tables were independently reviewed by two researchers.

Statisticalanalysis

Continuous variables were presented as ± standard error of mean (SEM) or medians (interquartile range, IQR) depending on whether they fitted the normal distribution, and the comparisons between two groups were performed by using Wilcoxon rank sum test. For qualitative variables, statistical description was expressed as frequency (percentage), and Fisher exact probability method was chosen for comparisons between two groups. All potential risk factors were included in a multivariable cox model with a lasso algorithm to screen the basic risk factors. Statistical software was R version 3.6.3 (The R Foundation), and all hypothesis tests were two-sided tests with a significance level of 0.05.

Results

General information

145 patients with severe and critical COVID-19 were set as the severe group and 147 patients with common COVID-19 were set as the mild group. Compared to mild group, patients in severe group were more likely to be male (63.9% vs 38.1%, $P < 0.001$)and older (67.97 ± 12.69 vs 54.14 ± 13.62, $P < 0.001$). There were more smokers (8.84% vs 1.36%, $P = 0.006$) and drinkers (4.08% vs 0%, $P = 0.0297$) in the severe group than in the mild group. Meanwhile, patients in severe group had more comorbidities such as Hypertension(48.97% vs 23.81%, $P < 0.0001$)(), coronary heart disease (22.07% vs 1.36%, $P < 0.0001$) ,chronic obstructive pulmonary disease (6.21% vs 1.36%, p = 0.0342),malignant tumor (7.59% vs 2.04%, $P = 0.0301$) and chronic kidney disease (3.45% vs 0% $P = 0.0291$) than that in the mild group. Details of other relevant information were shown in Table 1.

Table 1
Clinical features of COVID-19 between mild and severe groups

Variables	Mild group	Severe group	P value
Age, years, mean (sd)	54.14 (13.62)	68.19 (12.51)	< 0.0001
Male, n (%)	56 (38.1%)	92 (63.45%)	< 0.0001
BMI, kg/m2, mean (sd)	23.96 (2.04)	24.42 (2.02)	0.1163
Smoking history, n (%)	2 (1.36%)	13 (8.97%)	0.0032
Drinking history, n (%)	0 (0%)	6 (4.14%)	0.0142
Comorbidities, n (%)			
COPD	2 (1.36%)	9 (6.21%)	0.0342
Asthma	1 (0.68%)	0 (0%)	1.0000
Hypertension	35 (23.81%)	71 (48.97%)	< 0.0001
CHD	2 (1.36%)	32 (22.07%)	< 0.0001
Diabetes	16 (10.88%)	28 (19.31%)	0.0503
Malignantbtumor	3 (2.04%)	11 (7.59%)	0.0301
CKD	0 (0%)	5 (3.45%)	0.0291
CLD	0 (0%)	4 (2.76%)	0.0595
Symptoms, n (%)			
Chest tightness	65 (44.22%)	97 (66.9%)	< 0.0001
Dry cough	79 (53.74%)	96 (66.21%)	0.0322
Fever	118 (80.27%)	117 (80.69%)	1.0000
Running nose	2 (1.36%)	4 (2.76%)	0.4459
Sore throat	0 (0%)	3 (2.07%)	0.1212
Sputum	29 (19.73%)	32 (22.07%)	0.6671
Dyspnea	34 (23.13%)	63 (43.45%)	< 0.0001
Fatigue	101 (68.71%)	111 (76.55%)	0.1497
Anorexia	98 (66.67%)	104 (71.72%)	0.3765
Muscle ache	36 (24.49%)	34 (23.45%)	0.8913

Abbreviations:BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; CHD: Coronary heart disease; CKD: Chronic kidney disease; CLD: Chronic liver disease; IQR: Inter quartile range

Variables	Mild group	Severe group	P value
Nausea	12 (8.16%)	8 (5.52%)	0.4882
Diarrhea	14 (9.52%)	5 (3.45%)	0.0552
Headache	10 (6.8%)	15 (10.34%)	0.3027
Days from onset to admission, days, median (IQR)	5 (4, 7)	5 (3, 8)	0.7166
Abbreviations:BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; CHD: Coronary heart disease; CKD: Chronic kidney disease; CLD: Chronic liver disease; IQR: Inter quartile range			

Regarding clinical symptoms, the dyspnea, chest tightness and dry cough were more common in severe group (43.45%, 66.9% and 66.21%) than in mild group (23.13%, 44.22% and 53.74%). Details of other relevant information were shown in Table 1.

Laboratory test results

After admission, the first blood routine, biochemical, immune and coagulation tests were performed in the two groups. We observed substantial differences in laboratory findings in the two groups (Table 2).

Table 2
Laboratory test resultsof COVID-19 between mild and severe groups

Variables	Mild group	Severe group	*P* value
CRP,median(IQR),mg/L	14.96 (3.95, 41.16)	61.77 (23.03, 110.3)	< 0.0001
LY,median(IQR),10^9/L	1.11 (0.74, 1.46)	0.72 (0.5, 1.05)	< 0.0001
MO,median(IQR),10^9/L	0.38 (0.27, 0.52)	0.33 (0.22, 0.49)	0.1372
NE,median(IQR),10^9/L	3.19 (2.27, 4.44)	4.84 (3.38, 7.47)	< 0.0001
WBC,median(IQR),10^9/L	5.08 (3.71, 6.08)	6.14 (4.71, 8.68)	< 0.0001
PLT,,median(IQR),10^9/L	211 (163.5, 280)	170 (135, 241)	< 0.0001
Hb, median(IQR), g/L	125 (115, 138)	128 (117, 140)	0.3052
RBC,median(IQR),10^{12}/L	4.13 (3.78, 4.54)	4.19 (3.87, 4.63)	0.3186
PCT,median(IQR),ng/ml	0.02 (0.02, 0.05)	0.08 (0.04, 0.23)	< 0.0001
SAA,median(IQR), mg/L	114.65 (19.41, 300)	300 (153.03, 300)	< 0.0001
IL-1, median(IQR),pg/ml	5 (5, 5)	5 (5, 6.5)	0.0001
IL-6,median(IQR),pg/ml	6.12 (3.85, 13.1)	15.3 (9.8, 25.9)	< 0.0001
IL-10,median(IQR),pg/ml	5 (5, 6.15)	10.1 (6.7, 14.2)	< 0.0001
CD_4^+T, median(IQR), /ul	366 (268.5, 439.5)	136 (93, 196)	< 0.0001
CD_8^+T, median(IQR), /ul	231 (154.5, 300.5)	91 (63, 152)	< 0.0001
TotalTcell, median(IQR),/ul	652 (485, 750.5)	235 (180, 373)	< 0.0001
ALT, median(IQR),U/L	19 (10.5, 35)	26 (16, 44)	0.0006
AST, median(IQR),U/L	22 (18, 32.5)	33 (24, 50)	< 0.0001
ALP, median(IQR),U/L	56 (44.5, 70)	66 (51, 80)	0.0004
GGT,median(IQR),U/L	25 (18, 42)	37 (23, 52)	0.0001

Abbreviations: CRP:C-reactive protein; LY: Lymphocyte; MO: Monocyte; NE: Neutrophil; WBC:White blood cells; PLT: Platelets ; Hb : Hemoglobin ; RBC : Red blood cells ; PCT : Procalcitonin ; SAA：Serum amyloidA protein; IL-1: Interleukin-1; IL-6: Interleukin-6; IL-10: Interleukin-10;CD_4^+T:CD_4^+T lymphocytes; CD_8^+T :CD_8^+T lymphocytes; TotalT: Totallymphocytes ; ALT: Alanine aminotransferase; AST: Aspartate transaminase; ALP: alkaline phosphatase; GGT: Gamma glutamyl transferase; ALB:Albumin; TB:Total bilirubin; DB: Direct bilirubin; APTT:Activated partial thromboplastin time; PT:Prothrombin time; CK: Creatine kinase; α-HBDB: α-Hydroxybutyrate Dehydrogenase; LDH:Lactatedehydrogenase; BUN: Blood urea nitrogen; Cr:Creatinine; IQR: Inter quartile range

Variables	Mild group	Severe group	*P* value
ALB, median(IQR),g/L	36.5 (34.25, 40.2)	33.8 (30.7, 36.6)	< 0.0001
TB, median(IQR), umol/L	10.1 (7.45, 13.5)	12.7 (9.5, 17.1)	< 0.0001
DB, median(IQR), umol/L	1.9 (1.2, 2.7)	3.2 (2.2, 4.6)	< 0.0001
D-dimer,median(IQR),mg/L	0.5 (0.34, 0.8)	1 (0.62, 5.43)	< 0.0001
Fibrinogen,median(IQR), g/L	3.16 (2.61, 4.06)	3.92 (3.25, 4.34)	< 0.0001
PT, median(IQR), S	12.5 (12, 13.35)	13.2 (12.6, 14.3)	< 0.0001
APTT, median(IQR), S	30 (27.8, 33.05)	30 (28, 32.2)	0.9818
CK, median(IQR), U/L	54 (31.5, 93.5)	116 (60, 240)	< 0.0001
HBDB,median(IQR),U/L	170 (135.5, 216)	297 (220, 394)	< 0.0001
LDH, median(IQR), U/L	216 (180, 268)	347 (262, 495)	< 0.0001
BUN,median(IQR),mmol/L	4.09 (3.2, 5.53)	6.4 (4.92, 8.37)	< 0.0001
Cr, median(IQR), umol/L	63.2 (55.15, 77.65)	79.7 (62.4, 98.2)	< 0.0001

Abbreviations: CRP:C-reactive protein; LY: Lymphocyte; MO: Monocyte; NE: Neutrophil; WBC:White blood cells; PLT: Platelets ; Hb : Hemoglobin ; RBC : Red blood cells ; PCT : Procalcitonin ; SAA：Serum amyloidA protein; IL-1: Interleukin-1; IL-6: Interleukin-6; IL-10: Interleukin-10;CD_4^+T:CD_4^+T lymphocytes; CD_8^+T :CD_8^+T lymphocytes; TotalT: Totallymphocytes ; ALT: Alanine aminotransferase; AST: Aspartate transaminase; ALP: alkaline phosphatase; GGT: Gamma glutamyl transferase; ALB:Albumin; TB:Total bilirubin; DB: Direct bilirubin; APTT:Activated partial thromboplastin time; PT:Prothrombin time; CK: Creatine kinase; α-HBDB: α-Hydroxybutyrate Dehydrogenase; LDH:Lactatedehydrogenase; BUN: Blood urea nitrogen; Cr:Creatinine; IQR: Inter quartile range

The patients in severe group had persistent and more severe lymphopenia (0.72 (IQR, 0.5–1.05)) than mild group (1.11 (IQR, 0.74–1.46)); Median platelet counts were significantly lower in severe group (170 (IQR, 135–241)) than mild group (211 (IQR, 163.5–280)). The patients in severe group had more leukocytosis (6.14 (IQR, 4.71–8.68)) than mild group (5.08 (IQR, 3.71–6.08)). Concentrations of procalcitonin, high sensitivity C-reactive protein were significantly higher in severe group than in mild group (0.08 (IQR, 0.04–0.23) vs 0.02(IQR, 0.02–0.05), $P < 0.0001$), (300 (IQR, 153.03–300) vs 114.65(IQR, 19.41–300), $P < 0.0001$).

Concentrations of alanine aminotransferase, aspartate aminotransferase, total bilirubin, Direct bilirubin, alkaline phosphatase, and Gamma glutamyl transferase were significantly higher in severe group than in mild group. Albumin concentrations were significantly lower in severe group than in mild group(33.8 (IQR,30.7–36.6) vs 36.5 (IQR,34.25–40.2), $P < 0.0001$). Concentrations of blood urea nitrogen,creatinine, creatine kinase, α-hydroxybutyrate dehydrogenase and lactate dehydrogenase were markedly higher in severe group than in mild group.

Patients in the severe group more often had significantly lower concentrations of CD_4^+T lymphocyte, CD_8^+ T lymphocyte and total T lymphocyte count than did patients in the mild group. concentrations of interleukin 1, interleukin 6 and interleukin 10 were significantly higher in severe group than in mild group. Median prothrombin time was significantly longer in severe group (13.2 (IQR, 12.6–14.3)) than in mild group (12.5 (IQR, 12-13.35)), D-dimer and fibrinogen concentrations were markedly greater in severe group than in mild group.Details of other relevant information were shown in Table 2.

Radiological characteristics

The lung lesions inthe two groups were mostly distributed under the pleura, accompanied by multiple patchy or lumpy ground glass opacities, with or without pulmonary consolidation or white lung. In the severe group, the lung lesions were mainly distributed in two lungs, with multiple ground glass opacities (88.97% vs 78.91%, $P = 0.0252$), pulmonary consolidation (42.07% vs 19.05%, $P < 0.0001$) and white lung (46.21% vs 2.04%, $P < 0.0001$,) more common than in the mild group. See Table 3.

Table 3
Lung imaging and Outcome of COVID-19 between mild and severe groups

Variables	Mild group	Severegroup	*Pvalue*
Singlelungdistribution,n (%)	15 (10.2%)	0 (0%)	*< 0.0001*
Twolung distribution,n (%)	131 (89.12%)	145 (100%)	< 0.0001
Subpleural distribution,n (%)	126 (85.71%)	127 (87.59%)	0.7315
Bronchovascularbundle distribution,n (%)	62 (42.18%)	63 (43.45%)	0.9059
SingleGGO,n (%)	4 (2.72%)	0 (0%)	0.1225
MultipleGGO,n (%)	116 (78.91%)	129 (88.97%)	0.0252
PatchyGGO,n (%)	114 (77.55%)	125 (86.21%)	0.0682
LumpGGO,n (%)	30 (20.41%)	26 (17.93%)	0.6564
Consolidation,n (%)	28 (19.05%)	61 (42.07%)	< 0.0001
Whitelung,n (%)	3 (2.04%)	67 (46.21%)	< 0.0001
TraditionalChinese medicine, n (%)	71 (48.3%)	69 (47.59%)	0.9074
Oxygen therapy,n (%)	47 (31.97%)	142 (97.93%)	< 0.0001
Noninvasive ventilation,n (%)	0 (0%)	112 (77.24%)	< 0.0001
Invasive ventilation, n (%)	0 (0%)	15 (10.34%)	< 0.0001
Firstdailydoseof methylprednisolone mean (sd), mg	15.92 (24.43)	89.1 (30.46)	< 0.0001
Mortality rate, n (%)	0(0%)	51(35.17%)	< 0.0001
Cure rate, n (%)	147(100%)	94(64.83%)	< 0.0001
Abbreviations: GGO□ground glass opacity			

Treatment and outcome

All patients in the two groups were treated with antiviral, anti bacteria, nutrition, traditional Chinese medicine and symptomatic support. Compared with the mild group, the patients in the severe group received more methylprednisolone, oxygen therapy, noninvasive mechanical ventilation and invasive

mechanical ventilation, which was significantly higher than that in the mild group. In 145 severe cases, 96 patients were cured and discharged, accounting for 65.31%, 51 patients died, accounting for 34.69%. For the mild group, no dead patients were found and all of them were cured and discharged. There was statistical significance between this two groups, $P < 0.0001$. See Table 3.

Analysis of related risk factors

Multivariate analysis revealed thatage, CRP, CD_4^+ T lymphocyte count, CKand α-HBDB wereindependent risk factors for severity of COVID-19. Multivariable regression showed increasing the risk of exacerbation associated with older age (HR 1.15, 95% CI 1.07–1.24, per five year increment; $P < 0.0001$), increasing the risk of exacerbation associated with CRP (HR 1.18, 95% CI 1.03–1.34, per 20 mg/L increment; $P = 0.0167$), increasing the risk of exacerbation associated with CK (HR 1.08, 95% CI 1.00-1.16, per U/L increment; $P = 0.0467$), increasing the risk of exacerbation associated with α-HBDB (HR 1.15, 95% CI 1.06–1.26, per U/L increment; $P = 0.0012$) and increasing the risk of exacerbation associated with CD_4^+ T cell counts (HR 0.74, 95% CI 0.68–0.81, per U/L reduction; $P < 0.0001$).See Table 4.

Table 4
Exacerbation risk factors ofCOVID-19 in COXmodel using lassoalgorithm

Risk Factors	HR	95% CI	*P* value
Age	1.15	(1.07, 1.24)	0.0001
CRP	1.18	(1.03, 1.34)	0.0167
CD_4^+ T cell counts	0.74	(0.68, 0.81)	0.0001
CK	1.08	(1.00, 1.16)	0.0467
α-HBDB	1.15	(1.06, 1.26)	0.0012
Abbreviations:HR:Hazard ratio; CI: Confidence interval; CRP:C-reactive protein ; CK: Creatine kinase; α-HBDB: α-Hydroxybutyrate Dehydrogenase.			

Discussion

A recent epidemiological study by China CDC showed that the mortality rate of criticalCOVID-19 patients can be as high as 49% [10], which aroused significant awareness in clinical management.

In this study, all 292 patients with COVID-19 were from Wuhan. Lasso algorithm screened that age was the risk factor of severe patients. The risk of severe patients increased by 15.15% when the age increased by 5 years. In the severe group, most of the patients with COVID-19 were elderly patients with basic diseases. Hypertension, coronary heart disease, chronic obstructive pulmonary disease, malignant tumor and chronic kidney disease were more frequent among severe group than that in the mild group. In 145 severe cases, 51 patients died, accounting for 34.69% and 90.2% of the dead patients are over 60 years

old. Of the 51 deaths, 40 patients had underlying disease, the death rate of the patients with basic diseases was higher, accounting for 78.43%.The recent reports show that advanced age (> 60) and comorbidities (particularly hypertension) are believed to be risk factors for severe disease and death from SARS-Cov-2 infection[4, 5, 7]. which was consistent with the results of previous studies[5, 7, 11], it is consistent with our findings.

In this study, C-reactive protein (CRP) in the severe group was higher than that in the mild group. CRP was selected as the risk factor of severe patients by lasso algorithm. The risk of severe patients increased by 17.55% when CRP increased by 20 mg/L. Furthermore, we found that inflammatory markers such as SAA, IL-1, IL-6, IL-10, peripheral blood leukocytes, neutrophils and procalcitonin were significantly higher in severe patients. It indicated that severe patients might have had secondary bacterial infection, this may be closely related to death. Severe patients may suffer from inflammatory cytokine storms, which caused fatal organ dysfunction and closely related to mortality[12].

Through the lasso algorithm, wefound that creatine kinase (CK) and α - hydroxybutyrate dehydrogenase (α - HBDB) were independent risk factors for patients with severe illness.The risk of severe patients increased by 7.86% and 15.31% when CK increased by U/Land α - HBDB increased by U/Lrespectively. The CK mainly exists in skeletal muscle, cardiac muscle and smooth muscle. α - HBDH mainly exists in cardiac muscle and liver. We also found that the liver enzyme, LDH, Blood urea nitrogen and creatinine in the severe group were significantly higher than those in the mild group.This may be the results of multiple organ dysfunction caused by SARS-CoV-2 infection [13]. Recent research reported that severe and critical patients more often developed multi-organ dysfunction than that in mild patients [14]. A research reported that α - HBDH is an independent risk factor of SLE related to the liver injury[15].

We found that CD_4^+ T lymphocyte count is the risk factor of severe patients. The risk of severe patients increased by 25.58% when CD_4^+ T lymphocyte count reduced by 50/UL. In this study, CD_4^+ T lymphocyte count for 95.24% of these140 patients in the severe group is lower than the normal lower limiting value and the phenomenon indicated that the decrease of lymphocyte count may be an important factor to cause the aggravation of the patient's condition, which is consistent with the report of Central South Hospital[5]. Because of the continuous inflammatory reaction, lymphocyte apoptosis increased, the number decreased rapidly and the body entered the state of "immunosuppression" or "immune paralysis" [16]. In this situation, the proper use of immunosuppressive glucocorticoids may yield better results [17] .

The level of D-dimer, fibrinogen and PT in severe group was higher than that in mild group. The rise of D-dimer is influenced by many factors. Acute inflammatory response caused by severe infection can affect coagulation and fibrinolysis via many ways. Studies have shown that high levels of D-dimer are related to the 4-week mortality [18]and its mechanism may be related to hemodynamic changes caused by systemic pro-inflammatory cytokine response [19]. Recent study showed that elevated level of D-dimer may be associated with the fatal outcome of COVID-19 infection [8]. In our study, D-dimer elevation occurred in 47 of the 51 deaths in the severe group, it was similar to the outcomes as above.

The patients in the severe group showed multiple ground glass opacities of both lungs on the image, lung consolidation and white lung were more common than those in the mild group, similar to the research of Guan WJ [20], about 30% of patients withCOVID-19 will rapidly progress to ARDS [20]. These patients are more likely to develop to respiratory failure, severe pneumonia and ARDS.

This study found that α-HBDB is one of the independent risk factors for the onset of severe COVID-19 patients for the first time and it was not reported by any other relevant literatures before. But there are some limitations in this study, it's a single center retrospective study and no external validation cohort, it is hoped that the risk factors of severe COVID-19 can be verified through multi-center clinical research in the future.

In a word, as found by the cox regression, age, CRP, CK ,α-HBDB and CD_4^+ T lymphocyte count were the independent risk factors for the onset of severe COVID-19patients, Therefore, early attention to the above factors may be very helpful to improve the prognosis of COVID-19 in the future.

Declarations

Availability of data and materials

The datasets generated and analysed during the current study are included in this published article and its supplementary information files. More datasets are not publicly available due to the need for further reaserch, but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Hubei Provincial Hospital of Integrated Chinese & Western Medicine(No. 2020011).
Written informed consent was waived because of the rapid emergence of this serious epidemic.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contributions

YY and JZ are responsible for the whole manuscript. QY and JX helped with data entry and manuscript writing. ZF helped with study conception and data analysis. JY and FL helped with collection of laboratory data. All authors participated in the revision of this manuscript and approved the content.

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