Clinical characteristics and predictive value of low CD4^{+}T cell count in patients with moderate and severe COVID-19: A multicenter retrospective study

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Abstract

Background

In December 2019, coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, Hubei, China. And, it has become a global pandemic. Describe the patient's clinical symptoms in detail, finding markers that predict the prognosis of patients with COVID-19 are of great value.

Methods

In this multicenter, retrospective study, 476 patients with COVID-19 were recruited from a consecutive series. After screening, a total of 395 patients were included in this study. All-cause death was the primary endpoint. All patients were followed up from admission till discharge or death.

Results

The dominant symptoms observed in the study included fever on admission, cough, fatigue, and shortness of breath. The most frequent comorbidities were hypertension and diabetes. Compared with patients with higher $CD4^+$T cell levels, patients with lower $CD4^+$T cell levels were older and were more frequently male. Reduction of $CD8^+$T cell is an indicator of the severity of COVID-19. Both decreased $CD4^+$T cell [HR:13.659; 95%CI: 3.235-57.671] and $CD8^+$T cell [HR: 10.883; 95%CI: 3.277-36.145] were associated with in-hospital death in COVID-19 patients, but only decreased $CD4^+$T cell was an independent predictor of in-hospital death in COVID-19 patients.

Conclusions

Reductions in lymphocytes and lymphocyte subsets were common in COVID-19 patients, especially in severe cases. It was the $CD8^+$T cell, not the $CD4^+$T cell, that reflected the severity of the patient's disease. Only $CD4^+$T cell reduction was independently associated with increased in-hospital death in COVID-19 patients.

Trial registration: Prognostic Factors of Patients With COVID-19, NCT04292964. Registered 03 March 2020. https://clinicaltrials.gov/ct2/show/NCT04292964.

1. Background

In December 2019, an outbreak of coronavirus disease 2019 (COVID-19), an acute respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was detected in mainland China. Although the overall case fatality rate of patients with COVID-19 is relatively low [1], the number of deaths related to COVID-19 has already exceeded the sum of SARS and MERS, which has brought great harm to human beings. Moreover, the fatality rate of patients with severe COVID-19 is higher and the

harm is bound to be greater [2]. Describe the patient's clinical symptoms in detail, finding markers that predict the prognosis of patients with COVID-19 are of great value.

The decline of T-lymphocytes in peripheral blood is a typical laboratory characteristic of patients with COVID-19, especially in severe COVID-19 patients [3,4]. A recent study recruited 21 patients with COVID-19 including 11 severe COVID-19 patients and 10 moderate COVID-19 patients. The study showed an absolute number of T-lymphocytes, $CD4^+$T and $CD8^+$T cells decreased in almost all the patients with COVID-19, and significantly lower in severe COVID-19 patients (294.0, 177.5 and 89.0×10^6/L) than moderate COVID-19 patients (640.5, 381.5 and 254.0×10^6/L). Meanwhile, most patients did not show a decrease in B-lymphocytes count but showed a tendency to an increased B-lymphocytes count. This phenomenon suggested that SARS-CoV-2 infection may primarily affect T-lymphocytes particularly $CD4^+$T and $CD8^+$T cell [4]. T-lymphocytes play a critical role in antiviral immunity. $CD4^+$T lymphocyte subsets secrete a high level of effector cytokines, especially interferon-γ (IFN-γ), which are essential for virus clearance [5,6]. A previous study also showed that the drastic reduction in total lymphocytes indicated the consumed immune cells and the destructed cellular immune function by coronavirus [7]. However, there are not enough studies on whether $CD4^+$T cell predicts the prognosis of COVID-19 patients.

2. Methods

2.1 Subjects

Medical records from 476 patients with confirmed COVID-19 were collected in Hubei General Hospital and Chongqing Three Gorges Central Hospital. Missing $CD4^+$T cell count or CD^+8T cell count data (n=58), malignant tumor (n=8), younger than 18 years (n=11), eGFR≤30ml/min (n=3), and pregnant (n=1) were excluded, patients with immune system diseases or HIV, which may affect lymphocyte and subsets, were also excluded. Finally, 395 patients with COVID-19 were analyzed in this study (Figure 1). The positive infected cases were confirmed by testing new coronavirus nucleic acid by real-time fluorescent Polymerase Chain Reaction (RT-PCR). Patients with severe COVID-19 were defined according to the New Coronavirus Pneumonia Prevention and Control Program issued by the National health commission of the People's Republic of China (5th edition). Patients with respiratory distress (respiratory rates ≥30 per/min or resting oxygen saturation ≤93% or partial pressure of arterial oxygen (PaO2)/inspired oxygen fraction (FiO2) ≤300mmHg or respiratory failure requiring mechanical ventilation, were defined as severe COVID-19, and the remaining patients were defined as moderate COVID-19 patients. $CD4^+$T cell count, $CD8^+$T cell count, and lymphocytes count were divided into lower group and higher group according to the low value of laboratory reference values. The study was a multicenter, retrospective, observational registry with clinicaltrials.gov identifier NCT04292964. All study procedures were approved by the local ethics committee (approval NO. 20200701). All data were collected by experienced researchers using blinded methods.

2.2 Baseline data and follow-up

Demographic and clinical characteristics were collected from the electronic medical record system. Data collection of laboratory results were defined by the results of the first test after admission. The absolute number of lymphocytes was measured by an automatic blood cell analyzer. Peripheral blood lymphocyte subsets were detected by flow cytometry. Data from both clinical centers were standardized, and standardized forms were used to collect clinical data from COVID-19 patients. All COVID-19 patients in the study were followed up from admission till death or discharge. The outcome was defined as the in-hospital death rate.

2.3 Statistical analysis

Continuous data were expressed as mean ± standard deviation (SD) or median (interquartile range) according to the distribution. Categorical variables were presented as frequency rates with percentages. Continuous variables with normal distribution were compared using independent group T-test; otherwise, the Mann-Whitney U test. Categorical data were tested using the Chi-square test and Fisher's exact Chi-square test. Cox proportional-hazards models were used to perform univariate analyses and multivariate analyses to identify the association between $CD4^+$T cell count and in-hospital death. Kaplan-Meier survival analysis with a log-rank test was performed to estimate the cumulative survival rate of groups with higher or lower $CD4^+$T cell count. Statistical analyses were performed by the IBM SPSS Statistics 26.0 software. P (two-sided) value less than 0.05 was considered statistical significance.

3. Results

3.1 Baseline characteristics

Baseline characteristics are shown in Table 1. The average age was 53 years, and 204 (51.6%) were male. Among these cases, fever on admission (263, 66.6%) was the most common symptom. Cough, shortness of breath, fatigue, and sputum production were present in 257 patients (65.1%), 118 patients (29.9%), 107 patients (27.2%), and 102 patients (25.9%), respectively. Headache (36, 9.1%), nausea or vomiting (36, 9.1%), myalgia or arthralgia (34, 8.6%), sore throat (22, 5.6%), and chill (7, 6.7%) were rare in our study. The most frequent comorbidities were hypertension (102, 25.8%) and diabetes (47, 11.3%). The proportion of coronary heart disease, hepatitis B infection, and chronic obstructive pulmonary disease was 6.4% (25/392), 2.3% (9/392), and 1.5% (6/392), respectively.

According to the low value of laboratory reference values of $CD4^+$T cell count, the 395 COVID-19 patients were divided into two groups: lower $CD4^+$T cell group and higher $CD4^+$T cell group. Patients in the lower group were older (55.0±16.5 vs 51.3±14.8, P=0.033), contained more males (115/195 [59.0%] vs 89/111 [44.5%], P=0.004), and more likely to have shortness of breath (75/195 [38.5%] vs 43/200 [21.5%], P<0.001) and fever on admission (141/195 [72.3%] vs 122/200 [61.0%], P=0.017). And, there was no significant difference in the proportion of comorbidities, including hypertension, diabetes, coronary heart disease, hepatitis of B infection, and chronic obstructive pulmonary disease, between the two groups.

Analysis of moderate and severe COVID-19 patients alone also showed the same trend (Supplementary table1, Supplementary table 2).

3.2 Laboratory and Radiographic Findings

Of these 395 COVID-19 patients, median (IQR) values of Hs-CRP (5.0 [2.2-22.9] mg/L) and PCT (0.05 [0.03-0.08] ng/ml) were elevated, while the median (IQR) values of lymphocytes count, $CD4^+$T cell count, $CD8^+$T cell count were within standard ranges (Table1). In moderate patients, only the median (IQR) value of Hs-CRP was elevated. (Supplementary table1.). In severe COVID-19 patients, median (IQR) values of Hs-CRP, PCT, and D-dimer were elevated, while the median (IQR) values of lymphocytes count, $CD4^+$T cell count, $CD8^+$T cell count were decreased. (Supplementary table2). According to lung CT (computed tomography, CT) findings, in all COVID-19 patients, the proportion of ground-glass opacity and local patchy shadowing was 48.7% (170/349) and 38.7% (135/349), respectively.

In terms of laboratory findings, compared with patients in higher $CD4^+$T cell group, patients in the lower $CD4^+$T cell group showed lower median lymphocytes count (0.8 (0.6-1.0) vs 1.5 (1.2-1.8), P<0.001, cells×10^9/L), $CD8^+$T cell count (168.0 [107.0-250.0] vs 322.0 [244.3-443.5], P<0.001, cells/ul), CD4/CD8 (1.4 [1.1-1.9] vs 1.8 [1.4-2.3], P<0.001), but a higher median hypersensitive C-reactive protein (Hs-CRP) (8.2 [5.0-48.5] vs 4.9 [1.1-7.0], P<0.001, mg/L) and procalcitonin (PCT) (0.06 [0.04-0.11 vs 0.04 [0.02-0.06], P<0.001, ng/ml) (Table1). Analysis of moderate and severe COVID-19 patients alone showed that lymphocytes count and $CD8^+$T cell count were more commonly reduced in severe COVID-19 patients. There was no significant change in the proportion of $CD4^+$T cell lower than the lower limit of normal in moderate and severe COVID-19 patients, but the proportion of $CD8^+$T cells lower than the lower limit of normal in moderate and severe COVID-19 patients accounted for 36.0% (71/197) and 51.5% (102/198), respectively. (Figure 2A). The analysis also found that it is the $CD8^+$T cell count that reflects the severity of the patient's condition, not the $CD4^+$T cell count. (Figure 2B).

In terms of computed tomography findings, in moderate COVID-19 patients, compared with patients in the higher group, patients in the lower group more often represented as local patchy shadowing (45 [47.4%] vs 33 [32.4%], P=0.031). Ground-glass opacity and local patchy shadowing did not differ between the two groups in the entire patient population. (Table1).

3.3 Treatment and Clinical outcome

In all cases, the proportion of use of oxygen inhalation, and mechanical ventilation were 84.3% (328/389), and 7.7% (30/388), respectively. The most common therapy is treatment with antiviral treatment (388/395, 98.2%), followed by antibiotic treatment (179/395, 45.3%), glucocorticoids treatment (94/395, 23.8%), intravenous immunoglobulin treatment (71/395, 18.2%), and only four patients (4/395, 1.0%) were treated with antifungal drugs. During follow-up, 27 patients died (27/395, 6.8%), and the rest were discharged (368/395, 93.2%).

Compared with patients in the higher $CD4^+$T cell group, patients in the lower group needed more oxygen inhalation (174/193 ,90.2% vs 154/196, 78.6%, *P*=0.002), mechanical ventilation (26/193, 13.5% vs 4/195, 2.1%, *P*<0.001), antibiotic treatment (112/195, 57.4% vs 67/200, 33.5%, *P*<0.001) and glucocorticoids treatment (64/195, 32.8% vs 30/200, 15.0%, *P*<0.001). Other treatments were similar between the two groups, such as antiviral treatment, intravenous immunoglobulin treatment, and antifungal treatment. The case in-hospital death rate was significantly higher in patients with lower $CD4^+$T cell levels than in those with higher $CD4^+$T cell levels (25/195, 12.8% vs 2/200, 1.0%, *P*<0.001). The detailed treatment of moderate and severe COVID-19 patients was shown in supplementary table1 and supplementary table2.

3.4 Survival curves of in-hospital death

Kaplan-Meier survival curves of the COVID-19 patients grouped by $CD4^+$T cell count are shown in Figure3. The low $CD4^+$T cell group had a higher in-hospital death rate than the high $CD4^+$T cell group during the follow-up period (log rank<0.001). The same trend was also found in severe COVID-19 patients (log rank<0.001). Kaplan-Meier survival analysis was not performed on moderate COVID-19 patients because no patients died during follow-up.

3.5 Results of Cox proportional hazards analyses of in-hospital death

Cox proportional hazard regression analysis was performed to test the associations between the lower $CD4^+$T cell group and in-hospital death for COVID-19 patients (Supplementary Table3). Results of univariate analyses indicated that patients with lower $CD4^+$T cell count exhibited a 13.659-fold increase in in-hospital death compared to patients with higher $CD4^+$T cell count (hazard ratio (HR):13.659; 95% confidence intervals (CI):3.235-57.671). Meanwhile, age, history of hypertension, history of COPD, white blood cell count, lymphocyte count, $CD8^+$T cell lower group (HR: 10.883; 95%CI: 3.277-36.145), required mechanical ventilation or glucocorticoids or intravenous immunoglobulin treatment or antibiotic treatment or antifungal treatment were correlated with the risk of in-hospital death in patients with COVID-19.

Multivariate survival analysis was performed with Cox's proportional hazard regression model to identify the independent factors correlated with prognosis (Table2). After adjusting for age, sex, and temperature (Mode 1), the HR of the lower $CD4^+$T cell group for in-hospital death was 14.182 (95%CI: 1.884-106.786, *P*=0.010). After adjusting for a history of hypertension, a history of diabetes, and shortness of breath (Mode 2), the HR of the lower $CD4^+$T cell group for in-hospital death was 13.631 (95%CI: 3.190-58.243, *P*<0.001). After adjusting for white blood cells, platelet, and creatinine (Mode 3), the HR of the lower $CD4^+$T cell group for in-hospital death was 8.170 (95%CI: 1.877-35.566, *P*=0.005). After adjusting for hypersensitive C-reactive protein, procalcitonin, and D-dimer (Mode4), the HR of the lower $CD4^+$T cell group for in-hospital death was 10.644 (95%CI: 2.439-46.458, *P*=0.002). After adjusting for $CD8^+$T cell lower group and lymphocytes count lower group (Mode 5), the HR of the lower $CD4^+$T cell group for in-

hospital death was 13.650 (95%CI: 1.976-94.279, *P*=0.008); Besides, in this model, the HR of the lower $CD8^+$T cell group for in-hospital death was 2.873 (95%CI: 0.771-10.709, *P*=0.116) after adjusting for other factors, we thus concluded that reduced $CD4^+$T cell was a better predictor of in-hospital death. After adjusting for age, a history of hypertension, shortness of breath, white blood cell count platelet count, D-dimer, and CD4/CD8 (Mode 6), the HR of the lower $CD4^+$T cell count group for in-hospital death was 7.656 (95%CI: 1.610-36.396, *P*=0.010). Multivariate analysis demonstrated that presenting with lower $CD4^+$T cell count was an independent risk factor for in-hospital death. Variables like age, white blood cell count, and shortness of breath also showed significance for independently predicting in-hospital death in this study (Figure4). Similarly, Cox proportional hazards analyses were also performed on severe COVID-19 patients, and the results also suggested that lower $CD4^+$T cell count was an independent risk factor for in-hospital death (Supplementary table4, Supplementary table5, Supplementary figure1).

4. Discussion

This study revealed the relationship between the lymphocyte subsets of COVID-19 patients and the severity of COVID-19 and in-hospital mortality. The dominant symptoms observed in the study included fever on admission, cough, fatigue, and shortness of breath. The most frequent comorbidities were hypertension and diabetes. Compared with patients with higher $CD4^+$T cell levels, patients with lower $CD4^+$T cell levels were older and were more frequently male. In terms of laboratory findings, lymphocytes count, $CD4^+$T cell count, $CD8^+$T cell count were significantly lower in the lower group. Reduction of $CD8^+$T cell was an indicator of the severity of COVID-19. Both decreased $CD4^+$T cell and $CD8^+$T cell were associated with in-hospital death of COVID-19 patients but only decreased $CD4^+$T cell was an independent predictor of in-hospital death of COVID-19 patients.

We found $CD8^+$T cell reduction was associated with the severity of COVID-19. Previous studies suggested that $CD4^+$T cell and $CD8^+$T cell were reduced in the vast majority of patients with either severe or moderate COVID-19 patients [4, 8]. Reductions in $CD4^+$T cell and $CD8^+$T cell were associated not only with the severity of COVID-19 but also with adverse outcomes [8, 9]. In the present study, we found that decreased $CD4^+$T cell and $CD8^+$T cell were common in COVID-19 patients; there was no significant difference in the reduction of $CD4^+$T cell between moderate and severe COVID-19 patients, while $CD8^+$T cell was more likely to be reduced in severe COVID-19 patients, suggesting that the reduction of $CD8^+$T cell could reflect the severity of the disease. This result was similar to the previous report, which pointed out that the reduction of $CD8^+$T lymphocyte subsets was associated with the severity of COVID-19 [10]. The reason may be that $CD8^+$T cytotoxic cells can promote virus clearance by producing many bioactive molecules such as perforin, granzyme and interferon; thus decreased $CD8^+$T cell can reflect the severity of COVID-19[11].

We found it was $CD4^+$T cell reduction, not $CD8^+$T cell reduction, which was the independent risk for in-hospital death of COVID-19 patients. We conducted the univariate analysis, the same as previous reports.

The results confirmed that decreased $CD4^+$T cell and $CD8^+$T cell was associated with poor prognosis of COVID-19 patients. We also performed Cox's proportional hazard regression, which suggested that after adjusting for other confounding factors, only $CD4^+$T cell reduction was the independent risk for in-hospital death of COVID-19 patients. Lymphocyte and subsets play an important role in maintaining immune system function. $CD8^+$T cell is crucial to directly attacking and killing virus-infected cells, $CD4^+$T cell can affect the differentiation and maturation of other cells by producing cytokines and chemokines, and the secretion of interferon-γ is a T-cytokine with both antiviral and immune activity [12, 13]. Patients infected with SARS-CoV-2 show a Th1 cell response and use cellular immunity to control the infection [14]. Viral infection causes comprehensive changes in cellular immunity, manifested by lymphopenia, changes in T cell subpopulation distribution, and increased cytokine concentration [15]. But the mechanisms of SARS-CoV-2 infection leading to decreased lymphocyte and subsets remains unclear. It was reported that the elevated concentration of IL-10, Interleukin-6 (IL-6), and TNF-α were negatively correlated with the total T-cell count, $CD4^+$T cell count, and $CD8^+$T cell count, respectively. Compared with patients in the illness period, levels of IL-10, IL-6, and TNF-α in the patients in the decline stage decreased significantly, while the total T-cell counts, $CD4^+$T cell count, and $CD8^+$T cell count were recovered [16, 17]. The phenomena suggested the decrease of T-cells in COVID-19 patients may be due to the negative effects of high concentrations of TNF-α, IL-6, IL-10 in serum on the survival or proliferation of T-cells [16].And, studies reported angiotensin-converting enzyme 2 (ACE2) is expressed in white blood cells, lymphopenia may be due to the direct lethal effect of SARS-COV-2 on lymphocytes through its binding to ACE2 receptors[18, 19].

Increased age and increased white blood cell count in our study were associated with in-hospital death, which was similar to several reports. It was shown that the total case fatality rate increased with age in COVID-19 patients, possibly because they often had other chronic diseases, as well as a decrease in lymphocyte and subsets with age [20]. A previous study suggested that white blood cell count and neutrophil count of dead patients were higher than those of surviving patients, which may be related to cytokine storm caused by the invasion of SARS-Cov-2 [21]. It was reported patients with malignancy or immune system diseases may have an increased risk of severe COVID-19 and death [22]. To avoid these confounders, our study excluded all patients with malignancy or immune system diseases.

This study was limited by sample size and lack of dynamic detection of $CD4^+$T cell and $CD8^+$T cell. First, our study only analyzed 395 patients with COVID-19, the relatively small sample sizes may affect the statistical power. Secondly, the patients included in this study lacked dynamic measurements of $CD4^+$T cell and $CD8^+$T cell, which made the evaluation of the relationship between $CD4^+$T cell and disease changes in patients with COVID-19 incomplete.

5. Conclusions

In conclusion, the main findings of the study were that it was the $CD8^+$T cell, not the $CD4^+$T cell, that reflected the severity of the patient's disease; And, the high prognostic value of decreased $CD4^+$T cell in

patients with COVID-19. Both decreased $CD4^+$T cell and $CD8^+$T cell were associated with in-hospital death of COVID-19 patients, but only $CD4^+$T cell reduction was independently associated with increased in-hospital death of COVID-19 patients. Thus, in this acute-care setting, $CD4^+$T cells can provide early prognostic information in patients with COVID-19.

Abbreviations

COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell count; Hb, Hemoglobin; PLT, platelet; LYM, lymphocyte; ALT, alanine aminotransferase; Cr, creatinine; Hs-CRP, hypersensitive C-reactive protein; PCT, procalcitonin.

Declarations

Ethics approval and consent to participate: All study procedures were approved by the local ethics committee (approval NO. 20200701). Due to the urgency of the disease at the time, the patient's verbal consent was obtained during the data collection.

Consent for publication: Not Applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: All authors declare no conflict of interest.

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Authors' Contributions: W.X. participated in study design, analyzing data analysis, and manuscript writing. G.L., C.X., J.D., H.B., C.Y., L.P., and T.X. were involved in data collection. Q.S., C.G., and Z.D. were responsible for the study concept, design, and final approval of the manuscript. W.X. is the first author. All authors have read and approved the final manuscript.

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Tables

Table 1. Baseline characteristics of different degrees of $CD4^+$ T cell in all patients.

Variables	All(N=395)	CD4+T: lower than the normal low limit (N=195)	CD4+T: higher than the normal low limit (N=200)	*P*	Missing data
Baseline					
Male/female(n)	204/191	115/80	89/111	0.004	
Age(years)	53.1±15.7	55.0±16.5	51.3±14.8	0.033	
Temperature (℃)	36.8 (36.5-37.3)	36.9 (36.6-37.6)	36.8 (36.5-37.1)	0.036	31 (7.8%)
Heart rate (min)	85.0 (77.0-94.0)	85.0 (78.0-96.0)	84.5 (76.0-92.0)	0.103	4 (1.0%)
SBP (mmHg)	126.0 (116.0-136.0)	126.0 (115.0-136.5)	126.0 (117.0-136.0)	0.577	6 (1.5%)
DBP (mmHg)	78.0 (70.0-85.0)	76.0 (70.0-85.0)	78.0 (71.0-85.0)	0.741	6 (1.5%)
Symptoms and signs—No, %					
Fever on admission	263 (66.6%)	141 (72.3%)	122 (61.0%)	0.017	
Nasal congestion	2 (0.5%)	2 (1.0%)	0 (0%)	0.243	
Headache	36 (9.1%)	20 (10.3%)	16 (8.0%)	0.436	
Cough	257 (65.1%)	138 (70.8%)	119 (59.5%)	0.019	
Sore throat	22 (5.6%)	10 (5.1%)	12 (6.0%)	0.706	
Sputum production	102 (25.9%)	56 (28.9%)	46 (23.0%)	0.184	1 (0.3%)
Fatigue	107 (27.2%)	59 (30.4%)	48 (24.0%)	0.153	1 (0.3%)
Shortness of breath	118 (29.9%)	75 (38.5%)	43 (21.5%)	<0.001	
Nausea or vomiting	36 (9.1%)	23 (11.8%)	13 (6.5%)	0.068	
Myalgia or arthralgia	34 (8.6%)	20 (10.3%)	14 (7.0%)	0.249	
Chill	12 (3.0%)	8 (4.1%)	4 (2.0%)	0.223	
Throat congestion	3 (0.8%)	0 (0%)	3 (1.5%)	0.248	

Coexisting disorders—No, %					
Diabetes	47 (11.9%)	22 (11.3%)	25 (12.5%)	0.709	
Hypertension	102 (25.8%)	48 (24.6%)	54 (27.0%)	0.588	
Coronary heart disease	25 (6.4%)	15 (7.7%)	10 (5.1%)	0.277	3 (0.8%)
Hepatitis B infection	9 (2.3%)	6 (3.1%)	3 (1.5%)	0.334	3 (0.8%)
COPD	6 (1.5%)	5 (2.6%)	1 (0.5%)	0.119	3 (0.8%)
Laboratory findings					
WBC ($\times 10^9$/L)	5.3 (4.2-7.0)	5.0 (3.8-7.0)	5.6 (4.5-7.0)	0.008	2 (0.5%)
Hb (g/L)	131.0 (118.5-143.0)	132.0 (117.0-143.0)	129.0 (120.0-142.3)	0.809	2 (0.5%)
PLT ($\times 10^9$/L)	189.0 (145.5-252.0)	160.0 (129.0-214.0)	220.5 (170.0-364.0)	<0.001	2 (0.5%)
LYM ($\times 10^9$/L)	1.1 (0.8-1.5)	0.8 (0.6-1.0)	1.5 (1.2-1.8)	<0.001	6 (1.5%)
LYM<1.1$\times 10^9$/L	199 (51.2%)	163 (84.5%)	27 (13.8%)	<0.001	6 (1.5%)
ALT (U/L)	23.0 (15.0-39.0)	24.1 (15.4-38.8)	22.0 (15.0-39.0)	0.388	4 (1.0%)
Cr (umol/L)	64.0 (53.0-78.0)	66.5 (56.0-79.0)	61.0 (50.0-77.0)	0.005	5 (1.3%)
D-dimer (mg/L)	0.43 (0.24-0.99)	0.50 (0.28-1.12)	0.38 (0.22-0.84)	0.023	14 (3.5%)
K (mmol/L)	4.0 (3.7-4.3)	4.0 (3.6-4.3)	4.1 (3.7-4.3)	0.243	6 (1.5%)
Hs-CRP (mg/L)	5.0 (2.2-22.9)	8.2 (5.0-48.5)	4.9 (1.1-7.0)	<0.001	45 (11.4%)
PCT (ng/ml)	0.05 (0.03-0.08)	0.06 (0.04-0.11)	0.04 (0.02-0.06)	<0.001	21 (5.3%)
$CD4^+$T cell count	410.0 (265.0-567.0)	262.0 (188.0-325.0)	564.0 (478.5-716.0)	<0.001	
$CD8^+$T cell	246.0 (154.0-	168.0 (107.0-250.0)	322.0 (244.3-443.5)	<0.001	

count	348.0)				
CD4/CD8 ratio	1.6 (1.2-2.2)	1.4 (1.1-1.9)	1.8 (1.4-2.3)	<0.001	
Abnormalities on chest CT—No,%					
Ground-glass opacity	170 (48.7%)	78 (46.7%)	92 (50.5%)	0.473	46 (11.6%)
Local patchy shadowing	135 (38.7%)	71 (42.5%)	64 (35.2%)	0.159	46 (11.6%)
Treatment					
Oxygen inhalation	328 (84.3%)	174 (90.2%)	154 (78.6%)	0.002	6 (1.5%)
Glucocorticoids	94 (23.8%)	64 (32.8%)	30 (15.0%)	<0.001	
Antiviral treatment	388 (98.2%)	191 (97.9%)	197 (98.5%)	0.721	
Intravenous immunoglobulin	71 (18.2%)	37 (19.2%)	34 (17.3%)	0.625	5 (1.3%)
Antibiotic treatment	179 (45.3%)	112 (57.4%)	67 (33.5%)	<0.001	
Antifungal treatment	4 (1.0%)	2 (1.0%)	2 (1.0%)	1.000	
Clinical outcome					
Death (No,%)	27 (6.8%)	25 (12.8%)	2 (1.0%)	<0.001	

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; COPD, Chronic obstructive pulmonary disease; WBC, white blood cell count; Hb, Hemoglobin; PLT, platelet count; LYM, lymphocyte; ALT, alanine aminotransferase; Cr, creatinine; Hs-CRP, hypersensitive C-reactive protein; PCT, procalcitonin.

Table2. Results of multivariate Cox proportional-hazards regression analyzing the effect of baseline variables on in-hospital death in all patients with COVID-19.

Mode	HR (95%CI)	*P*
Not Adjusted $CD4^+$T, low vs. high	13.659 (3.235-57.671)	<0.001
Mode 1		
$CD4^+$T cell, low vs. high	14.182 (1.884-106.786)	0.010
Sex, male vs. female	1.383 (0.561-3.406)	0.481
Age, per 1 year	1.093 (1.052-1.135)	<0.001
Temperature, per 1℃	0.777 (0.445-1.354)	0.372
Mode 2		
$CD4^+$T cell, low vs. high	13.631 (3.190-58.243)	<0.001
Hypertension, yes vs. no	5.823 (2.595-13.070)	<0.001
Diabetes, yes vs. no	0.824 (0.322-2.113)	0.688
Shortness of breath, yes vs. no	7.848 (2.942-20.934)	<0.001
Mode 3		
$CD4^+$T cell, low vs. high	8.170 (1.877-35.566)	0.005
WBC, per 1×10^9/L	1.294 (1.193-1.404)	<0.001
PLT, per 1×10^9/L	0.992 (0.987-0.997)	0.003
Cr, per 1 umol/L	1.002 (0.995-1.009)	0.576
Mode 4		
$CD4^+$T cell, low vs. high	10.644 (2.439-46.458)	0.002
Hs-CRP, per 1 mg/L	0.989 (0.974-1.005)	0.193
PCT, per 1 ng/ml	1.017 (0.925-1.118)	0.724
D-dimer, per 1 mg/L	1.028 (1.018-1.038)	<0.001
Mode 5		
$CD4^+$T cell, low vs. high	13.650 (1.976-94.279)	0.008
$CD8^+$T cell, low vs. high	3.159 (0.853-11.707)	0.085
CD4/CD8 ratio, per 1 unit	1.422 (1.105-1.830)	0.006
LYM count, low vs. high	0.996 (0.306-3.243)	0.994
Mode 6		

$CD4^+$T cell, low vs. high	7.656 (1.610-36.396)	0.010
Age, per 1 year	1.074 (1.034-1.115)	<0.001
Hypertension, yes vs. no	2.031 (0.766-5.386)	0.154
Shortness of breath, yes vs. no	3.435 (1.167-10.114)	0.025
WBC, per 1×10^9/L	1.224 (1.097-1.366)	<0.001
PLT, per 1×10^9/L	0.996 (0.991-1.001)	0.149
D-dimer, per 1 mg/L	0.997 (0.992-1.002)	0.207
CD4/CD8 ratio, per 1 unit	1.106 (0.793-1.542)	0.552

Abbreviations: WBC, white blood cell count; PLT, platelet count; Cr, creatinine; Hs-CRP, hypersensitive C-reactive protein; PCT, procalcitonin; LYM, lymphocyte.

Figures

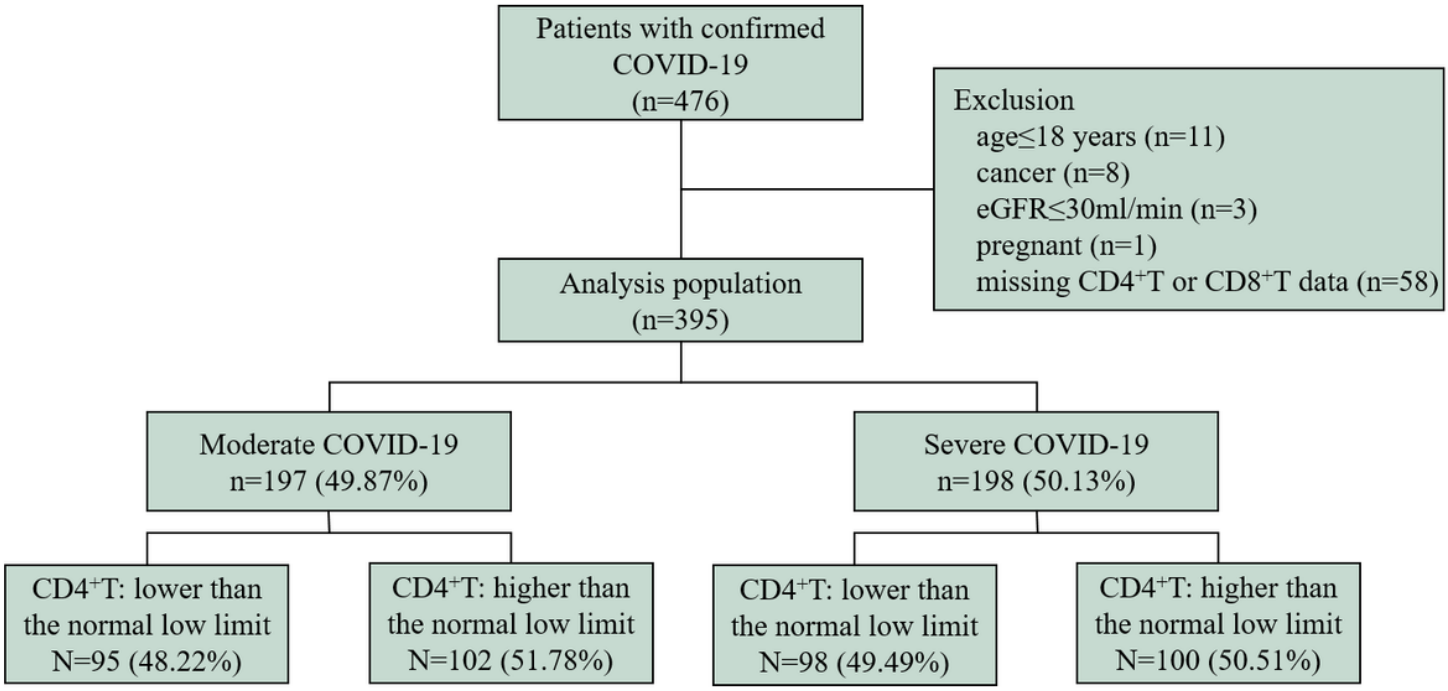

Figure 1

Flow diagram of Patient Recruitment

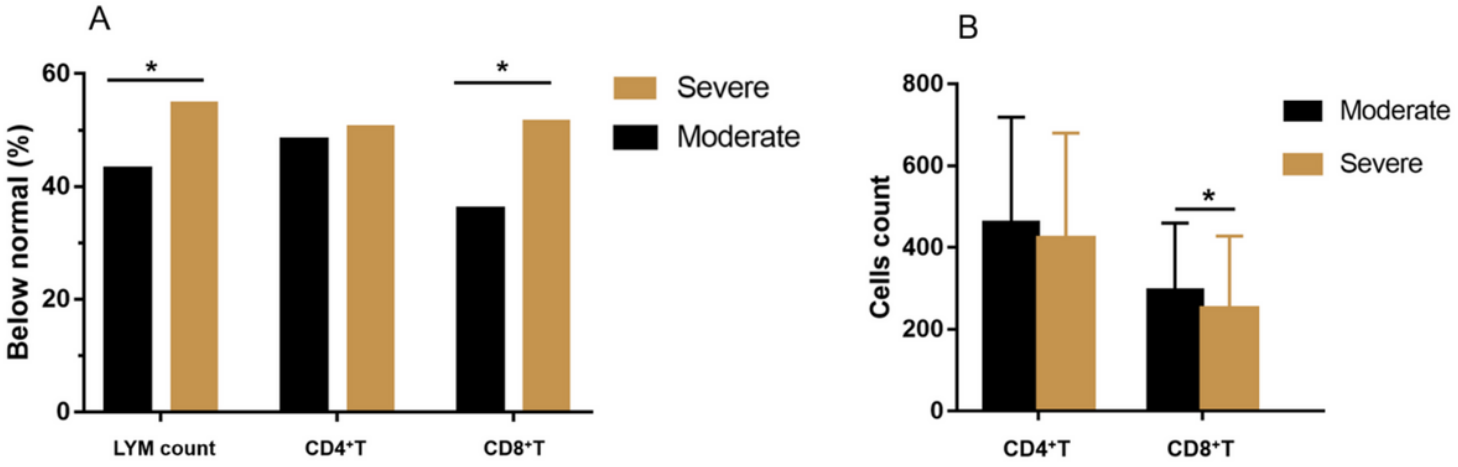

Figure 2

A: The histogram shows the proportion of moderate and severe patients with lymphocytes, CD4+T cell, and CD8+T cell below the lower limit of normal; B: The histogram shows the number of CD4+T cell and CD8+T cell in moderate and severe patients.

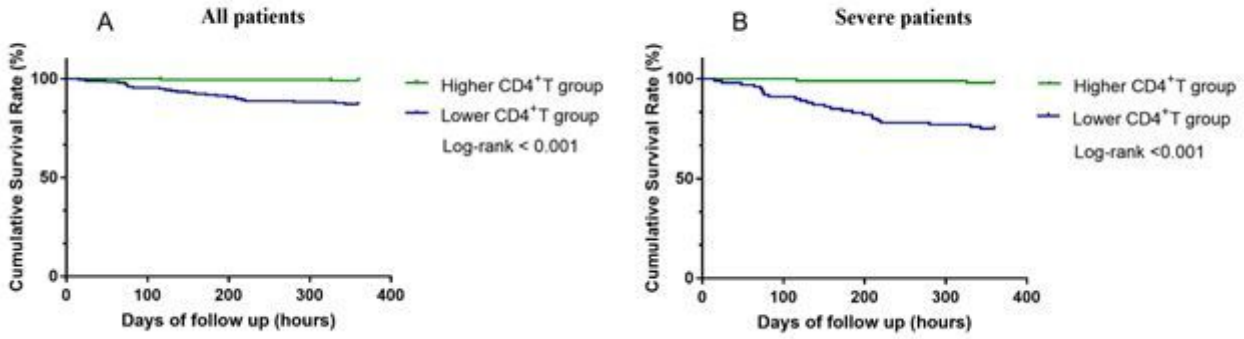

Figure 3

Kaplan-Meier plots showing the survival rate of COVID-19 patients who were stratified into two groups according to CD4+T cell count. (green line, higher CD4+T group; blue line, lower CD4+T group).

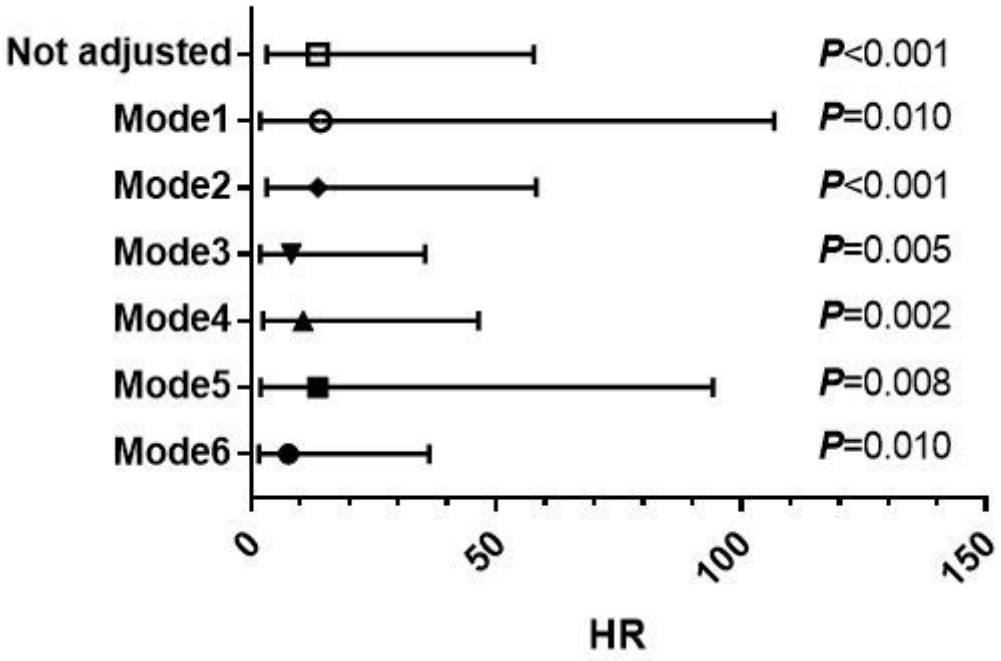

Figure 4

Forest plots of multivariate Cox proportional-hazards regression analyzing the effect of baseline variables on in-hospital death in all patients with COVID-19. Mode1: adjusted sex, age, and temperature; Mode2: adjusted hypertension, diabetes, and shortness of breath; Mode3: adjusted white blood cell count, platelet count, and Creatinine; Mode4: adjusted hypersensitive C-reactive protein, procalcitonin, and D-dimer; Mode5: adjusted CD8+T cell group, CD4/CD8 ratio, and lymphocyte count group; Mode6: adjusted age, hypertension, shortness of breath, white blood cell count, platelet count, D-dimer, and CD4/CD8 ratio.

Supplementary Files

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- Additionalfiles.docx