Prognostic value of CD4+T cell in patients with severe COVID-19

xuesong wen[1], Lei Gao[1], dan jiang[2], xiaocheng cheng[1], bin he[1], yue chen[1], peng lei[1], xiaowei tan[1], shu qin[1], guoqiang cai[3], and dongying zhang[1]

[1]Chongqing Medical University First Affiliated Hospital
[2]The First Branch of the First Affiliated Hospital of Chongqing Medical University
[3]Traditional Chinese Medicine hospital Dianjiang Chongqing

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Abstract

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. Finding markers that predict the prognosis of patients with severe COVID-19 are of great value. Methods In this single-center,retrospective study, 157 patients with severe COVID-19 were recruited from a consecutive series. After screening, a total of 105 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 cells level, patients with lower CD4+T cells level were older and were more frequently male. In terms of laboratory findings, lymphocyte percentage, lymphocyte absolute value, CD3+T cell count, CD4+T cell count, CD8+T cell count were significantly lower in low group than in high group. The case in-hospital death rate was significant higher in patients with lower CD4+T level than in those with higher CD4+T level. After adjusting for potential confounding factors, CD4+T cells count below normal values showed independent prognostic value for all-cause in-hospital death in patients with severe COVID-19. Conclusions In patients with severe COVID-19, lower CD4+T cells count are independently associated with an increased rate of in-hospital death.

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Introduction

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. As of April 15, the Chinese Center for Disease Control and Prevention announced a total of 83,797 confirmed cases and 3,352 deaths in 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]. Finding markers that predict the prognosis of patients with severe 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 patients[3,4]. A recent study recruited 21 patients with COVID-19 including 11 severe patients and 10 moderate patients. The study showed absolute number of T lymphocytes, $CD4^+$T and $CD8^+$T cells decreased in almost all the patients, and significantly lower in severe patients (294.0, 177.5 and 89.0×10^6/L) than moderate 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 cells[4]. T-lymphocytes play a critical role in antiviral immunity. $CD4^+$T lymphocyte subsets secretes high level of effector cytokines, especially interferon-γ (IFN-γ), which are essential for virus clearance[5,6]. 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 is no research concerning whether $CD4^+$T predicted outcomes of COVID-19 patients.

Results

Baseline characteristics

Baseline characteristics are shown in Table 1. The median age was 62 years (range, 49-69 years), and 53 (50.5%) were male. Among these cases, fever on admission (90, 85.7%) was the most common symptom. Cough, fatigue, shortness of breath, and sputum production were present in 65 patients (61.9%), 38 patients (36.2%), 37 patients (35.2), and 30 patients (28.6%), respectively. Myalgia or arthralgia (8, 7.6%), chill (7, 6.7%), nausea or vomiting (7, 6.7%), headache (4, 3.8%), throat congestion (2, 1.9%), and nasal congestion (1, 1.0%) were rare in our study. The most frequent comorbidities were hypertension (23, 21.9%) and diabetes (16, 15.2%). The proportion of coronary heart disease, hepatitis B infection, and chronic obstructive pulmonary disease was 8.6% (9/105), 1.9% (2/105), and 1.0% (1/105), respectively.

According to the normal value of $CD4^+$T cells, the 105 severe COVID-19 patients were divided into two groups: low $CD4^+$T cell count (<404 cells/ul) group and high $CD4^+$T cell count ([?]404 cells/ul) group. Patients in the low group compared with patients in the high group were older (66.0 [54.0-75.0] vs 57.5 [46.8-65.0], P =0.004), contained more males (31/47 [66.0%] vs 22/58 [37.9%],P =0.004), and more likely to have shortness of breath (23/47 [48.9%] vs 14/58 [24.1%], P =0.008) and chill (6/47 [12.8%] vs 1/58 [1.7%], P= 0.043). And, there were 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.

Laboratory and Radiographic Findings

The laboratory and radiologic findings are displayed in Table 1. Of these 105 patients, median (IQR) value of D-dimer (0.56 [0.34-3.95] mg/L) was elevated, while the median (IQR) values of red blood cell count (4.17 [3.72-4.57] cells$\times10^{12}$/L), Hemoglobin (125.0 [117.0-140.0] g/L), high density lipoprotein (0.90 [0.76-1.06] mmol/L), and $CD3^+$T absolute value (706.0 [459.5-921.0] cells/ul) were decreased. The median levels of other laboratory indicators were within standard ranges, such as white blood cell count, platelet count, lymphocyte percentage, lymphocyte count, alanine aminotransferase, aspartate transaminase, creatinine, estimated glomerular filtration rate, uric acid, electrolyte levels, total cholesterol, triglyceride, and low density lipoprotein. According to lung CT (computed tomography, CT) findings, the proportion of ground-glass opacity and local patchy shadowing was 47.6% (50/105) and 30.5% (32/105), respectively.

In terms of laboratory findings, compared with patients in the high $CD4^+$T cell count group, patients in the low $CD4^+$T cell count group showed lower median platelet count (176.0 [125.0-229.0] vs 230.5 [178.25-303.25],P =0.001, cells$\times10^9$/L), lymphocyte percentage (14.2 [6.3-23.5] vs 27.2 [21.9-35.6], P <0.001), lymphocyte count (0.79±0.314 vs 1.35±0.362, P <0.001, cells$\times10^9$/L), estimated glomerular filtration rate (90.48 [59.0-107.22] vs 101.2 [95.25-109.82], P =0.006, ml/min), total cholesterol (3.50 [3.09-4.03] vs 3.84 [3.41-4.52], P =0.016, mmol/L), low density lipoprotein (2.10 [1.74-2.60] vs 2.40 [2.02-2.97], P =0.031, mmol/L), $CD3^+$T cell count (437.0 [224.0-606.0] vs 881.5 [760.8-1034.2], P <0.001, cells/ul), $CD4^+$T cell count (240.0 [123.0-325.0] vs 546.5 [475.0-651.5], P <0.001, cells/ul), $CD8^+$T cell count (153.0 [64.0-242.0] vs 293.0 [226.8-424.3],

P <0.001, cells/ul), but a higher median creatinine level (68.5 [53.8-85.8] vs 55.5 [48.3-68.0],P =0.005, umol /L). In terms of computed tomography findings, compared with patients in the low group, patients in the high group more often represented as local patchy shadowing (23 [39.7%] vs 9 [19.1%], P =0.023), and the proportion of patients with ground-glass opacity was no significant difference between the two groups.

Treatment and Clinical outcome

In all cases, the proportion of use of oxygen inhalation, and mechanical ventilation were 81.0% (85/105), and 9.5% (10/105), respectively. The most common therapy is treatment with antiviral treatment (103/105, 98.1%), followed by antibiotic treatment (77/105, 73.3%), intravenous immunoglobulin treatment (49/105, 46.7%), glucocorticoids treatment (42/105, 40.0%), and only five patients (5/105, 4.8%) were treated with antifungal drugs. During follow-up, 22 patients died (22/105, 21.0%), and the rest were discharged (83/105, 79.0%).

Compared with patients in the high $CD4^+$T cells count group, patients in the low $CD4^+$T cells count group needed more oxygen inhalation (42/47, 93.3% vs 43/58, 78.2%,P =0.035), mechanical ventilation (8/47, 81.0% vs 2/58, 3.7%,P =0.041), and antibiotic treatment (40/47, 85.1% vs 37/57, 63.8%, P =0.014). Other treatments were similar between the two groups, such as glucocorticoids, antiviral treatment, intravenous immunoglobulin treatment, and antifungal treatment. The case in-hospital death rate was significant higher in patients with lower $CD4^+$T level than in those with higher $CD4^+$T level (20/47, 42.6% vs 2/58, 3.4%,P <0.001).

Survival curves of in-hospital death

Kaplan-Meier survival curves of the severe COVID-19 patients grouped by $CD4^+$T cells count are shown in Figure 2. The low $CD4^+$T cells count group (<404 cells/ul) had a higher in-hospital death rate than the high $CD4^+$T cells count group ([?]404 cells/ul) during the follow-up period (log rank<0.001).

Results of Cox proportional hazards analyses of in-hospital death

Cox proportional hazard regression analysis was performed to test the associations between the low $CD4^+$T cells count group and in-hospital death for severe COVID-19 patients. Results of univariate analyses indicated that patients with CD4+T<440 cells/ul exhibited a 15.72-fold increase in in-hospital death compared to patients with $CD4^+$T[?]440 cells/ul (hazard ratio (HR) :15.72; 95% confidence intervals (CI):3.67-67.35). Meanwhile, age, history of hypertension, white blood cell count, platelet count, lymphocyte count, lymphocyte count low group, creatinine, estimated glomerular filtration rate, D-dimer, sodium ions, $CD3^+$T cells low group, $CD8^+$T low group, presenting ground-glass opacity or local patchy shadowing on CT imaging, required mechanical ventilation or glucocorticoids or intravenous immunoglobulin treatment or antifungal treatment were correlated with the risk of in-hospital death in patients with severe COVID-19 (Table 2).

Multivariate survival analysis was performed with Cox's proportional hazard regression model to identify the independent factors correlated with prognosis. After adjusting for age, history of hypertension and history of coronary heart disease (Mode 1), the HR of the low $CD4^+$T cells count group for in-hospital death was 8.763 (95%CI: 1.925-39.885, P =0.005). After adjusting for history of diabetes, lymphocyte count low group and platelet count (Mode 2), the HR of the low $CD4^+$T cells count group for in-hospital death was 11.582 (95%CI: 2.269-59.125, P =0.003). After adjusting for D-dimer, creatinine and estimated glomerular filtration rate (Mode 3), the HR of the low $CD4^+$T cells count group for in-hospital death was 8.635 (95%CI: 1.878-39.701,P =0.006). After adjusting for $CD3^+$T low group, $CD8^+$T low group and white blood cell count (Mode 4), the HR of the low $CD4^+$T cells count group for in-hospital death was 8.028 (95%CI: 1.366-47.192, P =0.021). After adjusting for white blood cell count, age, platelet count and D-dimer (Mode 5), the HR of the low group for in-hospital, the HR of the low $CD4^+$T cells count group for in-hospital death was 5.754 (95%CI: 1.233-26.865, P =0.026). Multivariate analysis demonstrated that presenting with $CD4^+$T cells count below 404 cells/ul was an independent risk factor for in-hospital death. Variables like white blood cell count, age and platelet count also showed significance for independently predicting in-hospital death in this study (Table 3).

Discussion

This study for the first time showed the relationship between $CD4^+$T cells count and in hospital death in severe COVID-19 patients. 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 cells level, patients with lower $CD4^+$T cells level were older and were more frequently male. In terms of laboratory findings, lymphocyte percentage, lymphocyte absolute value, $CD3^+$T cell count, $CD4^+$T cell count, $CD8^+$T cell count were significantly lower in low group than in high group. The case in-hospital death rate was significant higher in patients with lower $CD4^+$T level than in those with higher $CD4^+$T level. After adjustment for potential confounding factors, the low group remained a significant predictor for in-hospital death.

Previous studies have shown that $CD4^+$T cells count was reduced significantly in COVID-19 patients[4]. It is suggested that $CD4^+$T cells and $CD8^+$T cells were reduced below the lower limit of normal in the vast majority of patients with either severe or moderate, and both of them were reduced profoundly in severe patients than in moderate patients[4]. In the present study, among 105 patients with severe COVID-19, 44.8% patients (47/105) showed decreased $CD4^+$T cells count and the in-hospital death was markedly higher in patients with decreased $CD4^+$T cells count than in patients with normal $CD4^+$T cells count (42.6% vs 3.4%, P <0.001). In addition, our study found that increased age, increased white blood cell count, and decreased platelet count were associated with in-hospital death, which were similar with several studies. Verity, et al. estimated that the total case fatality rate increased with age, with the case fatality rate of patients <60 years old being 0.32% (95% CI: 0.27-0.38) and the case fatality rate of patients [?]60 years old being 6.4% (95% CI: 5.7-7.2) , possibly because they often had other chronic diseases[8]. Wang, et al. 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[9]. Meanwhile, A meta-analysis showed that there was a significant reduction in platelets in patients dying from COVID-19, and low platelet count was associated with mortality in patients with COVID-19; The reason may be the decrease of the number of pulmonary vascular beds and the change of morphology that lead to deranged platelet defragmentation[10].

Several recent studies indicated that the absolute value of lymphocytes[1,11] and T-lymphocytes[3,12] were reduced in most patients with COVID-19. It was believed that SARS-CoV-2 may act mainly on lymphocytes, especially T-lymphocytes[4,7]. At present, the potential mechanisms undergoing $CD4^+$T cells count decrease induced by SARS-CoV-2 infection is still unknown. Researchers analyzed the clinical characteristics of patients with COVID-19, consistently found that patients with COVID-19, especially those with severe COVID-19, had significantly higher concentrations of Interleukin-10 (IL-10), interferon-inducible protein 10 (IP10) , monocyte chemo-attractant protein 1 (MCP-1/CCL2), macrophage inflammatory protein-1α (MIP1A/CCL3), tumor necrosis factor alpha (TNF-α)[2]. Meanwhile, it is reported that the concentration of IL-10, Interleukin-6 (IL-6), and TNF-α were negatively correlated with total T-cell counts, $CD4^+$T cells count, and $CD8^+$T cells 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 cells count, and $CD8^+$T cells count were recovered[12]. The phenomena suggested the decrease in the number of T-cells in patients with COVID-19 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[12]. In addition, Previous studies have shown that, in SARS patients, the formation of autoimmune antibodies or immune complexes induced by viral infection and the use of steroids may play an important role in lymphocytic decline[13].

This study was limited by sample size and lack of dynamic detection of CD4+T cells and CD8+T cells. First, our study only analyzed 105 patients with severe 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 cells and CD8+T cells count, which made the evaluation of the relationship between CD4 levels and disease changes in patients with severe COVID-19 incomplete.

In conclusion, the main finding of this study is the high prognostic value of decreased $CD4^+$T cells count in patients with severe COVID-19. Lower CD^+4 T cells count are independently associated with increased in-

hospital death. Thus, in this acute-care setting, $CD^{+}4$ T cells count can provide early prognostic information in patients with severe COVID-19.

Methods

Subjects

Medical records from 157 patients with confirmed severe COVID-19 were collected in in Hubei General Hospital during the management by national medical team. Missing CD4+T or CD+8T data (n=44), malignant tumor (n=3), stroke (n=3), and died within 24 hours of admission (n=2) were excluded. Finally, 105 patients 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. CD3+T cells count, CD4+T cells count, CD8+T cells count and lymphocyte count were classified as low group and high group according to the laboratory reference values (low group: CD3+T<723 cells/ul; CD4+T<404 cells/ul; CD8+T<220 cells/ul; lymphocyte count<1.1×109 cells/L). The study was a single-center, 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.

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. All the laboratory data were processed in a same laboratory with the same standard. All patients in the study were followed up from admission till death or discharge. The outcome was defined as the in-hospital death rate.

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 cells count and in-hospital death. Kaplan-Meier survival analysis with log-rank test was performed to estimate the cumulative survival rate of groups with higher or lower CD4+T cells count. Statistical analyses were performed by the IBM SPSS Statistics 20.0 software. P (two-sided) value less than 0.05 was considered statistical significance.

Study approval: The study was conducted in accordance with the "Declaration of Helsinki" and approved by the ethics committee of the first affiliated hospital of Chongqing medical university (approval No. 20200701). Due to the rapid emergence of this infectious disease, the written informed consent was not signed, but the patient was informed orally.

Author 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 manuscript. All authors have read and approved the final manuscript. W.X. is the first author.

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References

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med,* 2020 Feb 28, doi: 10.1056/NEJMoa2002032.

2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* , 2020 Feb 15;395(10223):497-506.

3. Wei-jie Guan, Zheng-yi Ni, Yu Hu, Wen-hua Liang, Chun-quan Ou, Jian-xing He, Lei Liu, Hong Shan, Chun-liang Lei, David SC Hui et al. Clinical characteristics of 2019 novel coronavirus infection in China. medRxiv 2020.02.06.20020974; doi: https://doi.org/10.1101/2020.02.06.20020974.

4. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, Wang T, Zhang X, Chen H, Yu H et al. Clinical and immunologic features in severe and moderate Coronavirus Disease 2019. *J Clin Invest* . 2020 Mar 27. doi: 10.1172/JCI137244.

5. Sarawar, S. R., M. Sangster, R. L. Coffman, P. C. Doherty. Administration of anti-IFN-gamma antibody to beta 2-microglobulin-deficient mice delays influenza virus clearance but does not switch the response to a T helper cell 2 phenotype. J. Immunol. 1994. 153: 1246–1253.

6. Topham, D. J., R. A. Tripp, S. R. Sarawar, M. Y. Sangster, P. C. Doherty. Immune CD4+ T cells promote the clearance of influenza virus from major histocompatibility complex class II2/2respiratory epithelium. J. Virol. 1996.70: 1288–1291.

7. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020 Feb 15;395(10223):507-513

8. Verity R, Okell LC, Dorigatti I, Winskill P, Whittaker C, Imai N, Cuomo-Dannenburg G, Thompson H, Walker PGT, Fu H et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. Lancet Infect Dis. 2020 Mar 30. doi: 10.1016/S1473-3099(20)30243-7.

9. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020 Feb 7. Doi: 10.1001/jama.2020.1585.

10. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. Clin Chim Acta. 2020 Mar 13; 506: 145-148. Doi: 10.1016/j.cca.2020.03.022.

11. Zhang BC, Zhou XY, Qiu YR, Feng F, Feng J, Jia YF, Zhu HC, Hu K, Liu JS, Liu ZM et al. Clinical characteristics of 82 death cases with COVID-19. MedRxiv, 2020.02.26.20028191; doi:*https://doi.org/10.1101/2020.02.26.20028191*.

12. Diao B, Wang CH, Tan YJ, Chen XW, Liu Y, Ning LF, Chen L, Li M, Liu YP, Wang G et al. Reduction and Functional Exhaustion of T Cells in Patients with Coronavirus Disease 2019 (COVID-19). MedRxiv, 2020.02.18.20024364; doi:*https://doi.org/10.1101/2020.02.18.20024364*.

13. Yang M, Li CK, Li K, Hon KL, Ng MH, Chan PK, et al. Hematological findings in SARS patients and possible mechanisms (review). Int J Mol Med. 2004;14(2):311-5.

Table 1. Baseline patient characteristics of different degrees of $CD4^+$ T cell.

Variables		$CD4^+T<404/ul$	$CD4^+T[?]4$
	All(n=105)	(n=47)	(n=58)
Male/female(n)	53/52	31/16	22/36
Age(years)	62.0(49.0-69.50)	66.0(54.0-75.0)	57.5(46.75-6
Smoking history—No, %	4(3.8%)	1(2.1%)	3(5.2%)
History of alcohol intake—No, %	1(1.0%)	1(2.1%)	0(0%)

Variables		$CD4^+T<404$/ul	$CD4^+T$[?]4
Symptoms and signs—No, %	Symptoms and signs—No, %	Symptoms and signs—No, %	Symptoms
Fever on admission	90(85.7%)	40(85.1%)	50(86.2%)
Nasal congestion	1(1.0%)	1(2.1%)	0(0%)
Headache	4(3.8%)	2(4.3%)	2(4.3%)
Cough	65(61.9%)	29(61.7%)	36(62.1%)
Sore throat	5(4.8%)	2(4.3%)	3(5.2%)
Sputum production	30(28.6%)	12(25.5%)	18(31.0%)
Fatigue	38(36.2%)	20(42.6%)	18(31.0%)
Shortness of breath	37(35.2%)	23(48.9%)	14(24.1%)
Nausea or vomiting	7(6.7%)	4(8.5%)	3(5.2%)
Myalgia or arthralgia	8(7.6%)	3(6.4%)	5(8.6%)
Chill	7(6.7%)	6(12.8%)	1(1.7%)
Throat congestion	2(1.9%)	0(0%)	2(3.4%)
Coexisting disorders—No, %	Coexisting disorders—No, %	Coexisting disorders—No, %	Coexisting
Diabetes	16(15.2%)	10(21.3%)	6(10.3%)
Hypertension	23(21.9%)	14(29.8%)	9(15.5%)
Coronary heart disease	9(8.6%)	6(12.8%)	3(5.2%)
Hepatitis B infection	2(1.9%)	2(4.3%)	0(0%)
COPD	1(1.0%)	1(2.1%)	0(0%)
SBP (mmHg)	129.0(118.0-137.0)	128.0(118.0-138.0)	129.0(118.7
DBP (mmHg)	80.0(73.0-84.0)	78.0(71.25-85.0)	80.0(73.0-83
Heart rate (min)	85.0(78.0-96.0)	84.0(78.0-97.0)	85.0(77.0-93
Laboratory findings	Laboratory findings	Laboratory findings	Laboratory
WBC ($\times 10^9$/L)	5.03(3.96-7.04)	5.59(3.86-8.20)	4.96(4.03-6.
RBC ($\times 10^{12}$/L)	4.2(3.7-4.6)	4.1±0.7	4.2±0.6
Hb (g/L)	125.0(117.0-140.0)	128.0±19.4	125.0±15.3
PLT ($\times 10^9$/L)	206.0(152.5-261.0)	176.0(125.0-229.0)	230.5(178.3
LYM (%)	22.9(12.9-29.8)	14.2(6.3-23.5)	27.2(21.9-35
LYM ($\times 10^9$/L)	1.13±0.5	0.79±0.3	1.35±0.4
LYM <1.1×109 cells/L	52(49.5%)	40(76.9%)	12(23.1%)
ALT (U/L)	27.0(17.8-43.0)	24.0(17.0-40.5)	31.5(19.0-45
AST (U/L)	29.0(20.0-42.0)	31.0(20.0-47.5)	25.5(20.3-38
Cr (umol/L)	60.5(49.0-78.0)	68.50(53.8-85.8)	55.50(48.3-6
eGFR (ml/min)	99.1(88.0-109.0)	90.5(59.0-107.22)	101.2(95.3-1
UA (umol/L)	247.5(193.5-332.8)	253.0(182.0-343.8)	241.0(203.5
D-D (mg/L)	0.56(0.34-3.95)	0.70(0.355-8.19)	0.54(0.34-3.
K (mmol/L)	4.1(3.6-4.4)	4.1(3.5-4.4)	4.1(3.7-4.4)
Na (mmol/L)	142.0(139.0-145.0)	141.5(139.0-146.0)	142.0(140.0
Cl (mmol/L)	105.0(102.7-108.1)	104.3(103.1-108.3)	105.5(102.1
TC (mmol/L)	3.64(3.27-4.32)	3.50(3.09-4.03)	3.84(3.41-4.
TG (mmol/L)	1.19(0.90-1.69)	1.23(0.95-1.63)	1.15(0.86-1.
HDL (mmol/L)	0.90(0.76-1.06)	0.90±0.338	0.90±0.234
LDL (mmol/L)	2.26(1.87-2.74)	2.10(1.74-2.60)	2.40(2.02-2.
CD3 cells count	706.0(459.5-921.0)	437.0(224.0-606.0)	881.5(760.8
CD4 cells count	437.0(268.5-561.0)	240.0(123.0-325.0)	546.5(475.0
CD8 cells count	241.0(131.0-333.5)	153.0(64.0-242.0)	293.0(226.7
CD4/CD8	1.76(1.31-2.29)	1.60(1.11-1.96)	1.88(1.44-2.
Abnormalities on chest CT—No,%	Abnormalities on chest CT—No,%	Abnormalities on chest CT—No,%	Abnormalit
Ground-glass opacity	50(47.6%)	18(38.3%)	32(55.2%)
Local patchy shadowing	32(30.5%)	9(19.1%)	23(39.7%)

Variables		$CD4^+T<404/ul$	$CD4^+T[?]4$
Treatment	Treatment	Treatment	Treatment
Oxygen inhalation	85(81.0%)	42(93.3%)	43(78.2%)
Mechanical ventilation	10(9.5%)	8(17.4%)	2(3.7%)
Glucocorticoids	42(40.0%)	26(53.1%)	23(39.7%)
Antiviral treatment	103(98.1%)	46(97.9%)	57(98.3%)
Intravenous immunoglobulin	49(46.7%)	26(55.3%)	23(39.7%)
Antibiotic treatment	77(73.3%)	40(85.1%)	37(63.8%)
Antifungal treatment	5(4.8%)	3(6.4%)	2(3.4%)
Clinical outcome	Clinical outcome	Clinical outcome	Clinical out
Death (No,%)	22(21.0%)	20(42.6%)	2(3.4%)

Abbreviations: COPD, Chronic obstructive pulmonary disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell count; RBC, red blood cell count; Hb, Hemoglobin; PLT, platelet count; LYM, lymphocyte count; ALT, alanine aminotransferase; AST, aspartate transaminase; Cr, creatinine; eGFR, estimated glomerular filtration rate; UA, uric acid; TC, total cholesterol; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein.

Table 2. Effects of various variables on in-hospital death in Cox regression analysis.

Characteristics	HR (95%CI)	*P*
Sex Female	-	
Male	1.851(0.776-4.412)	0.165
Age, per 1 years	1.122(1.071-1.174)	<0.001
History of hypertension No	-	
Yes	4.621(1.999-10.682)	<0.001
History of diabetes No	-	
Yes	1.709(0.631-4.634)	0.292
History of CHD No	-	
Yes	2.645(0.893-7.831)	0.079
History of COPD No	-	
Yes	4.681(0.628-34.888)	0.132
History of HBI No	-	
Yes	0.130(0.000-72.127)	0.527
SBP (mmHg)	1.010(0.988-1.032)	0.368
DBP (mmHg)	1.004(0.966-1.043)	0.840
Heart rate (min)	1.014(0.987-1.043)	0.314
WBC ($\times 10^9$/L)	1.236(1.140-1.340)	<0.001
RBC ($\times 10^{12}$/L)	0.858(0.452-1.626)	0.638
Hb (g/L)	1.008(0.982-1.035)	0.531
PLT ($\times 10^9$/L)	0.986(0.979-0.993)	<0.001
LYM ($\times 10^9$/L)	0.039(0.011-0.137)	<0.001
LYM <1.1×109 cells/L	5.288(1.788-15.636)	0.003
ALT (U/L)	1.004(0.988-1.019)	0.630
Cr (umol/L)	1.029(1.016-1.044)	<0.001
EGFR (ml/min)	0.971(0.957-0.984)	<0.001
UA (umol/L)	1.003(0.9999-1.006)	0.129
D-D (mg/L)	1.029(1.016-1.043)	<0.001
K^+ (mmol/L)	1.029(0.577-1.836)	0.923
Na^+ (mmol/L)	1.009(1.000-1.018)	0.044

Characteristics	HR (95%CI)	*P*
TC (mmol/L)	0.695(0.397-1.217)	0.204
TG (mmol/L)	1.096(0.834-1.441)	0.512
HDL (mmol/L)	0.241(0.051-1.134)	0.072
LDL (mmol/L)	0.606(0.286-1.280)	0.189
CD3<723 cells/ul No	0.089(0.021-0.383)	0.001
Yes	11.175(2.610-47.850)	0.001
CD4<404 cells/ul No	0.064(0.015-0.273)	<0.001
Yes	15.720(3.669-67.346)	<0.001
CD8<220 cells/ul No	0.117(0.035-0.397)	0.001
Yes	8.528(2.521-28.847)	0.001
CD4/CD8	1.054(0.845-1.316)	0.641
Ground-glass opacity Yes vs. No	0.288(0.106-0.781)	0.014
Local patchy shadowing Yes vs. No	0.204(0.048-0.872)	0.032
Oxygen inhalation Yes vs. No	26.743(0.213-3365.021)	0.183
Mechanical ventilation Yes vs. No	20.135(7.696-52.684)	<0.001
Glucocorticoids Yes vs. No	6.120(2.255-16.610)	<0.001
Antiviral treatment Yes vs. No	0.253(0.034-1.888)	0.180
Intravenous immunoglobulin Yes vs. No	4.257(1.569-11.550)	0.004
Antibiotic treatment Yes vs. No	35.287(0.748-1665.054)	0.070
Antifungal treatment Yes vs. No	4.016(1.183-13.628)	0.026

Abbreviations: COPD, Chronic obstructive pulmonary disease; CHD, coronary heart disease; HBI, Hepatitis B infection; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell count; RBC, red blood cell count; Hb, Hemoglobin; PLT, platelet count; LYM, lymphocyte; ALT, alanine aminotransferase; AST, aspartate transaminase; Cr, creatinine; eGFR, estimated glomerular filtration rate; UA, uric acid; TC, total cholesterol; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein.

Table3. Results of multivariate Cox proportional-hazards regression analyzing the effect of baseline variables on in-hospital death.

Mode	HR (95%CI)	*P*
Not Adjusted CD4+T, low vs. high	15.720(3.669-67.349)	<0.001
Mode 1	Mode 1	Mode 1
CD4+T, low vs. high	8.763(1.925-39.885)	0.005
Age, per 1 years	1.075(1.026-1.126)	0.002
Hypertension, yes vs.no	2.327(0.964-5.614)	0.060
CHD, yes vs. no	0.850(0.280-2.585)	0.775
Mode 2	Mode 2	Mode 2
CD4+T, low vs. high	11.582(2.269-59.125)	0.003
Diabetes, yes vs. no	1.135(0.413-3.120)	0.806
LYM count, low vs. high	0.865(0.247-3.026)	0.820
PLT, per 1×10^9/L	0.990(0.983-0.997)	0.003
Mode 3		
CD4+T, low vs. high	8.635(1.878-39.701)	0.006
D-D, per 1mg/L	1.021(1.006-1.037)	0.007
Cr, per 1 umol/L	1.009(0.987-1.031)	0.424
EGFR, per 1 ml/min	0.988(0.966-1.010)	0.283
Mode 4	Mode 4	Mode 4
CD4+T, low vs. high	8.028(1.366-47.192)	0.021

Mode	HR (95%CI)	*P*
CD3, low vs. high	1.120(0.127-9.907)	0.919
CD8+T, low vs. high	2.475(0.489-12.515)	0.273
WBC, per 1×10^9/L	1.161(1.070-1.261)	<0.001
Mode 5		
CD4+T, low vs. high	5.754(1.233-26.865)	0.026
WBC, per 1×10^9/L	1.204(1.084-1.337)	0.001
Age, per 1 years	1.085(1.030-1.143)	0.002
PLT, per 1×10^9/L	0..991(0.984-0.997)	0.005
D-D, per 1mg/L	0.980(0.957-1.003)	0.093

Abbreviations: CHD, coronary heart disease; SBP, systolic blood pressure; WBC, white blood cell count; PLT, platelet count; LYM, lymphocyte; AST, aspartate transaminase; Cr, creatinine; eGFR, estimated glomerular filtration rate; UA, uric acid; HDL, high density lipoprotein.

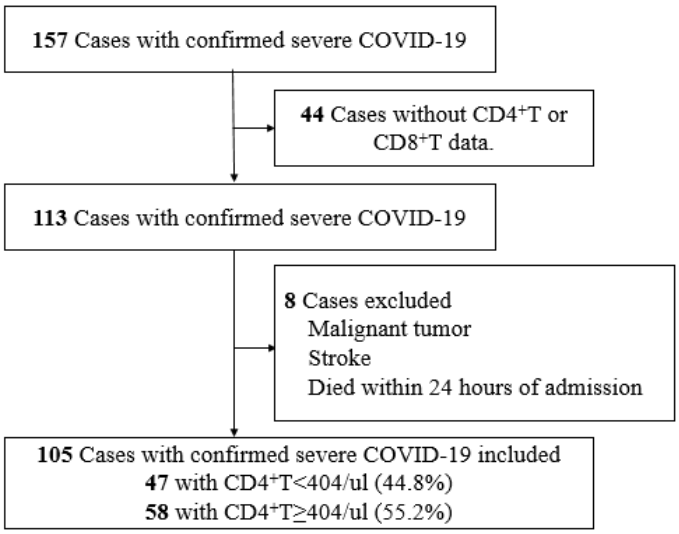

Figure 1: Flow diagram of Patient Recruitment

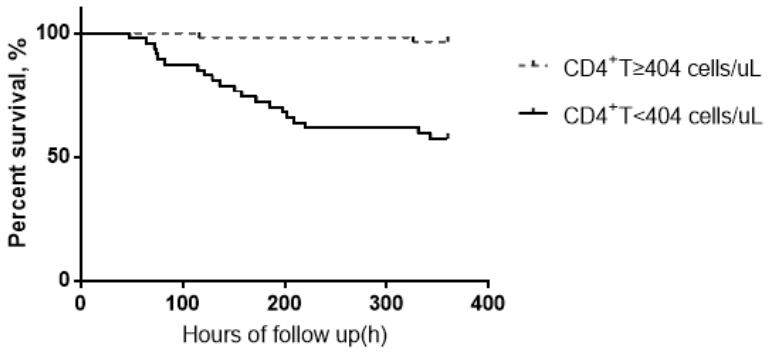

Figure 2. Kaplan-Meier plots showing the survival rate of severe COVID-19 patients who were stratified into two groups according to $CD4^+T$ cells count. (Dotted line, $CD4^+T$[?]404 cells/ul, n=58; Solid line, $CD4^+T$<404 cells/ul, n=47; log-rank test for trend, P<0.001).