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

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**To the Editor**

The decline of T lymphocytes in peripheral blood is a typical laboratory characteristic of patients with COVID-19, especially in severe patients[1,2]. T-lymphocytes play a critical role in antiviral immunity. CD4$^+$T lymphocyte subsets secretes high level of effector cytokines, especially interferon-$\gamma$ (IFN-$\gamma$), which are essential for virus clearance[3]. However, there is no research concerning whether CD4$^+$T predicted outcomes of COVID-19 patients.

**Methods**

Medical records from 157 patients with confirmed severe COVID-19 were collected in in Hubei General Hospital during the management by national medical team. A flow chart (Figure S1) describes patient inclusion. 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: CD4+T<404 cells/ul). The study was registry with clinicaltrials.gov identifier NCT04292964. All study procedures were approved by the local ethics committee (approval NO. 20200701). All patients in the study were followed up from admission till death or discharge. The outcome was defined as the in-hospital death rate.

**Results**

**Baseline characteristics**

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. Compared with patients in the high group, in terms of laboratory findings, patients in the low CD4$^+$T cell count group showed lower median platelet count, lymphocyte percentage, lymphocyte count, estimated glomerular filtration rate, total cholesterol, low density lipoprotein, CD3$^+$T cell count, CD4$^+$T cell count, CD8$^+$T cell count, but a higher median creatinine level. In terms of computed tomography findings, patients in the high group more often represented as local patchy shadowing. Detailed features of laboratory data, symptoms, treatments and outcomes are shown in the table1.

**Survival curves of in-hospital death**

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, Figure S2).

**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 indi-

cated 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 to identify the independent factors correlated with prognosis. In each model, CD4$^+$T (the low group vs. the high group) was significance which demonstrated that presenting with CD4$^+$T cells count below 404 cells/ul was an independent risk factor for in-hospital death. In addition, variables like white blood cell count, age and platelet count also showed significance for independently predicting in-hospital death in this study (Table S1).

## Discussion

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, possibly because they often had other chronic diseases[4]. 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[5]. 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[6].

Several recent studies indicated that T-lymphocytes[1,7]was reduced in most patients with COVID-19. It was believed that SARS-CoV-2 may act mainly on lymphocytes, especially T-lymphocytes[2,8]. At present, the potential mechanisms undergoing CD4$^+$T cells count decrease induced by SARS-CoV-2 infection is still unknown. Researchers 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[7]. 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[9].

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

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**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%) |
| Symptoms and signs—No, % | Symptoms and signs—No, % | Symptoms and signs—No, % | Symptoms a |
| 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%) |

| Variables | | CD4$^+$T<404/ul | CD4$^+$T[?]4 |
|---|---|---|---|
| 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(73.0-8: |
| Heart rate (min) | 85.0(78.0-96.0) | 84.0(78.0-97.0) | 85.0(77.0-9: |
| Laboratory findings | Laboratory findings | Laboratory findings | Laboratory |
| WBC ($\times10^9$/L) | 5.03(3.96-7.04) | 5.59(3.86-8.20) | 4.96(4.03-6. |
| RBC ($\times10^{12}$/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 ($\times10^9$/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(21.9-3! |
| LYM ($\times10^9$/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(19.0-4! |
| AST (U/L) | 29.0(20.0-42.0) | 31.0(20.0-47.5) | 25.5(20.3-3{ |
| Cr (umol/L) | 60.5(49.0-78.0) | 68.50(53.8-85.8) | 55.50(48.3-( |
| 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%) |
| 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%) |

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| Variables | | CD4$^+$T<404/ul | CD4$^+$T[?]4 |
|---|---|---|---|
| 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 Male vs. Female | 1.851(0.776-4.412) | 0.165 |
| Age, per 1 years | 1.122(1.071-1.174) | <0.001 |
| History of hypertension Yes vs. No | 4.621(1.999-10.682) | <0.001 |
| History of diabetes Yes vs. No | 1.709(0.631-4.634) | 0.292 |
| History of CHD Yes vs. No | 2.645(0.893-7.831) | 0.079 |
| History of COPD Yes vs. No | 4.681(0.628-34.888) | 0.132 |
| History of HBI Yes vs. No | 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 ($\times10^9$/L) | 1.236(1.140-1.340) | <0.001 |
| RBC ($\times10^{12}$/L) | 0.858(0.452-1.626) | 0.638 |
| Hb (g/L) | 1.008(0.982-1.035) | 0.531 |
| PLT ($\times10^9$/L) | 0.986(0.979-0.993) | <0.001 |
| LYM ($\times10^9$/L) | 0.039(0.011-0.137) | <0.001 |
| LYM <1.1$\times$109 cells/L | 5.288(1.788-15.636) | 0.003 |
| ALT (U/L) | 1.004(0.988-1.019) | 0.630 |
| Cr (umol/L) | 1.029(1.016-1.044) | <0.001 |
| EGFR (ml/min) | 0.971(0.957-0.984) | <0.001 |
| UA (umol/L) | 1.003(0.9999-1.006) | 0.129 |
| D-D (mg/L) | 1.029(1.016-1.043) | <0.001 |
| K$^+$ (mmol/L) | 1.029(0.577-1.836) | 0.923 |
| Na$^+$ (mmol/L) | 1.009(1.000-1.018) | 0.044 |
| 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 Yes vs. No | 11.175(2.610-47.850) | 0.001 |
| CD4<404 cells/ul Yes vs. No | 15.720(3.669-67.346) | <0.001 |
| CD8<220 cells/ul Yes vs. No | 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 |

| Characteristics | HR (95%CI) | $P$ |
|---|---|---|
| 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.