



Low CD4 T cell count predicts radiological progression in severe and critically ill COVID-19 patients: a case control study

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Background: Novel coronavirus disease (COVID-19) has spread globally and caused over 3 million deaths, posing great challenge on public health and medical systems. Limited data are available predictive factors for disease progression. We aim to assess clinical and radiological predictors for pulmonary aggravation in severe and critically ill COVID-19 patients.

Methods: Patients with confirmed COVID-19 in Renmin Hospital of Wuhan University, China, between Feb. 6th, 2020 and Feb. 21st, 2020 were retrospectively collected. Enrolled patients were divided into non-progression group and progression group based on initial and follow-up chest CTs. Clinical, laboratory, and radiological variables were analyzed.

Results: During the study period, 162 patients were identified and a total of 126 patients, including 97 (77.0%) severe cases and 29 (23.0%) critically ill cases were included in the final analysis. Median age was 66.0 (IQR, 56.0–71.3) years. Median time from onset to initial chest CT was 15.0 (IQR, 12.0–20.0) days and median interval to follow-up was 7.0 (IQR, 5.0–7.0) days. Compared with those who did not progress (n=111, 88.1%), patients in the progression group (n=15, 11.9%) had significantly higher percentage of peak body temperature >38 °C (P=0.002), lower platelet count (P=0.011), lower CD4 T cell count (P=0.002), lower CD8 count (P=0.011), higher creatine kinase level (P=0.002), and lower glomerular filtration rate (P=0.018). On both univariate and multivariable analysis, only CD4 T cell count <200/μL was significant (OR, 6.804; 95% CI, 1.450–31.934; P=0.015) for predicting pulmonary progression.

Conclusions: Low CD4 T cell count predicts progression of pulmonary change in severe and critically ill patients with COVID-19.

Keywords: Novel coronavirus disease (COVID-19); predictive factors; CD4 T cells; radiological progression

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Introduction

Coronavirus disease-19 (COVID-19) is the disease in humans caused by infection of the novel β coronavirus 2019-nCoV/SARS-CoV-2 (1). Which ranges from asymptomatic or mild

illness to severe respiratory tract infections, such as those seen in severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) (2,3). Patients may progress rapidly, posing enormous burden on the public health and

medical systems. As of May 24th, 2021, 166,860,081 cases have been confirmed globally and 3,459,996 deaths reported (4). Reported mortality ranges from 2% to 12% and could be as high as 52.4% in patients who develop ARDS (5).

The ability to predict disease aggravation is pivotal, especially when therapeutic options are limited. Like other viral pneumonia, computed tomographic (CT) is a main tool for assessing disease course and severity in COVID-19 (6-9). While prior studies have described clinical features and lung abnormalities in the course of COVID-19 (3,10-14), literature on factors predicting pulmonary progression remains scarce. In this study, we evaluated the potential clinical and radiological factors predicting radiological progression in severe and critically ill COVID-19 cases.

We present the following article in accordance with the STROBE reporting checklist (available at <https://dx.doi.org/10.21037/jtd-20-1848>).

Methods

Study design, participants, and data collection

In this case control study, we retrospectively collected consecutive severe and critically ill patients hospitalized for coronavirus pneumonia in the Renmin Hospital of Wuhan University (Wuhan, China) between Feb 6th 2020 and Feb 21st 2020. Those who hospitalized for less than 1 week or lacking follow-up CT were excluded. The hospital served as a designated center for management COVID-19 cases. The diagnosis and severity of COVID-19 were according to the Novel Coronavirus Pneumonia Diagnostic and Treatment Guideline issued by Chinese National Health Commission (version 7) (see [Table S1](#)) (15). Patients were categorized into two groups: (I) progression group (increased area of lung change in follow up chest CT); (II) non-progression group (improvement or no obvious change in follow up CT). Electronic medical and nursing records were reviewed for extracting data. Data of patients with complete demographic, clinical, laboratory, and radiological data were collected using standardized form. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Renmin Hospital's institutional ethics board (No. WDRY2020-K048) and individual consent for this retrospective analysis was waived.

Laboratory and imaging methods

SARS-CoV-2 infections were confirmed using real-time

reverse transcriptase-polymerase chain reaction assays (RT-PCR) via throat swab or sputum sample. Complete blood count, coagulation profile, biochemical parameters, myocardial enzymes, CD4 and CD8 T cell counts, C-reactive protein, and procalcitonin were collected routinely during hospitalization. Initial and follow up chest CT scan were done for patients upon admission and about 5-7 days later based on clinical needs. CT image analysis were performed by two experienced clinicians. Decisions were reached by consensus. The predominant change on chest CT and area of affected lungs were recorded and compared.

Statistical analysis

Continuous data are expressed as mean \pm SD or median (25th-75th percentiles). Chi-square analysis or Mann-Whitney U-test were used to measure the differences in variables where appropriate. Data analyses were performed using SPSS (22.0; SPSS Inc., Chicago, IL, USA). To evaluate the predictive factor for aggravation in lung changes in COVID-19 patients, multivariable analyses with logistic regression model were performed using variables with P value <0.10 on univariate analysis. P value of <0.05 was considered statistically significant.

Results

During the study period, a total of 162 severe or critically ill patients with COVID-19 were identified. 36 were excluded due to hospitalization for less than 1 week (n=7) or lacking follow-up CT (n=29) (see [Figure 1](#)). Of the enrolled 126 patients, 97 (77.0%) and 29 (23.0%) cases were severe and critically ill upon admission, respectively. Median time from disease onset to initial chest CT scan was 15.0 (IQR, 12.0-20.0) days. Median interval to follow-up CT was 7.0 (IQR, 5.0-7.0) days. On reexamination, 15 (11.9%) cases presented with progression (progression group) and 111 (88.1%) cases had no progression (non-progression group) in CT images. Nine of the severe cases and six of the critically ill cases had CT progression. Percentage of CT progression did not significantly differ between severe and critically ill patients (9.3% vs. 20.7%, P=0.096).

Baseline clinical characteristics of all cases and patients in each group are summarized in [Table 1](#). Seventy (55.6%) patients had at least one underlying disease. The most common were hypertension (34.1%) and diabetes mellitus (13.5%). The most common symptoms at onset were peak

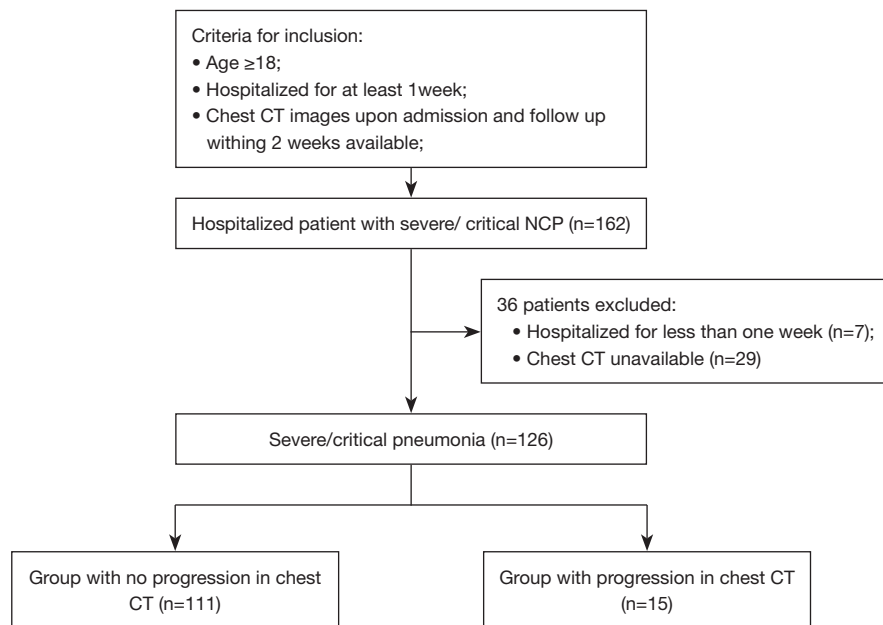


Figure 1 Study flowchart.

Table 1 Comparison of clinical characteristics of COVID-19 patient between progression and non-progression groups

Characteristic	Total (n=126)	Non-progression group (n=111)	Progression group (n=15)	P value
Male	74 (58.7%)	65 (58.6%)	9 (60%)	0.915
Age (median, IQR, y)	66.0 (56.0–71.3)	66.0 (56.0–71.3)	69.0 (54.0–75.0)	
Days from symptom onset to initial chest CT (median, IQR)	15.0 (12.0–20.0)	15.0 (12.0–20.0)	14.0 (11.0–18.0)	0.232
Days from initial chest CT to follow-up (median, IQR)	7.0 (5.0–7.0)	7.0 (5.0–7.0)	7.0 (5.0–8.0)	0.546
Comorbidities				
Hypertension	43 (34.1%)	40 (36.0%)	3 (20.0%)	0.219
Diabetes mellitus	17 (13.5%)	16 (14.4%)	1 (6.7%)	0.410
Underlying pulmonary diseases	5 (4.0%)	5 (4.5%)	0	1
Chronic kidney disease	4 (3.2%)	3 (2.7%)	1 (6.7%)	0.411
Presentations				
T _{max} ≥38 °C	85 (67.5%)	70 (60.1%)	15 (100%)	0.002*
Cough	85 (67.5%)	78 (70.3%)	7 (46.7%)	0.067
Chest tightness	47 (37.3%)	42 (37.8%)	5 (33.3%)	0.735
Fatigue	46 (36.5%)	40 (36.0%)	6 (40.0%)	0.765
Expectoration	30 (23.8%)	28 (25.2%)	2 (13.3%)	0.519
Diarrhea	19 (15.1%)	16 (14.4%)	3 (20.0%)	0.699

*P<0.05. COVID-19, coronavirus disease-19.

Table 2 Comparison of laboratory and radiological findings upon admission between COVID-19 patient groups

Variable	Total (n=126)	non–progression group (n=111)	progression group (n=15)	P value
PaO ₂ , mmHg	68.0 (59.0–80.0)	66.0 (59.0–79.5)	76.0 (63.0–85.0)	0.298
PaCO ₂ , mmHg	40.0 (35.0–44.0)	40.0 (35.0–44.8)	36.0 (34.0–40.0)	0.137
White blood cell count, ×10 ⁹ /L	5.7 (4.0–7.7)	5.8 (4.1–7.6)	4.5 (2.8–8.1)	0.503
Lymphocyte count, ×10 ⁹ /L	0.9 (0.6–1.2)	0.9 (0.6–1.2)	0.8 (0.6–1.0)	0.654
CD4 absolute count, /μL	291.0 (146.8–450.8)	307.5 (182.8–469.5)	129.0 (41.0–312.0)	0.002*
CD8 absolute count, /μL	149.0 (62.0–243.0)	157.0 (73.0–268.8)	57.5 (20.0–168.5)	0.011*
Neutrophil count, ×10 ⁹ /L	4.3 (2.7–6.4)	4.3 (2.8–6.3)	3.7 (1.8–6.6)	0.593
Hemoglobin, g/L	124.0 (112.8–137.0)	123.0 (112.0–136.0)	134.0 (118.0–138.0)	0.198
Platelet count, ×10 ⁹ /L	215.5 (160.0–277.3)	222.0 (166.0–282.0)	179.0 (129.0–205.0)	0.011*
C-reactive protein, mg/L	55.1 (12.5–95.0)	56.1 (11.8–95.1)	50.0 (30.0–93.0)	0.934
Alanine aminotransferase, U/L	29.5 (20.0–49.0)	30.0 (20.0–51.0)	26.0 (17.0–37.0)	0.2
Aspartate aminotransferase, U/L	33.0 (22.0–48.0)	33.0 (21.0–48.0)	39.0 (33.0–55.0)	0.153
Fast blood glucose, mmol/L	5.8 (5.0–7.2)	6.0 (5.1–7.5)	5.2 (4.8–6.1)	0.052
Creatine kinase, U/L	63.0 (37.0–106.3)	59.0 (34.0–99.0)	142.0 (60.0–230.0)	0.002*
Lactate dehydrogenase, U/L	323.0 (235.8–436.3)	318.0 (236.0–424.0)	381.0 (214.0–539.0)	0.374
Glomerular filtration rate, mL/min	95.9 (85.5–105.7)	97.0 (85.8–106.0)	90.0 (65.0–92.0)	0.018*
D-dimer, mg/L	1.3 (0.6–3.6)	1.3 (0.6–4.1)	1.4 (0.4–2.5)	0.44
Predominant change in initial chest CT				
Ground glass opacities	63 (50.0%)	54 (48.6%)	9 (60%)	0.409
Patchy consolidation	31 (24.6%)	27 (24.3%)	4 (36.4%)	0.843
Irregular solid nodules	18 (14.3%)	16 (14.4%)	2 (13.3%)	1
Fibrous stripes	14 (9.5%)	14 (12.6%)	0	0.216
Area of lung change				0.985
≤30%	24 (19.0%)	21 (18.9%)	3 (20.0%)	
30–50%	53 (42.1%)	47 (42.3%)	6 (40.0%)	
≥50%	49 (38.9%)	43 (38.7%)	6 (40.0%)	

*P<0.05. COVID-19, coronavirus disease-19.

body temperature >38 °C (67.5%), cough (67.5%), chest tightness (37.3%), and fatigue (36.5%). Comparison of laboratory examinations and chest CT features between progression and non-progression group are summarized in *Table 2*. Lung abnormalities of COVID-19 in HRCT are presented in *Figure 2*. The most common manifestation on HRCT was ground glass opacity (50.0%), followed by patchy consolidation (24.6%), irregular solid nodules (14.3%), and fibrous stripes (9.5%). Majority of the patients had abnormalities over 30% of the lung area. Pulmonary

change of 30–50% and ≥50% were seen in 42.1% and 38.9% of the patients, respectively.

Compared with non-progression group, patients who progressed were more likely to have peak body temperature >38 °C (100% *vs.* 60.1%, P=0.002), less likely to present with cough (46.7% *vs.* 70.3%, P=0.067), had lower platelet count [179.0 (129.0–205.0) *vs.* 222.0 (166.0–282.0), P=0.011], lower CD4 T cell count [129.0 (41.0–312.0) *vs.* 307.5 (182.8–469.5), P=0.002], lower CD8 cell count [57.5 (20.0–168.5) *vs.* 157.0 (73.0–268.8), P=0.011], higher

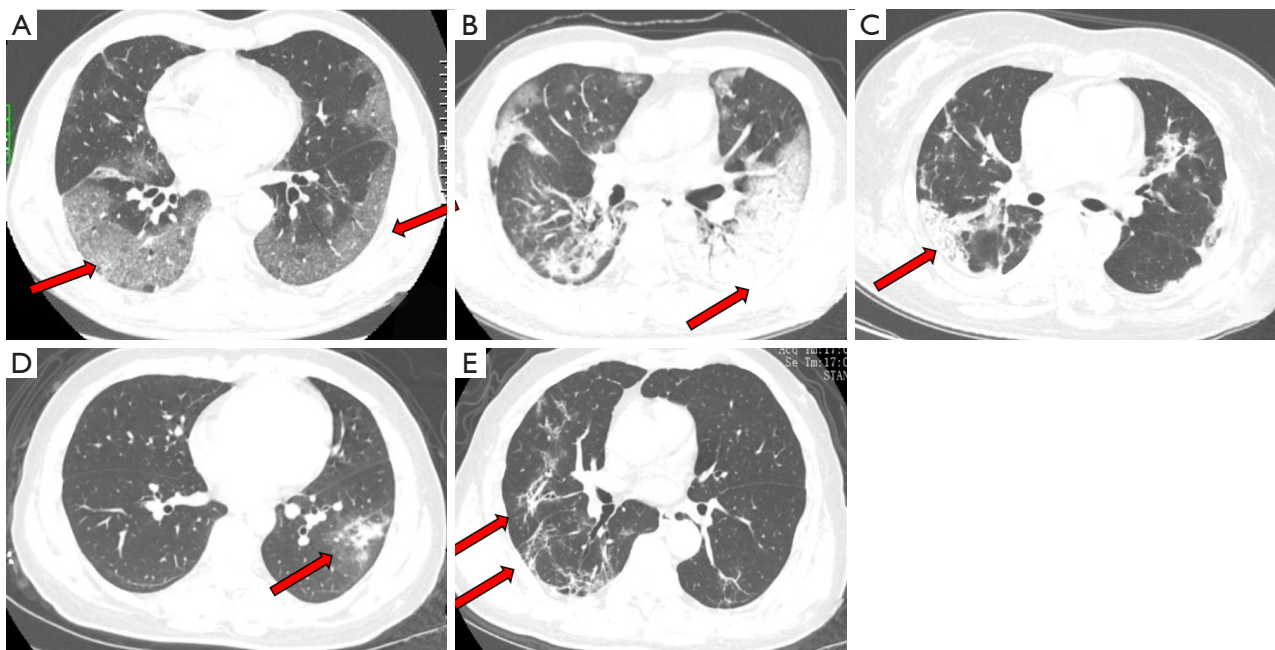


Figure 2 Lung abnormalities of COVID-19 in high resolution computed tomography. Red arrows indicate pulmonary lesions seen: (A) bilateral ground glass opacities of subpleural distribution, (B) consolidation with air bronchogram in the left lower lobe, (C) patchy consolidation in the right lower lobe, (D) irregular solid nodules in the left lower lobe, (E) thin fibrous stripes. COVID-19, coronavirus disease-19.

Table 3 Univariate and multivariable analysis with logistic regression model for predicting pulmonary lesion progression in severe and critical COVID-19 patients

Variable	Univariate analysis		Multivariable analysis	
	OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Cough	2.701 (0.906–8.058)	0.075	2.434 (0.604–9.803)	0.211
Fever ≥ 38.0 °C	1.982 (0.665–5.904)	0.22	1.693 (0.413–6.933)	0.464
Platelet count $<125 \times 10^9/L$	2.273 (0.555–9.309)	0.254	1.733 (0.310–9.694)	0.531
Absolute CD4 cell count $<200/\mu L$	6.048 (1.763–20.750)	0.004*	6.804 (1.450–31.934)	0.015*
absolute CD8 cell $<220/\mu L$	3.300 (0.251–43.470)	0.364	1.618 (0.205–12.796)	0.648
eGFR <90 mL/min	1.823 (0.613–5.419)	0.28	1.175 (0.271–5.090)	0.829
CK >198 U/L	1.540 (0.184–12.857)	0.69	0.236 (0.043–1.285)	0.095
Blood glucose ≥ 7.0 mmol/L	2.633 (0.562–12.335)	0.219	4.374 (0.738–25.912)	0.104

* $P < 0.05$. COVID-19, coronavirus disease-19.

creatinine kinase level [142.0 (60.0–230.0) *vs.* 59.0 (34.0–99.0), $P=0.002$], lower glomerular filtration rate [90.0 (65.0–92.0) *vs.* 97.0 (85.8–106.0), $P=0.018$], and lower blood glucose [5.2 (4.8–6.1) *vs.* (5.1–7.5), $P=0.052$]. No significant difference existed in the predominant CT pattern or area of affected lungs between the progression group and the non-

progression group.

The following categorical variable were entered in logistic regression analysis (see *Table 3*): symptom of cough, fever ≥ 38.0 °C, platelet count $<125 \times 10^9/L$, absolute CD4 T cell count $<200/\mu L$, absolute CD8 cell count $<220/\mu L$, GFR <90 mL/min, CK >198 U/L, and blood glucose ≥ 7.0 mmol/L.

On both univariable and multivariable analysis, absolute CD4 T cell count $<200/\mu\text{L}$ was the only factor significantly associated with progression in lung involvement ($P=0.004$ and $P=0.015$, respectively).

Discussion

In this study, we described the clinical and radiological features of severe and critically ill COVID-19 cases, and demonstrated that CD4 T cell count $<200/\mu\text{L}$ was significantly related to the progression of chest CT abnormalities in those patient groups.

It is worth noting that lung changes are essentially affected by disease course. Peak stage of lung involvement is approximately 10 days (9–13 days) after initial onset of symptoms (16). In our study, the initial radiological evaluations were performed upon hospital admission with a median of 15 days (range 12th–20th) after disease onset, with no significant difference in time between the progression group and non-progression group. By that time, patients had already gone through the early stage and progressive stage. Hence, our finding that low level of CD4 T count predicts radiological progress is not affected by COVID-19 disease course.

Although not statistically significant, we found that ground glass opacities and patchy consolidation was more frequently seen in the progression group. In addition, no patients with the predominant pattern of fibrous stripes aggravated. The latter finding is consistent with the fact that in COVID-19, like other viral pneumonia, fibrotic changes are seen during remission stage and may remain after recovery (6,16,17).

Major gap remains in the understanding of pathogenicity of novel coronavirus disease. However, a number of similarities exists between SARS-CoV, SARS-CoV-2, and other members of human coronaviruses. In all cases, the immune system plays crucial role in pathologies (18). Prior studies in infections caused by MERS, SARS, and SARS-CoV-2 demonstrated that marked lymphopenia including a dramatic loss of CD4 T cell were observed in severe cases and correlated with disease severity (19–23). Severe SARS patients have a delayed development of adaptive immune response, which is the main reason for SARS patients to develop life-threatening illness compared with other mild HCoV-229E (24,25). The decrease in CD4 T cell may be a result of T-cell infection, impaired T cell functions, and apoptosis caused by coronaviruses (26). Conversely, those with low

level of T cells show weakened responses to viruses, which may in turn lead to pneumonia progression (27,28).

Our finding that CD4 T cell count $<200/\mu\text{L}$ predicts pulmonary progression is consistent with prior research findings in HCoVs, and supports the speculation that immune deficiency is associated with disease deterioration. It highlights the importance of evaluating cellular immunity in the management of COVID-19 patients, as well as searching for new therapeutic options using immunoenhancers. Currently, several drugs including remdesivir, hydroxychloroquine, and chloroquine are administered in multiple countries, or under clinical trials. Nonetheless, no specific immunoenhancer has been recommended. The effectiveness of those used extensively during SARS and MERS outbreak, including interferons, intravenous gammaglobulin (IVIG), and thymosin is yet to be proven in COVID-19.

This study has a few limitations. First, this was a retrospective study done in a single center, which served as a center for severe and critically ill patients. Whether the same finding applies in mild to moderate cases is worth looking into. Second, other factors that may influence the extent of pulmonary involvement, such as medication upon admission or bacterial co-infections, were not included in the analysis. Well-designed prospective studies will help to elucidate the correlation between other possible parameters and radiological changes in the future. Third, clinical parameters such as symptoms and time to hospital discharge were not recorded during follow-up. Further research about the relationship between chest CT progression and clinical status is needed.

In conclusion, our study demonstrated that absolute CD4 T cell count $<200 \mu\text{L}/\text{L}$ predicts pulmonary progression in severe and critically ill COVID-19 patients, highlighting the importance of evaluating cellular immunity and close monitoring of those with low CD4 T cell counts.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://dx.doi.org/10.21037/jtd-20-1848>

Data Sharing Statement: Available at <http://dx.doi.org/10.21037/jtd-20-1848>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jtd-20-1848>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Renmin Hospital's institutional ethics board (No. WDRY2020-K048) and individual consent for this retrospective analysis was waived.

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