

Dynamic change in lymphocyte count in the early stage is a potential predictor of the severity of COVID-19

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Research article

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Abstract

Background Lymphopenia is associated with COVID-19 severity. Herein we describe the dynamic changes in lymphocyte count during hospitalization and explore a possible association with the severity of COVID-19.

Methods In this retrospective study, 13 non-severe COVID-19 patients diagnosed at admission were enrolled. One patient progressed to severe disease. Dynamic changes in lymphocyte count and CT score of all patients were analyzed.

Results Lymphocyte count changed significantly in the non-severe patients over time (admission vs day 5, $P=0.685$; day 5 vs day 15, $P<0.001$). Lymphocyte count of the severe patient fluctuated, and even decreased within the first 12 days post-admission, before increasing gradually. Chest CT scores of nine (75%) non-severe patients on the 5th day of hospitalization were higher than at admission, but decreased gradually thereafter (admission vs day 5, $P<0.001$, day 5 vs day 15, $P=0.004$). In the severe patient, CT score continued to increase for 2 weeks after admission, before decreasing gradually.

Conclusions Non-severe COVID-19 patients had significantly increased lymphocyte count and decreased CT score 1 week after illness onset. Dynamic change in lymphocyte count in the early stages of COVID-19 may be helpful to identify the patients who are more likely to develop severe or critical illness.

Introduction

Since the emergence of Coronavirus Disease 2019 (COVID-19) in Wuhan, Hubei province, in December 2019, the disease has rapidly spread throughout China and many other countries [1–4]. Nearly 20% of patients have demonstrated severe or critical illness [5]. Older patients (> 65 years) with comorbidities and acute respiratory distress syndrome (ARDS) are at increased risk of death [6]. It is important to identify and manage the severe or critically ill patients as early as possible.

Lymphopenia is a reference index in the diagnosis of COVID-19 according to the diagnosis and treatment protocols from the National Health Commission of the People's Republic of China [7, 8]. Thirty five percent of non-severe COVID-19 patients had mild lymphopenia [9]. However, more pronounced lymphopenia occurred in more than 80% of critically ill patients [6]. Zhong et al also found that severe COVID-19 patients had more prominent lymphopenia compared with non-severe patients [5]. A recent study by Li et al identified that lymphopenia was one of the risk factors for severe/critical COVID-19 [10]. These results suggested that the severity of lymphopenia was associated with the severity of COVID-19. However, studies regarding the dynamic change in lymphocyte count in COVID-19 patients, and the relationship between this and disease severity are limited.

Typical chest computed tomography (CT) findings of COVID-19 include multifocal bilateral ground glass opacity (GGO) with patchy consolidations, prominent peripheral subpleural distribution and preferred posterior or lower lobe predilection [11]. Consolidation, linear opacities, crazy-paving pattern, bronchial

wall thickening, high CT score and extrapulmonary lesions were CT features of severe/critical COVID-19 [10]. CT score could also reflect the severity of lung abnormalities of non-severe COVID-19 patients [12].

This study aims to describe the dynamic change in lymphocyte count and CT score during hospitalization of patients with COVID-19 outside Wuhan and explore a possible connection between the dynamic change in lymphocyte count and severity of the disease.

Methods

Patients

We retrospectively enrolled 13 non-severe COVID-19 patients diagnosed at admission in the First Affiliated Hospital of Xi'an Jiaotong University from January 22, 2020 to February 2, 2020 into the study. One patient developed to severe COVID-19 during hospitalization. Based on the diagnosis and treatment protocols from the National Health Commission of the People's Republic of China, the diagnostic criteria were: 1, epidemiological history—travel/residence in Wuhan or exposure to fevered patients with respiratory symptoms from Wuhan within 14 days before the onset of illness; 2, clinical manifestations—fever, imaging characteristic of pneumonia, and/or normal or decreased white blood cells count or decreased lymphocyte counts; 3, laboratory diagnosis—real-time fluorescence polymerase chain reaction-determined positivity for severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) in throat swabs or lower respiratory tract. Severe patients were defined as meeting any of the following conditions: 1, severe respiratory distress (respiratory rate ≥ 30 breaths/min); 2, oxygen saturation (SpO₂) <93% in resting state; 3, arterial oxygen tension (PaO₂)/inspiratory oxygen fraction (FiO₂) ≤ 300 mmHg [7, 8]. The study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University, with a waiver of informed consent (XJTU1AF2020LSK-010).

Epidemiological, demographic, clinical, laboratory, radiologic assessments (chest CT), management, and outcome data during hospitalization were obtained from patients' medical records. All patients were treated in isolation and received antiviral treatment, including lopinavir/ritonavir tablets (500 mg twice daily, orally) and arbidol hydrochloride tablets (200 mg three times daily, orally). Blood samples were taken from each patient upon admission and then every second day, and underwent CT scans with a mean interval of 4 ± 1 days. All patients were followed up until discharge or at least 15 days.

CT Protocol

Chest CT scans were performed using a single inspiratory phase in two commercial multi-detector CT scanners (Philips Brilliant 16, Philips Medical Systems, Amsterdam, Netherlands). To minimize motion artifacts, patients were instructed on breath-holding; CT images were then acquired during a single breath-hold. For CT acquisition, the tube voltage was 120kVp with automatic tube current modulation. From the raw data, CT images were reconstructed with a matrix size of 512×512 as axial images (thickness of 1.0mm and increment of 1.0mm).

CT Score

The major CT demonstrations were described using internationally standard nomenclature defined by the Fleischner Society glossary and peer-reviewed literature on viral pneumonia, using terms including GGO, crazy-paving pattern, and consolidation [13,14]. A semi-quantitative scoring system was used to quantitatively estimate the pulmonary involvement of all these abnormalities on the basis of the area involved [15]. Each of the five lung lobes was visually scored from 0–5 as follows: 0, no involvement; 1, <5% involvement; 2, 5%–25% involvement; 3, 26%–49% involvement; 4, 50%–75% involvement; 5, >75% involvement. The total CT score was the sum of the individual lobar scores and ranged from 0 (no involvement) to 25 (maximum involvement).

The CT images were independently reviewed by two experienced radiologists with 5 years of experience. When there was a disagreement, the diagnosis was made by an expert with more than 10 years of experience in respiratory imaging.

Statistical Analysis

Continuous variables were reported as means \pm standard deviation (SD), except that days from illness onset to admission or diagnosis were presented as medians and interquartile range (IQR) because of abnormal distribution. Categorical variables were reported as the number of patients and percentages. Wilcoxon tests were used to test if the variables related to the time of recovery were different between the patients with normal lymphocyte count at time of admission (group 1) versus those with counts below the normal level upon admission (group 2). Mixed model repeated-measure analysis of variance (ANOVA) was used to determine if the lymphocyte count or CT score changed significantly over time. Contrasts were used to test for significant changes in the lymphocyte count or CT score between different time points. All analyses were performed with SAS 9 software (SAS institute, Cary, NC). $P \leq 0.05$ was considered statistically significant.

Results

Demographic and Clinical Characteristics of Non-severe Patients at Admission

Thirteen COVID-19 patients who presented with non-severe disease upon admission were enrolled in the study. The demographic and clinical characteristics of the 12 non-severe patients are shown in Table 1. The demographic and clinical characteristics of the single patient who developed to severe COVID-19 during hospitalization are described separately. The average age of the 12 non-severe patients was 40 ± 13 years, ranging from 22 to 89 years. Seven (58.33%) patients were male. No patient had a history of direct contact with wildlife, while 10 (83.33%) patients were local residents of Wuhan, or had been to Wuhan, or had contact with people from Wuhan. There were four groups of family clusters (two families, each with three patients, and two families, each with two patients). Most of the patients (11/12, 91.67%) presented with fever, while two thirds (8/12, 66.67%) presented with dry cough. The median days from illness onset to admission or diagnosis was 2 (IQR, 1–3) and 2 (IQR, 1–4), respectively.

Here: Table 1. Demographics and Clinical Characteristics of Non-severe Patients at Admission

Laboratory and Radiologic Findings of Non-severe Patients at Admission

Among the twelve non-severe patients, 11 (91.7%) of them showed normal or decreased white blood cell (WBC) count. Six patients (50%) had lymphopenia, two (16.7%) had decreased platelet count, four (33.33%) demonstrated elevated C-reactive protein (CRP) and five (41.67%) showed elevated interleukin-6 (IL-6). All patients had normal levels of procalcitonin, but three had elevated alanine transaminase (ALT) and aspartate aminotransferase (AST) at admission.

Chest CT imaging of all patients showed multiple GGO under the pleura of both lungs, which were consistent with the early manifestations of COVID-19 (Table 2).

Here: Table 2. Laboratory and Radiographic Findings of Non-severe Patients at Admission

Clinical Characteristics Following Progression to Severe COVID-19 During Hospitalization

A 54-year-old woman was admitted to hospital after 2 days of fever and dry cough with a history of contact with people from Wuhan within 7 days preceding illness onset. She had no underlying diseases. Her body temperature was slightly elevated (37.6°C) and other vital signs were stable. Laboratory examination showed lymphopenia ($0.99 \times 10^9/L$), and other laboratory findings were normal. She was diagnosed with COVID-19 (non-severe) at admission. However, following the 10th day of hospitalization, she experienced obvious shortness of breath both at rest and upon exercising. Her diagnosis was revised to COVID-19 (severe) because of increased respiration rate (31bpm), decreased pulse oxygen saturation without oxygen (90%) and progressive pulmonary opacities found at repeat chest CT on day 12 of hospitalization. After several days of high flow oxygen therapy through a nasal catheter and symptomatic treatment, she recovered gradually with relief of respiratory symptoms and improvement of pulse oxygen saturation. Repeat chest CT also showed improvement (Figure 1).

Figure 1. Dynamic change in chest CT images in a severe COVID-19 patient during hospitalization.

(A) Day 1. A small region of subpleural GGO in the left lower lobe (white arrow). (B–E) Days 3–13, diffuse GGO in the lower lobe of both lungs. (F) GGO obviously absorbed, which then develop into linear opacities and subsequent consolidation.

Dynamic Change in Lymphocyte Count During Hospitalization

Lymphocyte count changed significantly in the non-severe patients over time ($P=0.012$). There were no significant differences in lymphocyte count between admission and day 5 of hospitalization ($P=0.69$). However, lymphocyte count increased gradually from day 5 post-admission (hospitalization day 5 vs day 15, $P<0.001$; Figure 2A). Conversely, the lymphocyte count of the severe COVID-19 patient fluctuated throughout the 15 day period, and even decreased within the first 12 days after hospitalization, before increasing gradually (Figure 2B).

Figure 2. Dynamic change in lymphocyte count during hospitalization.

(A) Dynamic change in lymphocyte count in non-severe COVID-19 patients; (B) Dynamic change in lymphocyte count in the severe COVID-19 patient.

Dynamic Change in Chest CT Score During Hospitalization

Chest CT scores of nine (75%) non-severe COVID-19 patients on day 5 of hospitalization were significantly higher than those obtained at time of admission; however, they decreased gradually from day 5 until day 15 post-hospitalization (admission vs hospitalization day 5, $P < 0.001$; hospitalization day 5 vs day 15, $P = 0.004$). Conversely, in the severe patient, the CT score continued to increase over the 2-week post-admission period before decreasing gradually (Figure 3).

Figure 3. Dynamic change in chest CT score during hospitalization.

(A) Dynamic change in CT score in non-severe COVID-19 patients; (B) Dynamic change in CT score in the severe COVID-19 patient.

Subgroup Analysis of Dynamic Change in Chest CT Score During Hospitalization

The non-severe patients were divided into two subgroups (group 1, patients with normal lymphocyte count at admission; group 2, patients with lymphocyte count below normal at admission). CT scores of the patients in group 2 appeared to be higher than counterparts in group 1 during hospitalization. Furthermore, CT scores of the patients in group 2 on day 5 after admission were significantly higher than those observed at time of admission, but decreased gradually from day 5 of hospitalization (admission vs hospitalization day 5, $P = 0.008$, hospitalization day 5 vs day 15, $P = 0.044$). Conversely, CT scores of the patients in group 1 did not show significant changes over time (Figure 4).

Figure 4. Dynamic change in CT score according to lymphocyte count at admission

Group 1, patients with normal lymphocyte count at admission; Group 2, patients with lymphocyte count below normal at admission.

Discussion

Our study found that the lymphocyte count of non-severe COVID-19 patients did not change significantly within the first 5 days following admission, but then continued to rise until the patients were discharged from hospital. Conversely, the lymphocyte count of the single severe COVID-19 patient fluctuated below the normal level before the disease progressed to the severe state. Since most of our patients were admitted within 2 days of illness onset, it would appear that patients without increase in lymphocyte count during the second week following illness onset may be more likely to develop to severe COVID-19. The dynamic change in lymphocyte count in the early stages might be an important predictor of

development of severe disease. This readily measurable parameter might help doctors to identify patients at risk of severe COVID-19 as early as possible.

Lymphopenia is common in critically ill patients with severe acute respiratory syndrome coronavirus (SARS-CoV) or Middle East respiratory syndrome coronavirus (MERS-CoV) infection because invasion by viral particles causes the destruction of lymphocytes. Therefore, we postulate that SARS-CoV-2 might mainly act on lymphocytes, especially T lymphocytes, as does SARS-CoV and MERS-CoV [16, 17, 18]. The virus could inhibit the body's cellular immune function and induce a cytokine storm, leading to disease exacerbation in some patients [18].

CT score had been used to evaluate the severity of pneumonia caused by SARS-CoV and SARS-CoV-2. The CT scores of severe/critical COVID-19 patients were significantly higher than those of non-severe COVID-19 patients [10, 12, 15]. In this study, CT score of patients with mild disease increased significantly within 5 days following admission, and then decreased significantly. Conversely, the CT score of the patient developing severe COVID-19 continued to increase before severe symptoms occurred. Taken together, these findings indicate that lung impairment could begin to recover after about 1 week of illness among mildly ill patients.

Several studies have reported that lymphopenia might be a critical factor associated with disease severity [5, 10]. The CT scores of severe and critical COVID-19 patients were significantly higher than those of patients with non-severe disease [10]. We performed subgroup analyses among our cohort of non-severe COVID-19 patients. CT scores of the patients in group 2 on day 5 after admission were significantly higher than those observed at time of admission, but decreased gradually from day 5 of hospitalization. CT scores of the patients in group 1 did not show significant changes over time. This might be because lung invasion in group 1 patients was mild at admission, so recovery was too small to be statistically tested. In addition, patients in group 2 took longer for body temperature to return to normal compared with group 1 patients (median, 8 days vs. 5 days, $P = 0.05$). These results suggested that patients with lymphocyte counts below the normal level in the early period of illness onset may have more severe pulmonary lesions and thus are likely to recover more slowly than patients with normal lymphocyte counts. However, no statistical difference was found in CT scores between the two groups because of the limited sample size.

Our study has some limitations. First, just 13 patients with confirmed COVID-19 were included in this study, with only one patient developing to severe disease. More patients are needed to analyze whether the dynamic change in lymphocyte count is associated with disease severity. Second, we did not investigate the influence of SARS-CoV-2 on patients' lymphocyte subsets, particularly the percentages and absolute counts of T lymphocytes.

In conclusion, non-severe COVID-19 patients had significantly increased lymphocyte counts and decreased CT scores 1 week after illness onset. Dynamic change in lymphocyte count in the early stages of COVID-19 may be helpful to identify patients who are more likely to develop severe or critical illness.

Declarations

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Conflict of interest

All authors declare that they have no competing interests.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University, with a waiver of informed consent (XJTU1AF2020LSK-010).

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

No

Authors' contributions

JZ analyzed and interpreted the patient data regarding COVID-19. YHD performed the analysis of chest CT image. XZ was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Demographics and Clinical Characteristics of Non-severe Patients at Admission^a

Characteristics	All patients (n=12)
Age, year	40±13
Male, n (%)	7 (58.33%)
Had comorbidities, n (%)	4 (33.33%)
Epidemiology history within 14 days, n (%)	
Residents of Wuhan	3 (25%)
Recently been to Wuhan	3 (25%)
Contact with people from Wuhan	2 (16.67%)
Taken the train through Wuhan with people from Wuhan getting on	2 (16.67%)
Family cluster	2 (16.67%)
Febrile days	1.83±1.69
Maximum temperature before admission, n (%)	
<37.3°C	1 (8.33%)
37.3-38°C	4 (33.33%)
38.1-39°C	6 (50%)
39.1-40°C	1 (8.33%)
Concomitant symptoms, n (%)	
Dry cough	8 (66.67%)
Short of breath	2 (16.67%)
Feeble	1 (8.33%)
Pharyngalgia	1 (8.33%)
Days from illness onset to admission, median (IQR)	2 (1,3)
Days from illness onset to diagnosis, median (IQR)	2 (1,4)

^aDays from onset of disease to admission or diagnosis were reported as median (IQR), while the remaining continuous variables were reported as means±SD; categorical variables were reported as the number of patients (percentages).

Table 2. Laboratory and Radiographic Findings of Non-severe Patients at Admission

Laboratory and radiographic indices	All patients (n=12)
Blood routine, mean±SD	
WBC count ($\times 10^9/L$)	5.36±2.54
Neutrophil count ($\times 10^9/L$)	3.80±2.19
Lymphocyte count ($\times 10^9/L$)	1.0±0.33
Platelet count ($\times 10^9/L$)	179.75±52.13
Hemoglobin (g/L)	148±19.54
Red blood cell count ($\times 10^{12}/L$)	5.15±0.64
Blood biochemistry, mean±SD	
ALT (U/L)	33.17±22.43
AST (U/L)	30.17±10.45
Infection-related biomarkers, mean±SD	
CRP (mg/L)	13.2±8.26
IL-6 (pg/mL)	12.1±13.44
Radiographic findings, n (%)	
GGO	12(100%)
Crazy-paving pattern	3(25%)
Consolidation	4(33.3%)
Air bronchogram	6(50%)
CT score, mean±SD	3.17±2.29

Figures

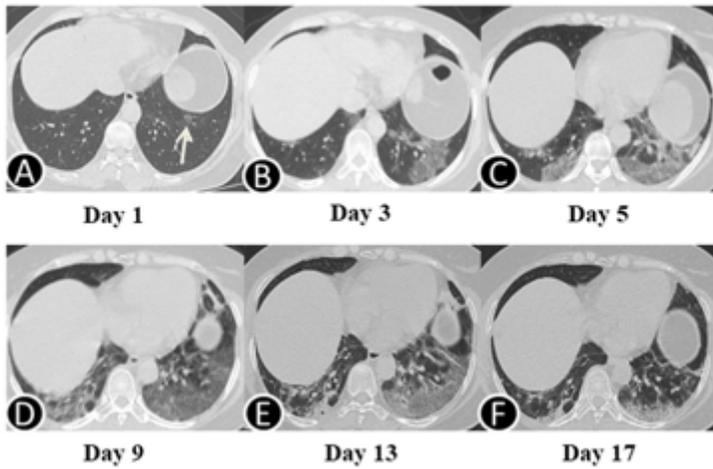


Figure 1

Dynamic change in chest CT images in a severe COVID-19 patient during hospitalization. (A) Day 1. A small region of subpleural GGO in the left lower lobe (white arrow). (B–E) Days 3–13, diffuse GGO in the lower lobe of both lungs. (F) GGO obviously absorbed, which then develop into linear opacities and subsequent consolidation.

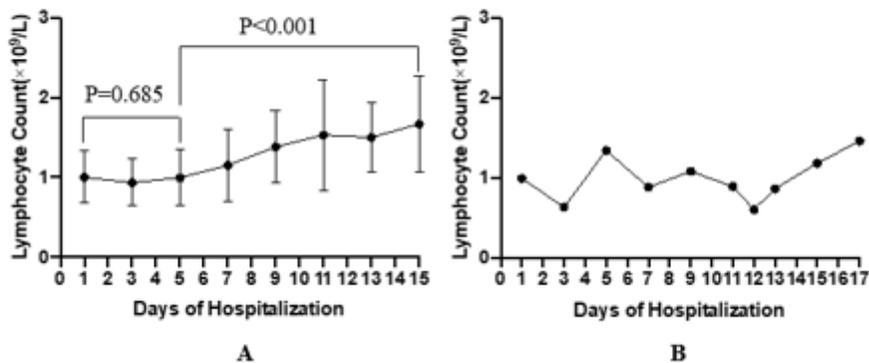


Figure 2

Dynamic change in lymphocyte count during hospitalization. (A) Dynamic change in lymphocyte count in non-severe COVID-19 patients; (B) Dynamic change in lymphocyte count in the severe COVID-19 patient.

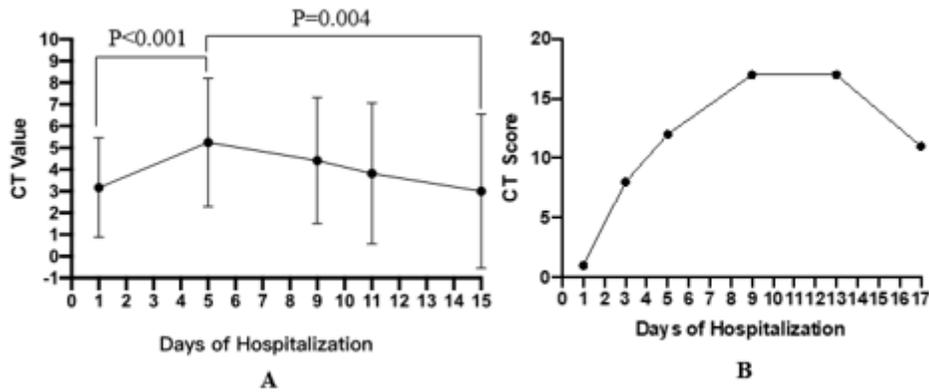


Figure 3

Dynamic change in chest CT score during hospitalization. (A) Dynamic change in CT score in non-severe COVID-19 patients; (B) Dynamic change in CT score in the severe COVID-19 patient.

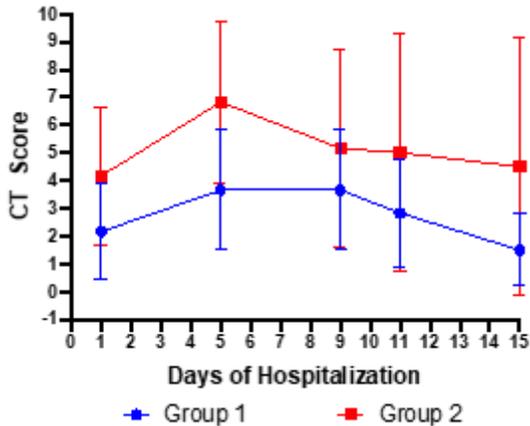


Figure 4

Dynamic change in CT score according to lymphocyte count at admission Group1, patients with normal lymphocyte count at admission; Group 2, patients with lymphocyte count below normal at admission.