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ORIGINAL ARTICLE

Patients without Increased Lymphocyte Counts and Decreased CT Scores During the Early 2nd Week of Illness Onset may Develop to Severe COVID-19

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SUMMARY

Background: **Lymphopenia and high CT score is associated with COVID-19 severity. Herein we describe the change pattern in lymphocyte count and CT score 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. Change patterns in lymphocyte counts and CT scores of all patients were analyzed.**
Results: **Lymphocyte count increased gradually from day 5 post-illness onset (day 5 vs. day 15, p = 0.001). Lymphocyte count of the severe patient fluctuated at low levels throughout the 15-day period. Chest CT scores of non-severe patients increased significantly during the first 5 days of illness onset, but decreased gradually beginning day 9 (illness onset vs. day 5, p = 0.002, day 9 vs. day 15, p = 0.015). In the severe patient, CT score continued to increase over the 11 days post-illness onset period.**
Conclusions: **Non-severe COVID-19 patients had significantly increased lymphocyte counts and decreased CT scores beginning day 5 and day 9 of illness onset, respectively. The patients without increased lymphocyte counts and decreased CT scores during the early 2nd week of illness onset may develop to severe COVID-19.**
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KEYWORDS

COVID-19, lymphocyte count, CT score, dynamic change

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 to the globe [1-4]. Nearly 20% of patients have demonstrated severe or critical illness [5]. The mortality rate of critically ill patients was nearly 60% at 28 days [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. Thirty-five percent of non-severe COVID-19 patients had mild lymphopenia [7]. 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 as one of the risk factors for severe/critical COVID-19 [8]. The lymphocyte counts in patients with a mortal outcome remained at a low level [9,10]. Progressive decline in lymphocyte count was a warning indicator for severe COVID-19 cases. These results suggested that the change pattern of lymphopenia may be a predictor of the severity of COVID-19.

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 [8]. CT score could also reflect the severity of lung abnormalities of non-severe COVID-19 patients [12]. However, studies regarding the change pattern of lymphocyte count and CT score in COVID-19 patients and the relationship between them and disease severity are limited.

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

MATERIALS AND METHODS

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/minute); 2) oxygen saturation (SpO_2) < 93% in resting state; 3) arterial oxygen tension (PaO_2)/inspiratory oxygen fraction (FiO_2) ≤ 300 mmHg. 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. Patients underwent CT scans with a mean interval of 4 ± 1 days. All patients were followed up until discharge or at least 15 days.

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 120 kVp 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 1.0 mm and increment of 1.0 mm).

The major CT demonstrations were described using international standard nomenclature defined by the Fleischner Society glossary and peer-reviewed literature on viral pneumonia, using terms including GGO, crazy-paving pattern, and consolidation [16,17]. A semi-quantitative scoring system was used to quantitatively estimate the pulmonary involvement of all these abnormalities on the basis of the area involved [18]. 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.

Continuous variables were reported as means ± 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. 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

Table 1. Demographic characteristics of Non-severe Patients at Admission.

Characteristics	All patients
Age, year	40 ± 13
Male, n (%)	7 (583.33%)
Had comorbidities, n (%)	
Epidemiology history within 14 days, n (%)	3 (25%)
Residents of Wuhan	3 (25%)
Recently been to Wuhan	2 (16.67%)
Contact with people from Wuhan	2 (16.67%)
Family cluster	2 (16.67%)
Febrile days	1.83 ± 1.69
Maximum temperature before admission, n (%)	
< 37.3℃ 1	1 (8.33%)
37.3 - 38℃	4 (33.33%)
38.1 - 39℃	6 (50%)
39.1 - 40℃	1 (8.33%)
Concomitant symptoms, n (%)	
Dry cough	8 (66.67%)
Shortness of breath	2 (16.67%)
Feeble	1 (8.33%)
Pharyngalgia	1 (8.33%)
Days from illness onset to admission, median (IOR)	2 (1,3)
Davs from illness onset to diagnosis, median (IOR)	2 (1,4)

[a] - Days 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).

between different time points. All analyses were performed with SAS 9 software (SAS institute, Cary, NC, USA). $p \leq 0.05$ was considered statistically significant.

RESULTS

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 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 70 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.

Among the twelve non-severe patients, 11 (91.7%) 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 (PCT), 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 (shown in Table 2).

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

Table 2. Laboratory and radiographic findings of non-severe patient at admission.

Laboratory and radiographic indices	All patients
Blood routine, mean ± SD	
WBC count (× 10^9/L)	**5.36 ± 2.54**
Neutrophil count (× 10^9/L)	**3.80 ± 2.19**
Lymphocyte count (× 10^9/L)	**1.0 ± 0.33**
Platelet count (× 10^9/L)	**179.75 ± 52.13**
Hemoglobin (g/L)	**148 ± 19.54**
Red blood cell count (× 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**
PCT (ng/ml)	**0.05 ± 0.01**
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**

lymphopenia (0.99 × 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 (31 bpm), decreased pulse oxygen saturation without oxygen (90%), and progressive pulmonary opacities found in 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 (shown in Figure 1).

There were no significant differences in lymphocyte count between day 1 and day 5 of illness onset ($p = 0.658$). However, lymphocyte count increased gradually following day 5 post-illness onset (illness onset day 5 vs. day 15, $p = 0.001$; shown in Figure 2A). In contrast, the lymphocyte count of the severe COVID-19 patient fluctuated at a low level throughout the 15-day period (shown in Figure 2B).

Chest CT scores of non-severe COVID-19 patients on day 5 of illness onset were significantly higher than those obtained at the time of illness onset, but maintained a stable state from day 5 to day 9 (illness onset vs. day 5, $p = 0.002$; day 5 vs. day 9, $p = 0.855$). Then they decreased gradually from day 9 until day 15 post-illness onset (day 9 vs. day 15, $p = 0.015$). In contrast, in the severe patient, the CT score continued to increase over the 11-day post-illness onset period (shown in Figure 3).

DISCUSSION

This study showed that the lymphocyte count of non-severe COVID-19 patients did not change significantly within the first 5 days of illness onset, but rose gradually beginning on day 5 until the patients were discharged from hospital. Cao et al. reported that lymphocyte count was lowest on day 7 after illness onset and improved during hospitalization in COVID-19 survivors, whereas severe lymphopenia was observed until death in non-survivors [16]. It would appear that increased lymphocyte count beginning in the early 2nd week of illness onset may be a sign of recovery. Progressive decline in lymphocyte count is a warning indicator for severe COVID-19 cases according to the diagnosis and treatment protocols from the National Health Commission of the People's Republic of China. On the other hand, we found that lymphocyte count of the single severe COVID-19 patient fluctuated at a low level,

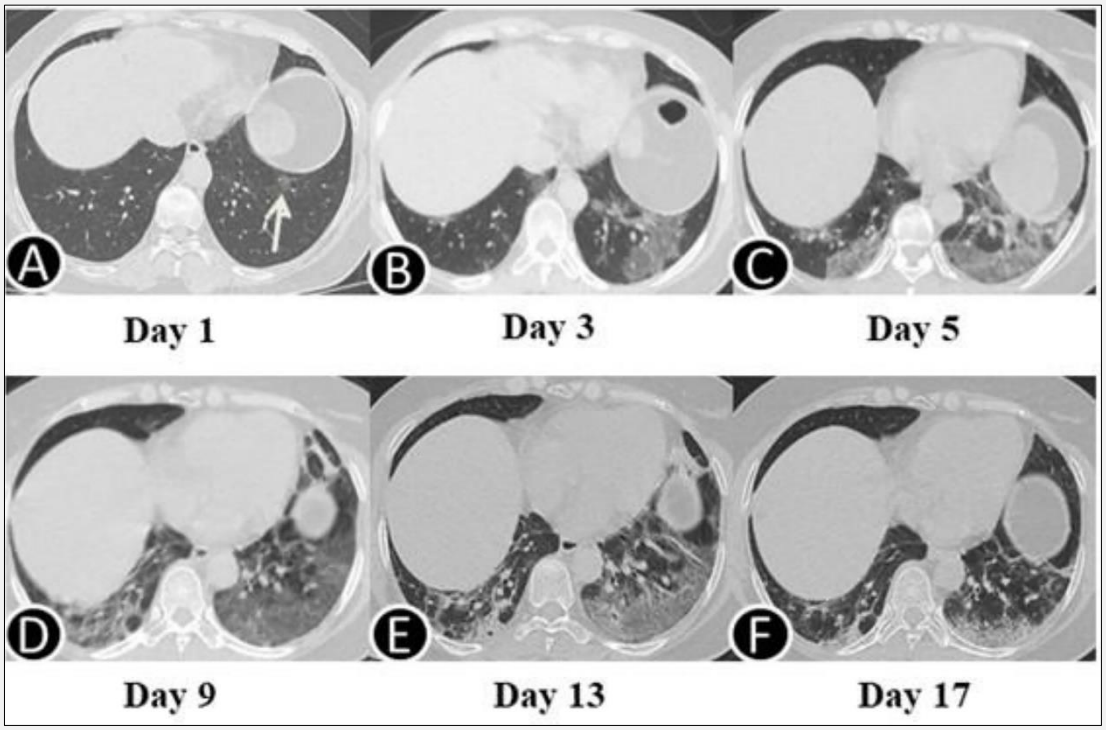

Figure 1. Dynamic change in chest CT images in a severe COVID-19 patient during hospitalization.

(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.

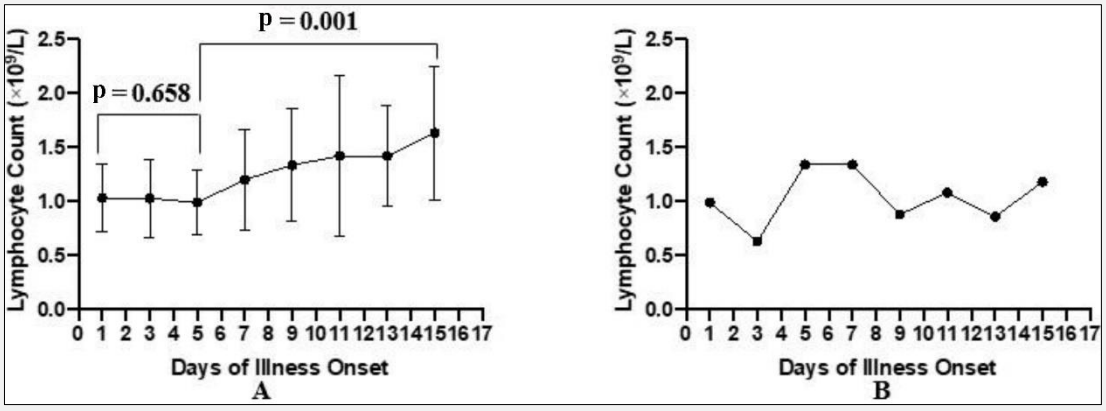

Figure 2. Dynamic change in lymphocyte count during hospitalization.

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

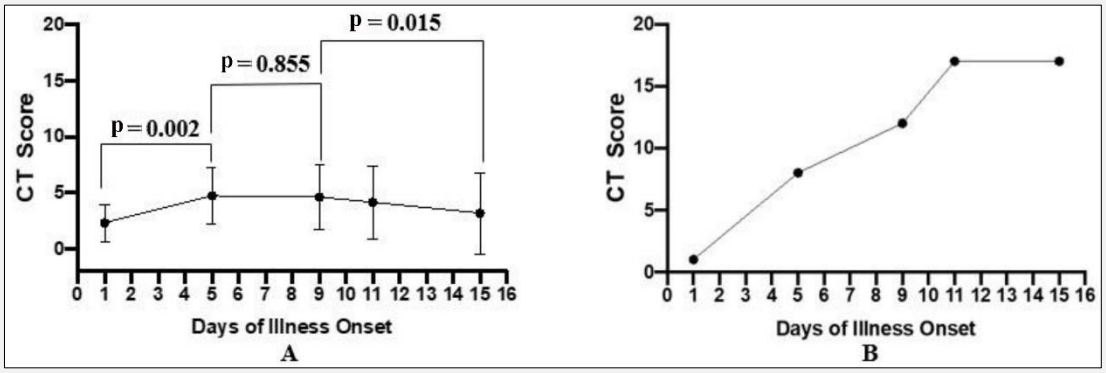

Figure 3. Dynamic change in chest CT score during hospitalization.

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

rather than progressively declining during the first 2 weeks following illness onset in this study. It would appear that the patients whose lymphocyte count did not increase during the 2nd week of illness onset may also develop severe COVID-19.

To our knowledge, rapid progression of intrapulmonary lesions in a short time is another predictor for severe COVID-19. CT score had been used to evaluate the severity of pneumonia caused by SARS-CoV-2, and it was significantly higher in severe patients than non-severe patients [8,12,15]. In this study, the CT score of non-severe COVID-19 patients increased significantly within the first 5 days of illness onset, but maintained a stable state for about 4 days, and then decreased gradually beginning day 9 after illness onset. The CT score of the patient developing severe COVID-19 kept increasing until day 11 following illness onset, and then maintained a stable state for about 4 days. In addition, the severe patient had a higher top CT score than non-severe patients. We speculated that patients without decreased CT score during the early 2nd week following illness onset may likely develop severe COVID-19. Taken together, we hold the opinion that patients without increased lymphocyte counts and decreased CT scores during the early 2nd week following illness onset may develop severe COVID-19. It might help doctors to identify patients at risk of severe COVID-19 as early as possible.

Only 13 patients with confirmed COVID-19 were included in this study, with only one patient developing severe disease. We did not investigate the influence of SARS-CoV-2 on patients' lymphocyte subsets, particularly the percentages and absolute counts of T lymphocytes due to the limitations of detection conditions.

CONCLUSION

In conclusion, non-severe COVID-19 patients had significantly increased lymphocyte counts and decreased CT scores beginning day 5 and day 9 following illness onset, respectively. Patients without increased lymphocyte counts and decreased CT scores during the early 2nd week following illness onset may develop severe COVID-19.

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Declaration of Interest:
None to declare

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