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ORIGINAL ARTICLE

Asthma and Lower Airway Disease

The role of peripheral blood eosinophil counts in COVID-19 patients

Guogang Xie[1] | Fengming Ding[1] | Lei Han[1] | Dongning Yin[1] | Hongzhou Lu[2] | Min Zhang[1]

[1]Department of Respiratory and Critical Care Medicine, Shanghai General Hospital, Shanghai JiaoTong University School of Medicine, Shanghai, China

[2]Department of Clinical Laboratory, Shanghai Public Health Clinical Center, Fudan University, Shanghai, China

Correspondence

Min Zhang, Respiratory and Critical Care Medicine, Shanghai General Hospital, Shanghai JiaoTong University School of Medicine, 100 Haining road, Hongkou District Shanghai, 200080 China.
Email: 13482345145@163.com

Hongzhou Lu, Department of Clinical Laboratory, Shanghai Public Health Clinical Center, Fudan University, 2901 Caolang Road, Jinshan District, Shanghai, 201508 China.
Email: luhongzhou@fudan.edu.cn

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Abstract

Background: Coronavirus disease 2019 (COVID-19) emerged in Wuhan city and rapidly spread globally outside China. We aimed to investigate the role of peripheral blood eosinophil (EOS) as a marker in the course of the virus infection to improve the efficiency of diagnosis and evaluation of COVID-19 patients.

Methods: 227 pneumonia patients who visited the fever clinics in Shanghai General Hospital and 97 hospitalized COVID-19 patients admitted to Shanghai Public Health Clinical Center were involved in a retrospective research study. Clinical, laboratory, and radiologic data were collected. The trend of EOS level in COVID-19 patients and comparison among patients with different severity were summarized.

Results: The majority of COVID-19 patients (71.7%) had a decrease in circulating EOS counts, which was significantly more frequent than other types of pneumonia patients. EOS counts had good value for COVID-19 prediction, even higher when combined with neutrophil-to-lymphocyte ratio. Patients with low EOS counts at admission were more likely to have fever, fatigue, and shortness of breath, with more lesions in chest CT and radiographic aggravation, and longer length of hospital stay and course of disease than those with normal EOS counts. Circulating EOS level gradually increased over the time, and was synchronous with the improvement in chest CT (12 days vs 13 days, $P = .07$), later than that of body temperature (12 days vs 10 days, $P = .014$), but earlier than that of the negative conversion of nucleic acid assays (12 days vs 17 days, $P = .001$).

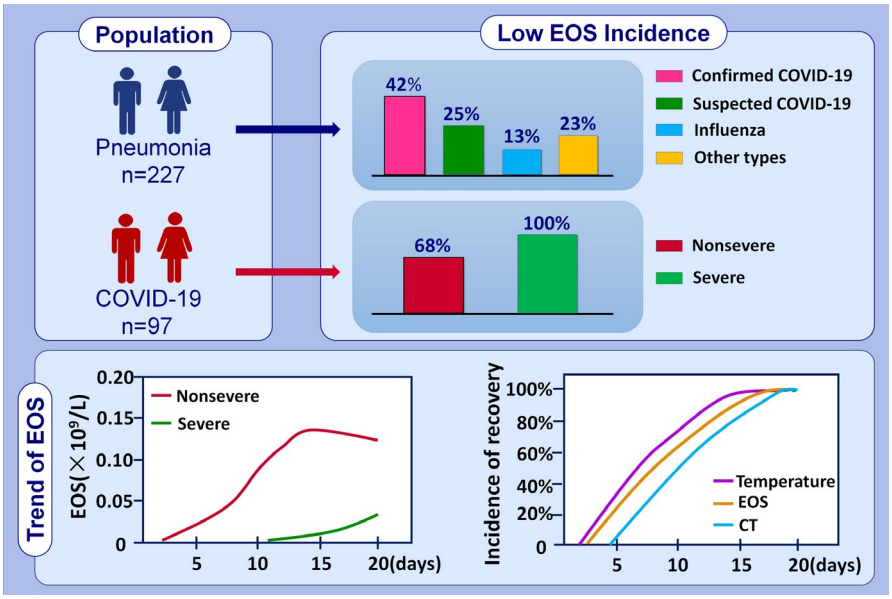
Conclusion: Peripheral blood EOS counts may be an effective and efficient indicator in diagnosis, Evaluation, and prognosis monitoring of COVID-19 patients.

KEYWORDS

COVID-19, diagnosis, peripheral blood eosinophils, pneumonia, prognosis

Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CT, computed tomography; EOS, eosinophils; ESR, erythrocyte sedimentation rate; HRCT, high-resolution computed tomography; ICU, intensive care unit; IFN-γ, interferon-γ; IL-13, interleukin-13; IL-1β, interleukin-1β; IL-4, interleukin-4; IL-5, interleukin-5; IL-8, interleukin-8; IQR, interquartile range; MERS, Middle East respiratory syndrome; NLR, neutrophil-to-lymphocyte ratio; PaO_2, arterial partial pressure of oxygen; RANTES, regulated on activation normal T-cell expressed and secreted; RBC, red blood cell; ROC, receiver operating characteristic; RSV, respiratory syncytial virus; SARS, severe acute respiratory syndrome; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Th2, T-helper 2 cell; TNF-α, tumor necrosis factor α; VEGF, vascular endothelial growth factor; WBC, white blood cell; WHO, World Health Organization.

Guogang Xie, Fengming Ding, and Lei Han contributed equally to this work and should be considered as cofirst authors.



GRAPHICAL ABSTRACT

The circulating eosinophil counts decrease dramatically in most COVID-19 patients. Low eosinophil counts and slow recovery may be related to severe conditions. The restore of eosinophil counts is synchronous with the improvement of chest CT, later than that of body temperature, but earlier than the negative conversion of nucleic acid assays.

Abbreviations: COVID-19, coronavirus disease 2019; CT, computed tomography; EOS, eosinophil.

1 | INTRODUCTION

Since December 2019, many pneumonia patients with unknown cause have emerged in Wuhan, the capital city of Hubei Province in China. Fever, fatigue, and dry cough are common symptoms at the onset, and progressive dyspnea occurs in severe cases. The typical chest CT findings showed peripheral pulmonary plaques and interstitial lesions, which were very similar to viral pneumonia.[1] This pathogen has currently been named severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), which has a phylogenetic similarity to SARS-CoV.[2,3] By the time of writing, the number of patients infected by the virus has now reached 143 000 and over 100 countries have reported confirmed cases.

To prevent transmission, how to figure out the potential suspected COVID-19 pneumonia patients and isolate them immediately is now the priority for physician in fever clinics in China. And also, for the confirmed COVID-19 patients, most patients have mild symptoms, which may be indistinguishable clinically from common cold at the early stage of infection. However, in a median of 8 days from onset,[4] nearly 15%-20% of them will exacerbate with progressive dyspnea abruptly and rapidly develop into acute respiratory distress syndrome or end-organ failure. The characteristics of potential critical patients are still unclear. Therefore, how to use appropriately simple and effective method to screen out potentially serious patients is important for the prognosis of the disease.

In the process of diagnosing and treating COVID-19 patients, we found that peripheral blood eosinophils (EOS) significantly reduced among most patients regardless of the severity of the diseases at the early stage, which had not been reported in severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS),[5,6] or the other types of pneumonia. Here, we aim to discuss this interesting phenomenon and try to clarify its clinical significance in COVID-19. We hope our findings of the EOS in convenient routine blood test will be helpful for differential diagnosis and evaluating the prognosis of COVID-19 patients.

2 | METHODS

2.1 | Study population

Firstly, patients who visited the fever clinics of Shanghai General Hospital (Shanghai, China) between January 22 and February 6, 2020, diagnosed of pneumonia were involved in this study. Among these patients, there were confirmed COVID-19 patients, suspected patients, influenza pneumonia patients, and pneumonia patients infected with other pathogens. Suspected patients were defined according to the fourth edition of Prevention and Control Guidance for COVID-19 published by the National Health Commission of China. Once COVID-19 was suspected, they were isolated immediately, and reported to Local Center for Disease Control for real-time reverse transcription-polymerase chain reaction (RT-PCR) tests (Shengjie Health Technology Corp) intended for the qualitative detection of nucleic acid from SARS-CoV-2 in nasopharyngeal swab. The sequences of the primer and probe target to envelope gene of SARS-CoV-2 were: 5′-ACTTCTTTTTCTTGCTTTCGTGGT-3′ (forward),

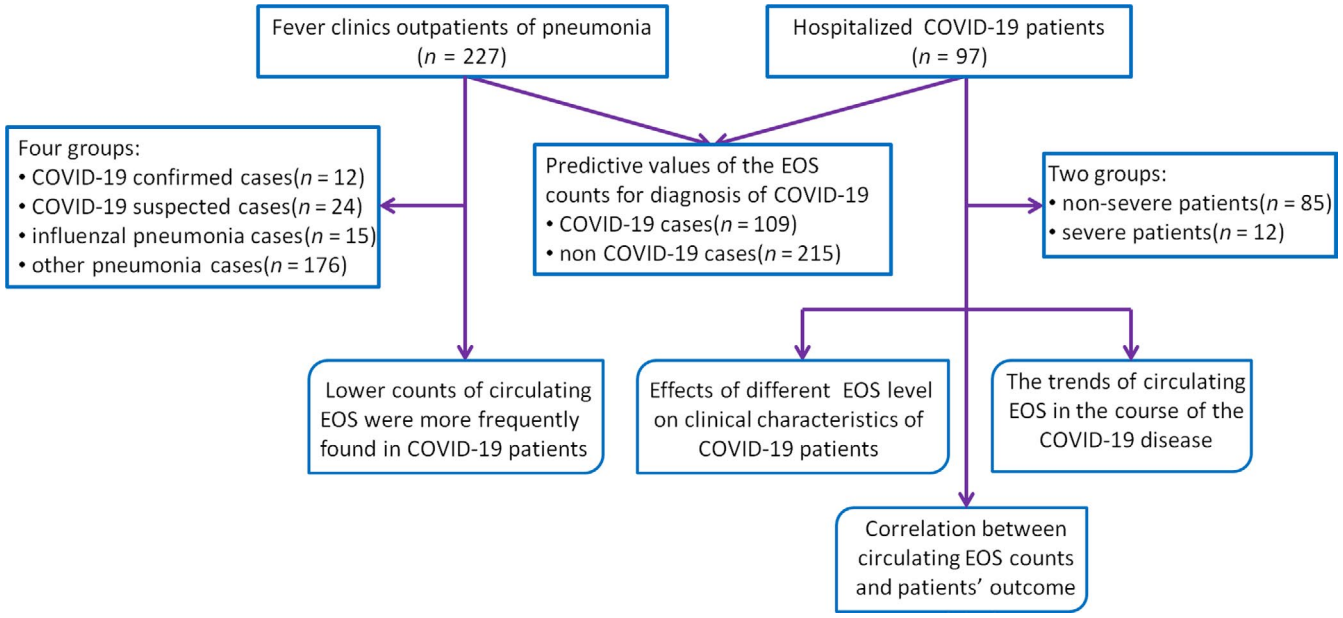


FIGURE 1 schematic overview of the study design (unmarked)

5′-GCAGCAGTACGCACACAATC-3′ (reverse), and the probe 5′CY5-CTAGTTACACTAGCCATCCTTACTGC-3′BHQ1 (Figure 1).

Secondly, we obtained data of hospitalized COVID-19 patients who admitted to Shanghai Public Health Clinical Center from January 20 to February 20, 2020. COVID-19 was confirmed according to WHO interim guidance.[7]

This is a retrospective cohort study. The Ethics Committee of Shanghai General Hospital approved this study and granted a waiver of informed consent from study participants.

2.2 | Data collection

Characteristics of subjects from the Shanghai General Hospital were collected as follows: age; gender; duration of fever; accompanying symptoms of fever; COVID-19–related epidemiological history; and body temperatures. Blood routine tests included the following parameters: red blood cell (RBC) counts, hemoglobin, white blood cell (WBC) counts, percentage and absolute counts of neutrophils, lymphocytes, monocytes, EOS, and basophils, and C-reactive protein (CRP). Chest HRCT scans (slice thickness was 0.625 mm, GE Medical System) were performed.

In Shanghai Public Health Clinical Center, we reviewed electronic records to collect clinical charts, nursing records, laboratory findings, and radiologic assessments for all patients. Radiologic assessments included chest radiography or computed tomography (CT). Laboratory and radiologic examinations were performed every 2-3 days. The end point was discharge from hospital or death. Epidemiological, demographic, clinical, laboratory, management, and outcome data were collected and recorded with standardized data collection forms. Throat swab samples were obtained from all patients once a day and tested using real-time reverse transcription-polymerase chain reaction assays.

All data were recorded and checked separately by two qualified researchers.

2.3 | Definitions

Fever was defined as an axillary temperature above 37.5°C. Hypoxemia was defined as arterial oxygen tension (PaO2) below 60 mm Hg when breathing air, or PaO_2 over inspiratory oxygen fraction (FIO_2) of less than 300 mm Hg. Severe and nonsevere cases were defined according to WHO interim guidance.[7] Influenza pneumonia was diagnosed based on chest CT showing interstitial lesions, accompanied by flu-like symptoms (fever > 38.5℃, accompanied by cough or sore throat) and positive serum influenza A or B IgM. Decrease in circulating EOS counts was defined as the absolute value of peripheral blood EOS being below the lower limit of the normal range of the test ($<0.02 \times 10^9$/L), so was lymphopenia ($<1.0 \times 10^9$/L). Fatigue was defined as a feeling of extreme physical or mental tiredness. Shortness of breath, or dyspnea, was defined as a feeling of difficult or labored breathing that was out of proportion to the patient's level of physical activity.

2.4 | Statistical analysis

Continuous variables were expressed as mean (SD) and compared with t test if they were normally distributed, and median (IQR) and compared with the Mann-Whitney U test if they were not; categorical variables were expressed as counts with percentages

TABLE 1 Clinical characteristics of patients with COVID-19, suspected cases, influenza, and other type of pneumonia at fever clinics (unmarked)

Parameters (reference values)	COVID-19 cases (n = 12)	Suspected cases (n = 24)	Influenza pneumonia (n = 15)	Other pneumonia (n = 176)
Age, y	51.0 (34.0-68.0)	45.0 (35.0-63.0)	53.0 (34.0-75.0)	52.0 (32.0-73.0)
Sex (male/female)	06 June	16 August	09 June	92/84
Symptoms				
Duration of fever, days	3 (1-4)	3 (0-4)	3 (1-4)	4 (2-5)
Sore throat	4/12 (33.3%)	7/24 (29.2%)	6/15 (40.0%)	65/176 (36.9%)
Cough	9/12 (75.0%)	16/24 (66.7%)	9/15 (60.0%)	145/176 (82.4%)
Sputum production	3/12 (25.0%)	8/24 (33.3%)	4/15 (26.7%)	66/176 (37.5%)
Fatigue	8/12 (66.7%)	14/24 (58.3%)	10/15 (66.7%)	70/176 (39.8%)
Shortness of breath	1/12 (8.3%)	2/24 (8.3%)	2/15 (13.3%)	32/176 (18.2%)*,***
Nausea or vomiting	1/12 (8.3%)	1/24 (4.2%)	1 (6.7%)	10/176 (5.7%)
Diarrhea	1/12 (8.3%)	3/24 (12.5%)	1 (6.7%)	15/176 (8.5%)
Blood parameter counts				
White blood cell (4.0-10.0 × 10^9/L)	5.2 (4.1-6.8)	6.53 (4.6-8.6)	7.8 (4.4-10.9)*,**	8.95 (6.3-10.4)*,***
<4	2/12 (16.7%)	4/24 (16.7%)	2/15 (13.3%)	8/176 (4.5%)
4-10	10/12 (83.3%)	19/24 (79.2%)	10/15 (66.7%)	124/176 (70.5%)
>10	0	1/24 (4.2%)	3/15 (20%)	45/176 (25.6%)
Neutrophils (2.0-6.0 × 10^9/L)	3.2 (2.3-3.9)	4.7 (2.9-5.3)	5.94 (2.71-7.65)*,***	6.61 (4.21-7.92)*,***
<2	1/12 (8.3%)	1/24 (4.2%)	2/15 (13.3%)	6/176 (3.4%)
2-6	11/12 (91.7%)	20/24 (83.3%)	7/15 (46.7%)	83/176 (47.2%)
> 6	0	3/24 (12.5%)	6/15 (40%)	88/176 (50.0%)
Lymphocytes (1.0-3.5 × 10^9/L)	1.4 (0.8-1.8)	1.4 (0.8-1.7)	1.2 (0.7-1.8)	1.5 (0.9-2.0)
<1	4/12 (33.3%)	8/24 (33.3%)	7/15 (46.7%)	48/176 (27.3%)
≥1	8/12 (66.7%)	16/24 (66.7%)	8/15 (53.3%)	129/176 (73.3%)
Monocytes (0.1-0.6 × 10^9/L)	0.44 (0.34-0.57)	0.49 (0.36-0.64)	0.51 (0.39-0.64)	0.63 (0.42-0.75)
<0.6	10/12 (83.3%)	15/24 (62.5%)	9/15 (60%)	96/176 (54.5%)
≥0.6	2/12 (16.7%)	9 (37.5%)	6/15 (40%)	81/176 (46.0%)
Eosinophils (0.02-0.5 × 10^9/L)	0.03 (0.0.01-0.04)	0.08 (0.02-0.13)#	0.09 (0.02-0.10)*,***	0.08 (0.01-0.10)*,***
0	3/12 (25%)	1/24 (4.2%)	0	8/176 (4.5%)
<0.02	5/12 (41.7%)	6/24 (25%)	2/15 (13.3%)	40/176 (22.7%)
≥0.02	7/12 (58.3%)	18/24 (75%)	13/15 (86.7%)	128/176 (72.8%)
Hemoglobin (115-150 g/L)	140 (129-157)	145 (124-160)	142 (116-152)	144 (120-156)
Platelet (100-400 × 10^9/L)	148 (112-206)	164 (119-193)	147 (106-187)	163 (121-186)
Neutrophils (40%-70%)	62.6 (55.7-76.0)	70.1 (58.8-78.6)	72.4 (65.3-80.6)	73.2 (65.1-83.1)
Lymphocytes (20%-50%)	27.6 (16.2-35.9)	20.7 (12.1-26.8)	18.6 (10.9-23.9)	18.9 (11.4-24.6)
Monocytes (3%-10%)	8.8 (7.3-11.4)	7.8 (5.5-9.6)	7.75 (5.2-8.3)	7.45 (5.2-9.0)
Eosinophils (0.4%-8%)	0.6 (0.2-0.8)	1.1 (0.2-2.4)*,***	1.4 (0.3-2.4)*,***	0.9 (0.1-1.3)*,***
C-reactive protein (0-10 mg/L)	16.0 (3.6-21.2)	45.0 (5.0-52.1)*,**	13.9 (3.2-16.5)	43.4 (5.5-63.0)*,**

Note: Data are median (IQR) or n/N(%),where N is the total number of patients with available data.

P values comparing the group of COVID-19 cases and other groups are from chi-squared test or Mann-Whitney U test.

*$P < .05$.

**$P < .01$.

and compared with chi-square test or Fisher's exact test. Pearson correlation analysis was used to investigate the correlation of continuous variables. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic ability. A two-sided α of less than 0.05 was considered statistically significant. All the analyses were performed with the use of SPSS (version 20.0).

3 | RESULTS

3.1 | EOS findings in COVID-19 group comparing with other types of pneumonia groups

A total of 227 fever clinics outpatients of pneumonia were enrolled, 36 cases of suspected patients were isolated immediately, and finally, 12 cases were confirmed with COVID-19. The pathogen was not clearly identified in the remaining suspected COVID patients, but they were all received close observation and their conditions were significantly improved in the end. Meanwhile, 15 cases of influenza pneumonia, and 176 cases of other types of pneumonia were diagnosed. Conditions of the patients on admission are shown in Table 1. There was no significant difference in age and gender among the patients in each group. Duration of fever was 1.43 ± 0.67 days for total subjects. No significant difference in the median interval from the onset of fever to hospital visit of each group of patients was found. In addition to fever, the most common symptoms were cough and fatigue. Fatigue was more common in COVID-19 patients, suspected patients, and influenza pneumonia patients than other types of pneumonia patients (66.7%, 58.3%, 66.7% vs 39.8%).

For blood parameters, lower counts of EOS were more frequently found in COVID-19 group compared with the other three groups. Three COVID-19 patients' circulating EOS vanished, while the patients in other groups rarely shared the same results. Lower percentages of white blood cells and neutrophils were found both in COVID-19 patient group and suspected patient group compared with the other types of pneumonia group, while no difference was seen in lymphocytes.

CRP was higher in other types of pneumonia subjects than in confirmed and suspected COVID-19 patients (Table 1).

The data of EOS counts and neutrophil-lymphocyte ratio (NLR) of all patients with COVID-19 (109 cases) and non–COVID-19 pneumonia (215 cases) were extracted, whose predictive values were evaluated by means of ROC curves. The EOS counts had AUC of 0.74 and the cutoff value was 0.015 for the diagnosis of COVID-19, while NLR had AUC of 0.73 and the cutoff value was 2.425 for the diagnosis of COVID-19. The combination of the EOS counts and NLR had a better diagnosis value (AUC = 0.82) for COVID-19 than either indicator (Figure 2, Table 2).

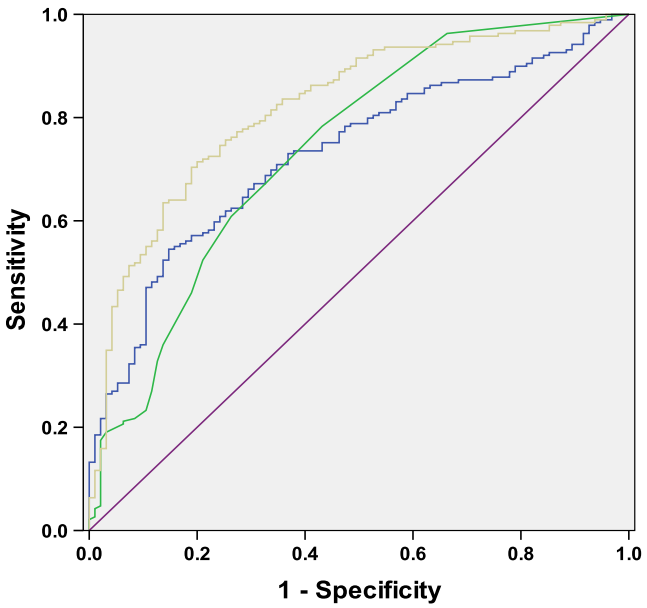


FIGURE 2 ROC curve analysis was performed to evaluate the diagnostic ability of COVID-19 (unmarked). The EOS counts (green line) had AUC of 0.74, and the cutoff value was 0.015; NLR (blue line) had AUC of 0.73, and the cutoff value was 2.425; the combination of the EOS counts and NLR (yellow line) has a better diagnosis value (AUC = 0.82) for COVID-19 than either indicator

3.2 | EOS findings in nonsevere and severe COVID-19 patients

We collected 97 hospitalized patients with laboratory-confirmed COVID-19 including 85 nonsevere patients and 12 severe patients in Shanghai Public Health Center for analysis. All nonsevere patients and nine severe patients had been discharged, while three severe patients had received mechanical ventilation and one of them had died finally. The median age of the patients was 46.0 years (IQR 32.0-61.0; Table 3) with the median age of severe patients (52.0, IQR 35.0-66.0) being older than nonsevere patients (45.0, IQR 32.0-60.0) ($P = .092$). More than half of the infected patients were men (54.6%), and the gender ratio of male to female was almost equal (43/42) in nonsevere patients, while the majority of severe patients were male (83.3%). In all the patients, 67.0% of patients never smoked and nearly half of the patients (47 [48.4%]) had at least one underlying comorbidity including hypertension (20.6%), cardiovascular disease (7.2%), and diabetes (5.2%), which were comparable in two groups. The most common symptoms were cough (68.0%), followed by fever (60.8%), fatigue (38.1%), sputum production (37.1%), and shortness of breath (21.6%). Symptoms presented by subjects in severe patient group include fever (91.7%), cough (66.7%), and shortness of breath (83.3%), similar to the results of other studies,[8] while only 12.9% of the nonsevere patients developed shortness of breath. On admission, all patients with chest CT scan had abnormal results, the majority (83.5%) had multilobular lesions, which could be seen in most COVID-19 severe patients (91.7%). The representative chest CT images showed bilateral multiple lobular and subsegmental areas of ground-glass opacities or consolidation. The median interval from the onset of symptoms to hospital admission for all patients was 7 days (IQR, 5-8) with no significant difference between severe and nonsevere patients ($P = .314$), followed by median time of hospitalization as 12 days (IQR, 9-14), and the total disease course was 19 days (IQR, 13-23). The length of hospitalization and the total course of illnesses in severe patients were significantly longer than nonsevere patients ($P = .045$), as expected (Table 3).

TABLE 2 Predictive values of EOS counts, NLR and their combination in diagnosis of COVID-19

Characteristic variables	AUC	Cutoff values[a]	Sensitivity, %	Specificity, %	95% CI	*P* value
EOS	0.739	0.015	68.2	75.0	0.676, 0.802	.002
NLR	0.731	2.425	67.2	72.3	0.672, 0.790	.003
EOS + NLR	0.821	—	77.0	87.2	0.770, 0.872	<.001

[a]The cutoff points were selected by maximizing the sum of sensitivity and specificity.

EOS counts decreased below 0.02×10^9/L in 71.7% of COVID-19 patients, including 45.4% of patients dropped below the lower limit of detection, and the EOS counts decreased below the lower limit of detection in all 12 severe patients. In contrast, the reduction of lymphocytes in these two patients' groups was not shown significant difference, with 35.3% in nonsevere patients and 41.4% in severe patients, respectively. However, there was a positive correlation between EOS and lymphocyte levels in the two groups of patients ($r = 0.414$, $P < .05$). We also found significant differences in neutrophil-to-lymphocyte ratio (NLR) ($P = .026$) and plasma D-dimer level ($P = .014$) between severe and nonsevere patients (Table 4).

3.3 | Effects of different EOS levels on clinical characteristics of patients with COVID-19

We divided COVID-19 patients into two groups based on the circulating EOS counts when admitted to the hospital, low EOS group ($<0.02 \times 10^9$/L) and normal EOS group ($\geq 0.02 \times 10^9$/L). No significant differences in gender ($P = .063$), age ($P = .314$), and median interval from onset to hospitalization ($P = .104$) were identified between two groups. The proportion of patients in low EOS group who developed fever (71.0% vs 35.7%, $P = .001$), fatigue (44.9% vs 21.4%, $P = .013$), and shortness of breath (24.6% vs 14.3%, $P = .028$) was significantly higher than that of normal EOS group. Moreover, low EOS group had more lesions on chest CT than the group with normal EOS group (3.0, IQR 1.0-5.0 vs 2.0, IQR 1.0-3.0, $P = .04$). The incidence of radiographic aggravation was also higher in patients with low EOS (66.7%) than patients with normal EOS (25%) ($P = .001$). Compared with patients with normal EOS counts, the length of hospital stay ([12.0 days, IQR 8.0-17.0] vs [9.0 days, IQR 7.0-14.0], $P = .039$) and course of disease ([20.0 days, IQR 15.0-24.0] vs [16.0 days, IQR 13.0-20.0], $P = .018$) were both longer in patients with low EOS (Table 5).

3.4 | The trends of circulating EOS in the course of the COVID-19 disease

We started to calculate the course of the disease from the onset. Available data of peripheral blood EOS counts from all discharged patients were superimposed according to the distribution. The average value of the EOS counts in the same course was regarded as the value of the day, and the incidence of EOS reduction (the ratio of the number of EOS counts below 0.02×10^9/L to the total number of EOS counts) on every day since onset was also calculated. It showed that EOS in peripheral blood decreased significantly from the onset. In the first 4 days of the course, EOS level of the patients was lower than normal significantly with over 80% of EOS counts below $0.02 \times 10^{9/}$L on the fourth day. EOS level gradually increased over the time, and fully recovered and reached its peak on the 16th day. At the same time, the incidence of EOS reduction progressively decreased and dropped below the lower limit of detection on the 18th day, suggesting that all patients' EOS counts return to normal level (Figure 3A). However, lymphocytes did not show such a significant trend (Figure 3B).

We also compared the recovery trend of EOS in severe and nonsevere patients. The EOS counts of severe patients began to recover slowly after ten days since onset, while those of nonsevere patients recover much faster from the trough point on the 4th day (Figure 3C). Thus, there were obvious differences in recover speed according to disease severity.

3.5 | Correlation between circulating EOS counts and patients' outcome

Assessment on the improvement in disease was done according to normal body temperature, improvement in chest CT evidence, and negative conversion of nucleic acid assays. We compared the recovery time of EOS counts in peripheral blood with the above three indicators, and found that the recovery time of EOS counts was slightly shorter than that of chest CT (12 days, IQR 8-14 vs 13 days, IQR 8-16), though there was no statistical difference ($P = .07$), and their improvements were almost synchronous (Figure 3D,G). The recovery time of EOS counts was longer than that of body temperature (12 days, IQR 8-15 vs 10 days, IQR 7-13, $P = .014$), with an average extension of about 2 days (Figure 3E,H), but was shorter than that of nucleic acid assays turning negative (12 days, IQR 8-15 vs 17days, IQR 13-20, $P = .001$), with an average of 5 days in advance (Figure 3F,I).

We also superimposed the incidence of the recovery (the ratio of the number of normal cases to the total cases) of the above indicators including body temperature, improvement of chest CT, and EOS counts, observing their changing trends according to the course of

TABLE 3 Clinical characteristics of the patients, according to disease severity (unmarked)

	Total (n = 97)	Nonsevere (n = 85)	Severe (n = 12)	*P* value
Age, years	46.0 (32.0-61.0)	45.0 (32.0-60.0)	52.0 (35.0-66.0)	.092
Sex (male/female)	53/44	43/42	10-Feb	.003
BMI (kg/m2)	23.6 (21.4-25.4)	23.5 (21.1-25.0)	23.8 (22.4-25.6)	.179
Smoking history				
Never smoked	65/97 (67.0%)	59/85 (69.5%)	6/12 (50.0%)	.132
Former smoker	12/97 (12.4%)	11/85 (12.9%)	1/12 (8.3%)	.108
Current smoker	20/97 (20.6%)	15/85 (17.6%)	5/12 (41.7%)	.027
Complications				
Hypertension	20/97 (20.6%)	16/85 (18.8%)	4/12 (33.3%)	.042
Coronary heart disease	7/97 (7.2%)	5/85 (5.9%)	2/12 (16.7%)	.032
Diabetes	5/97 (5.2%)	3/85 (3.5%)	2/12 (16.7%)	.068
Cerebrovascular disease	2/97 (2.1%)	2/85 (2.4%)	0	.164
COPD	3/97 (3.3%)	2/85 (2.4%)	1/12 (4.2%)	.247
Asthma	1/97 (1.0%)	1/85 (1.1%)	0	.366
Gout	3/97 (3.3%)	2/85 (2.4%)	1/12 (4.2%)	.184
Hypothyroidism	1/97 (1.0%)	1/85 (1.1%)	0	.326
Malignant tumor	1/97 (1.0%)	1/85 (1.1%)	0	.413
Hepatitis B infection	2/97 (2.1%)	2/85 (2.4%)	0	.268
Chronic renal disease	2/97 (2.1%)	1/85 (1.1%)	1/12 (4.2%)	.182
Symptoms				
Fever	59/97 (60.8%)	48/85 (56.5%)	11/12 (91.7%)	.022
Sore throat	23/97 (23.7%)	21/85 (24.7%)	2/12 (16.7%)	.164
Cough	66/97 (68.0%)	58/85 (68.2%)	8/12 (66.7%)	.709
Sputum production	36/97 (37.1%)	32/85 (37.6%)	4/12 (33.3%)	.685
Fatigue	37/97 (38.1%)	31/85 (36.5%)	6/12 (50.0%)	.076
Shortness of breath	21/97 (21.6%)	11/85 (12.9%)	10/12 (83.3%)	.006
Nausea or vomiting	9/97 (9.3%)	8/85 (9.4%)	1/12 (4.2%)	.308
Diarrhea	6/97 (6.2%)	5/85 (5.9%)	1/12 (4.2%)	.646
Radiologic assessments				
Single lobe	16/97 (16.5%)	15/85 (17.6%)	1/12 (8.3%)	.034
Multiple lobe	81/97 (84.5%)	70/85 (82.4%)	11/12 (91.7%)	.614
Duration of disease, days				
From onset to admission	7.0 (5.0-8.0)	7.0 (5.0-8.0)	6.0 (3.0-6.0)	.314
From admission to discharge	12.0 (9.0-14.0)	11.0 (9.0-13.0)	18.0 (15.0-23.0)	.017
Total	19.0 (13-23.0)	18.0 (13-20.0)	23.0 (19.0-25.0)	.045
Outcome				
Discharge	94/97 (96.9%)	85/85 (100%)	9/12 (75.0%)	.032
Mechanical ventilation	3/97 (3.1%)	0	3/12 (25.0%)	.078
Death	1/97 (1.0%)	0	1/12 (8.3%)	.132

Data are median (IQR) or n/N (%), where N is the total number of patients with available data.

P values comparing the group of nonsevere and severe patients are from chi-squared test or Mann-Whitney U test.

The primary composite end point was discharged from hospital, or death.

the disease. We can clearly observe fully recovered body temperature on 15th day, which was in the first place, the second place was EOS on 18th day, and then followed chest CT image on 19th day in all discharged patients (Figure 3J).

4 | DISCUSSION

In previous reports, patients hospitalized with SARS-COV-2 infection showed leukopenia and lymphopenia,[4,9] which is similar to SARS

TABLE 4 Laboratory findings of COVID-19 patients on admission to hospital (Unmarked)

Parameters (reference values)	Total (n = 97)	Nonsevere (n = 85)	Severe (n = 12)	*P* value
White blood cell (4.0-10.0 × 10^9/L)	5.0 (3.7-5.9)	5.1 (3.8-5.9)	4.3 (3.4-4.9)	.108
<4	28/97 (28.9%)	24/85 (28.2%)	4/12 (33.3%)	—
4-10	68/97 (70.1%)	60/85 (70.6%)	8/12 (66.7%)	—
>10	1/97 (1.0%)	1/85 (1.2%)	0	—
Neutrophils (2.0-6.0 × 10^9/L)	3.3 (2.3-3.7)	3.3 (2.3-3.8)	3.4 (2.2-4.1)	.275
<2	13/97 (13.4%)	10/85 (11.8%)	3/12 (25.0%)	—
2-6	76/97 (78.4%)	68/85 (80.0%)	8/12 (66.7%)	—
>6	8/97 (8.2%)	7/85 (8.2%)	1/12 (8.3%)	
Lymphocytes (1.0-3.5 × 10^9/L)	1.3 (0.8-1.7)	1.3 (0.8-1.6)	1.2 (0.6-2.3)	.293
<1	35/97 (36.1%)	30/85 (35.3%)	5/12 (41.7%)	—
≥1	62/97 (63.9%)	55/85 (64.7%)	7/15 (58.3%)	—
Monocytes (0.1-0.6 × 10^9/L)	0.5 (0.3-0.6)	0.5 (0.3-0.6)	0.6 (0.2-0.7)	.141
<0.6	70/97 (72.2%)	64/85 (75.3%)	6/12 (50.0%)	—
≥0.6	27/97 (27.8%)	21/85 (24.7%)	6/12 (50.0%)	—
Eosinophils (0.02-0.5 × 10^9/L)	0.02 (0-0.04)	0.03 (0-0.04)	0	.001
0	44/97 (45.4%)	32/85 (37.6%)	12/12 (100%)	—
<0.02	69/97 (71.1%)	57/85 (67.9%)	12/12 (100%)	—
≥0.02	28/97 (28.9%)	28/85 (32.9%)	0	—
NLR	2.74 (2.03-3.96)	2.49 (1.73-3.55)	3.0 (1.56-6.55)	.026
Hemoglobin (115-150 g/L)	140 (124-155)	141 (126-157)	137 (117-153)	.722
Platelet (100-400 × 10^9/L)	147 (122-201)	154 (128-205)	144 (117-192)	.164
Neutrophils (40%-70%)	71.4 (55.6-77.4)	71.3 (56.2-78.5)	71.9 (52.6-77.8)	.845
Lymphocytes (20%-50%)	19.3 (13.0-25.9)	19.4 (13.4-25.6)	18.6 (12.5-26.7)	.441
Monocytes (3%-10%)	8.0 (5.6-9.7)	7.9 (5.8-9.2)	8.3 (5.4-10.1)	.383
Eosinophils (0.4%-8%)	0.9 (0-1.6)	1.2 (0-2.2)	0	.001
C-reactive protein (0-10 mg/L)	16.8 (3.4-26.8)	15.5 (1.8-19.1)	20.4 (7.6-38.4)	.314
Albumin (30-55 g/L)	36.2 (32.8-41.2)	37.5 (34.3-43.8)	29.1 (26.5-31.3)	.003
ESR (0-10 mm/h)	60 (22-92)	62 (29-87)	56 (16-94)	.703
D-dimer (0-0.5 mg/L)	0.68 (0.33-0.84)	0.65 (0.28-0.72)	1.25 (0.48-3.56)	.014
Duration of disease, days				
From onset to admission	7.0 (5.0-8.0)	7.0 (5.0-8.0)	6.0 (3.0-6.0)	.092

Note: Data are median (IQR) or n/N (%), where N is the total number of patients with available data.

P values comparing the group of nonsevere and severe patients are from chi-squared test or Mann-Whitney U test.

and MERS infections and indistinguishable from other viral respiratory infections such as influenza.[10] Our study discovered that fewer patients with SARS-COV-2 appeared leukopenia, less than half had lymphopenia, while nearly three-quarters had a reduction in circulating EOS, even disappeared at the onset of disease and regardless of the severity of the disease. It was a unique characteristic compared with other types of pneumonia and may have a role in diagnosis in COVID-19 patients, which was not mentioned before. The clinical course of COVID-19 demonstrated the complexity of the COVID-19 profile with different clinical presentations. Clinical manifestations ranged from asymptomatic cases to patients with mild and severe symptoms, with or without pneumonia.[11] It was difficult to distinguish the radiologic manifestations between patients infected with SARS-COV-2 and other respiratory pathogens, and almost half COVID-19 patients' temperature was normal at the beginning. Our analysis of fever clinics patients with pneumonia found that EOS counts of peripheral blood in patients with COVID-19 were significantly reduced, which was further confirmed by the data in hospitalized COVID-19 patients. Data analysis showed that decreased EOS counts were more common in COVID-19 patients than other types of pneumonia, and no significant difference was identified between severe and nonsevere patients, which was also mentioned in patients from Wuhan[12,13] or outside Wuhan.[14] Nearly half patients, especially for the severe patients, could not be detected circulating EOS at all, demonstrating that the decreased EOS counts may be an important diagnostic clue for SARS-CoV-2 infection in suspected

TABLE 5 Clinical characteristics of the study patients, according to eosinophils level on admission (unmarked)

	Low EOS ($<0.02 \times 10^9$/L), n = 69	Normal EOS ($\geq 0.02 \times 10^9$/L), n = 28	*P* value
Age, years	47.0 (34.0-62.0)	43.0 (30.0-58.0)	.341
Sex (male/female)	40/29	13/15	.063
BMI (kg/m^2)	23.6 (21.4-25.3)	23.5 (21.0-25.6)	.232
Symptoms			
Fever	49/69 (71.0%)	10/28 (35.7%)	.001
Cough	45/69 (65.2%)	21/28 (75.0%)	.084
Sputum production	27/69 (39.1%)	9/28 (32.1%)	.766
Fatigue	31/69 (44.9%)	6/28 (21.4%)	.013
Shortness of breath	17/69 (24.6%)	4/28 (14.3%)	.028
Lesion numbers on chest CT	3.0 (1.0-5.0)	2.0 (1.0-3.0)	.04
Incidence of imaging aggravation			
After admission	46/69 (66.7%)	7/28 (25.0%)	0.001
Duration of disease			
From onset to admission	7.0 (4.0-9.0)	7.0 (5.0-11.0)	.104
From admission to discharge	12.0 (8.0-17.0)	9.0 (7.0-14.0)	.039
Total	20.0 (15.0-24.0)	16.0 (13.0-20.0)	.018

Note: Data are median (IQR) or n/N(%), where N is the total number of patients with available data. *P* values comparing the group of low EOS and normal EOS are from chi-square test or Mann-Whitney U test.

patients with atypical symptoms and radiographic infiltration with or without lymphopenia. The good value of EOS counts for COVID-19 prediction was shown in our study, when combined with NLR, the predictive value was even higher, indicating the advantage of the E (EOS counts $< 0.017 \times 10^9$/L) NL (NLR < 2.425) model over EOS alone in COVID-19 prediction. Currently, COVID-19 patients were confirmed or excluded by nucleic acid assay, while false negative was unavoidable.[15] In our study, according to peripheral blood EOS counts or ENL model, though the nucleic acid was negative, the possibility of false negative should also be considered.

So far, chest CT infiltration range might be helpful to figure out the potential critical patients at the early stage, but nonsevere patients also presented with diffuse abnormal damage without hypoxemia, while some patients with a small part of lung involved at the beginning quickly developed to severe cases. Some researchers reported that patients with age ≥50 and NLR ≥3.13 facilitated severe illness.[16] In our study, the majority of mild COVID-19 patients had a significant decrease in EOS level from the onset, and then increased gradually. The maximum EOS reduction was on 4th day from onset and began to restore in two-thirds of nonsevere patients within the following 3 days, while all severe patients remained undetected. The restore of EOS counts was almost synchronous with the improvement in chest CT, and it was later than that of body temperature, but was earlier than that of the negative conversion of nucleic acid assays. Patients with low EOS counts at admission were more likely to have fever, fatigue, and shortness of breath with more deterioration of lung by CT scan than those with normal EOS counts, suggesting that low EOS counts may be related to severe conditions. The insight can also be convinced by the monitor of EOS in severe patients. That means we should pay more attention to monitoring the circulating EOS, and if it failed to be increased timely, and remained at low level, severe stage may develop soon. Meanwhile, increase in circulating EOS may indicate the favorable prognosis in COVID-19 patients.

Why circulating EOS disappeared at the onset of COVID-19 patients regardless of severity is still mysterious. EOS develop in the bone marrow microenvironment from multipotent hematopoietic stem cells, which give rise to a population of unique eosinophil-committed progenitors that are capable of terminally differentiating into mature EOS.[17] The mature EOS enter the bloodstream and have a half-life of 18 hours in blood, then pass through capillaries and are recruited into connective tissue by deformation movement and are common in the respiratory, intestinal, and urogenital tracts.[18] EOS increase highly in parasitic infection and allergic diseases, while it significantly decreases in patients with acute infectious diseases such as typhoid, with major surgery and burns, and sepsis. A recent study showed that numbers of mature eosinophils in the blood and bone marrow markedly declined compared with baseline after endotoxin administration for 4 hours, whereas numbers of all eosinophil progenitors did not change.[19] In COVID-19, the reduction of peripheral blood EOS that began early regardless of severity may

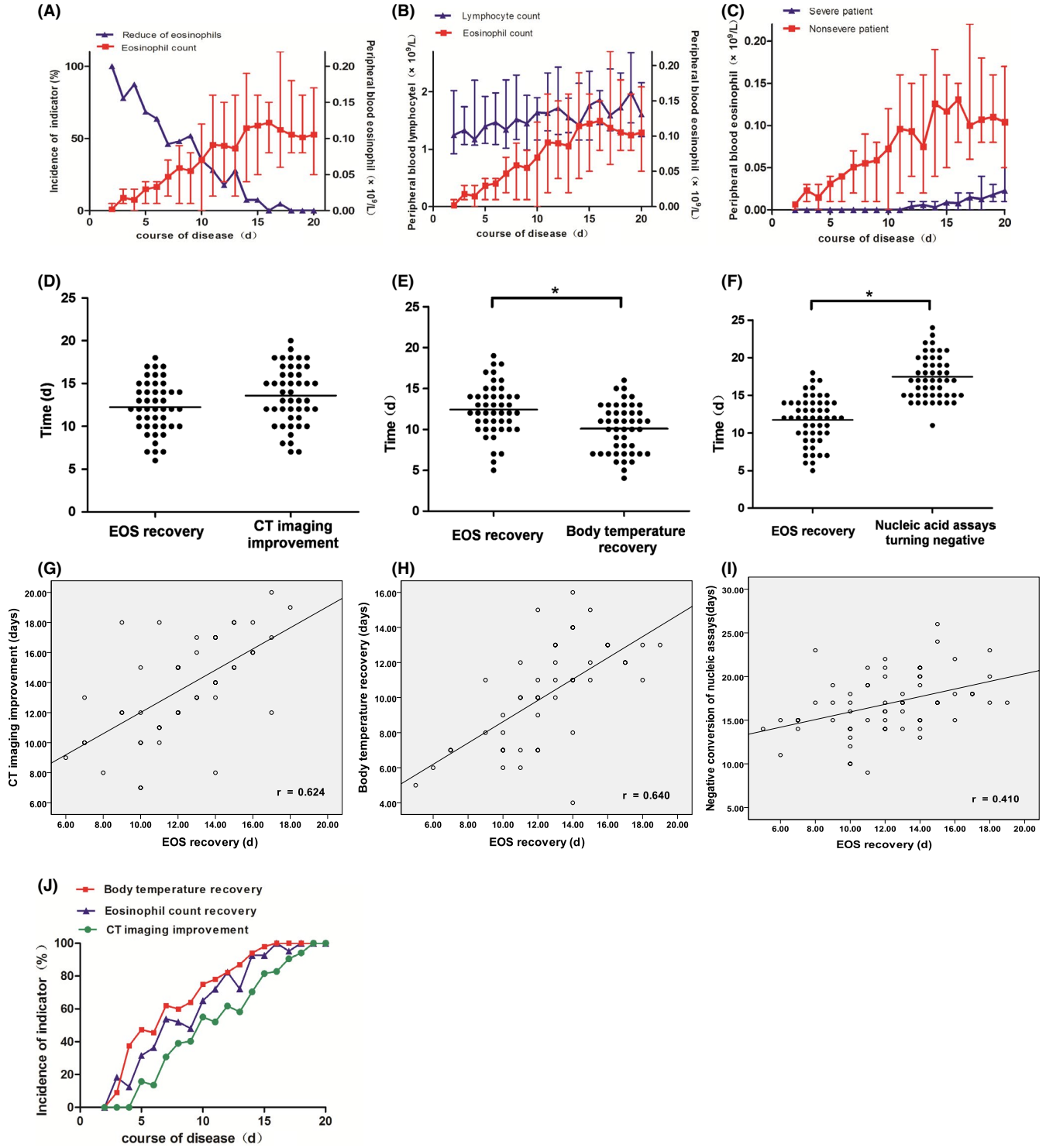


FIGURE 3 Changes in peripheral blood EOS in the course of disease (unmarked). A. Change in peripheral blood EOS counts and the incidence of EOS reduction in the course of disease. B. Change in peripheral blood EOS and lymphocyte counts in the course of disease. C. Change in peripheral blood EOS counts of nonsevere and severe patients in the course of disease. D-F. Comparison of recovery time of EOS counts with that of chest CT, body temperature, and negative conversion of nucleic acid assays. G-I. Correlation analysis of recovery time of EOS counts with that of chest CT, body temperature, and negative conversion of nucleic acid assays. J. Comparison of the incidence of the recovery of body temperature, improvement of chest CT, and EOS counts in the course of disease

be caused by decrease in bone marrow release and increase in organ recruitment. Most viral infections caused decrease in circulating EOS in the blood except human immunodeficiency virus infection.[20] In a variety of viral infections, including viral myocarditis and respiratory syncytial virus (RSV) pneumonia,[21] tissue EOS in the absence of blood EOS has been described. Whether

EOS play a role in antiviral defense, are responsible for tissue destruction, or are simply recruited to sites of tissue damage is unknown. Data from experimental murine infection with RSV and with influenza A support the hypothesis that EOS play a predominantly protective role.[22,23] When examining the role of EOS in antiviral host defense, researchers found that EOS, along with neutrophils, were recruited to the lung tissue early in the course of infection and following infection and preceded the developments of respiratory symptoms.[24] Percopo et al[22] found that EOS were antiviral and promoted survival in lethal pneumovirus of mouse infection using a mouse model of Th2 cytokine-driven asthmatic inflammation. Considering the large risk of infection, no BALF sample was collected from mild patients in this study, while samples of sputum from mild patients and BALF from severe patients did not count the number of EOS. Therefore, although the CT imaging findings of chronic eosinophilic pneumonia were similar to COVID-19, there was still no definite evidence of the accumulation of EOS in the lungs of COVID-19 patients so far.[25,26] It had been observed for a long time that viral infection was closely related to bone marrow suppression,[27]which was mainly caused by the direct or immune damage of the virus to bone marrow stem cells or stromal cells, resulting in microenvironment destroy. Whether SARS-COV-2 could also affect bone marrow function through the above mechanism and cause the decrease in peripheral blood eosinophils was still unknown. On the other hand, Huang et al[4] noted that patients infected with SARS-CoV-2 had high amounts of initial plasma IL-1β, IL-8, IFN-γ, TNF-α, and VEGF concentrations in both ICU patients and non-ICU patients than in healthy adults, instead of plasma level of IL-4, IL-5, IL-13, and RANTES. So we speculated that a large number of peripheral blood neutrophils might be recruited to the lungs with accelerating the generation of neutrophils in bone marrow. Due to the shift in the production of neutrophils, EOS could be then less produced. Though EOS decreased regardless of severity, EOS counts decreased seriously in severe patients, which may rely on that during acute lung injury, secretion of corticosteroids by adrenal glands increased under the stress and then EOS release in bone marrow was suppressed.[28] Corticosteroids promote cell death and clearance of EOS, and impair EOS survival and differentiation,[29] but intranasal corticosteroid (including spray) seemed not to affect the course of COVID-19.[30]

Our study has some deficiencies. Firstly, laboratory and radiologic examinations could not be performed every day, so these data were not continuous monitoring results. Secondly, the sample size of severe patients enrolled in our study was relatively small.

In conclusion, peripheral blood EOS counts may be a more convenient and effective indicator in addition to other blood parameters and CT scan in diagnosis and evaluation of COVID-19 patients. Circulating EOS level lower than 0.02×10^9/L may not only play a role in identifying suspect patients, which would be better combined with NLR in confirming the diagnosis, but also be important in predicting severe status and indicating the favorable prognosis. Moreover, the test of peripheral blood EOS counts is fast, simple, and inexpensive, which can be chosen as an effective monitor parameter during the diagnosis and treatment of COVID-19.

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CONFLICT OF INTEREST

None of the authors have any conflict of interest to declare.

AUTHOR CONTRIBUTION

Guogang Xie: Writing the article. Fengming Ding: Collection and check of data. Lei Han: Data analysis and interpretation. Dongning Yin: Data check. Hongzhou Lu: Research concept and design. Min Zhang: Research concept and design, Final approval of article.

ORCID

Min Zhang https://orcid.org/0000-0002-9591-9524

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