

The Clinical Implication of Dynamic Hematological Parameters in COVID-19: A Retrospective Study in Chongqing, China

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Purpose: To analyze the clinical characteristics of patients with coronavirus disease 19 (COVID-19) in Chongqing, and identify the potential hematological markers for reference.

Patients and Methods: 78 COVID-19-infected patients in Chongqing were recruited and divided into the non-severe and the severe group. The clinical characteristics and hematological features of the patients of the two groups were compared. Receiver-operating characteristic curves (ROC) were calculated to evaluate the diagnostic performance of potential markers, and the dynamic changes of blood routine analyzing items were compared between the non-severe and severe groups.

Results: 78 patients (median age of 45 years, 41 females and 37 males) were enrolled. The patients in the severe group exhibited significantly lower lymphocyte ($P < 0.05$) but higher neutrophil to lymphocyte ratio (NLR) ($P < 0.05$) than the patients in the non-severe group. The highest area under the ROC curve (AUC) was lymphocyte (0.74). The patients in the severe group had a lower level of lymphocyte during hospitalization ($P < 0.01$) and lymphocyte-monocyte ratio (LMR) in the progressive and convalescent phases ($P < 0.05$) than the patients in the non-severe group. However, the level of neutrophil of the patients in the severe group was higher in the progressive phase ($P < 0.05$), and so was NLR in the acute, progressive, and convalescent-phase ($P < 0.05$).

Conclusion: Infected with COVID-19 changed the levels of lymphocyte, neutrophil, LMR, and NLR in the blood, and these analyzing items were significantly different between the non-severe and severe groups. Furthermore, the dynamic changes of lymphocyte and NLR levels may help discriminate the severe group from the non-severe group.

Keywords: COVID-19, lymphocyte, neutrophil, neutrophil-lymphocyte ratio

Introduction

The emergence of COVID-19 marked the third time that a highly pathogenic coronavirus has been introduced to humans in the 21st century.¹ Globally, as of 6:00 pm, 15 July 2021, there have been over 188,128,952 confirmed cases of COVID-19, including 4,059,339 deaths (2.2% mortality), reported by the World Health Organization (WHO). Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) resulted in enormous loss of life and serious economic burden in the affected areas. At present, the majority of previous studies on the clinical and hematological parameters of COVID-19-infected patients at admission did not receive drug treatment,²⁻⁷ and there were few studies on dynamic changes with the patient's disease course.^{8,9}

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Several hematological changes were reported in COVID-19 patients, including leukocytosis, decreased lymphocyte count, elevated levels of D-dimer, neutrophilia, thrombocytopenia, eosinopenia, and basopenia.^{7,10–12} And the patients with severe disease had more prominent laboratory abnormalities than those with non-severe disease.¹⁰

Compared with other laboratory tests, the complete blood count (CBC), including the number of white blood cells (WBCs), neutrophils, lymphocytes, is an inexpensive and easy screening technique, and they are sensitive to many pathological changes and may assist in diagnosis when the cause of the disease is unknown. Lymphopenia is a typical laboratory abnormality observed in Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)¹³ and Middle East Respiratory Syndrome Coronavirus (MERS-CoV)¹⁴ infections. It's reported to be associated with disease severities.¹⁵ NLR and LMR are both promptly accessible parameters that can be calculated based on CBC. Elevated NLR leads to poor prognosis.¹⁶ NLR reflects the balance of the body's innate (neutrophil) and adaptive (lymphocyte) immune responses,¹⁷ and has prognostic value in various conditions such as cardiovascular disease,¹⁸ solid tumors,¹⁹ and Rheumatoid Arthritis,²⁰ etc. High monocyte count and low lymphocyte count indicate increased mortality and declined prognosis in a variety of disorders.²¹ It's reported that LMR is a highly sensitive analyzing item used for diagnosis of diabetes,²² large B-cell lymphoma,²³ cardiovascular diseases,^{21,24,25} and COVID-19,²⁶ and so on.

In this study, we analyzed the data of neutrophil, lymphocyte, monocyte, NLR, and LMR of selected COVID-19-infected patients in Chongqing. And we analyzed the associations of blood analyzing items with the different severity groups of COVID-19.

Materials and Methods

Data Collection

We conducted a retrospective study on the clinical features and blood routine results of patients with COVID-19. Routine blood tests were performed using the SYSMEX XE-2100 hematology analyzer and its original matching reagents.

A total of 78 patients infected with SARS-CoV-2 in Chongqing Public Health Medical Center were enrolled from 26 January 2020 to 16 May 2020, of which 61 cases were non-severe type (including asymptomatic infection, mild and moderate) and 17 cases were severe type (including severe and critical). All cases were defined by the eighth edition diagnosis and treatment plan for COVID-19 issued by the National

Health Commission of the People's Republic of China. The SARS-CoV-2 virus nucleic acid detection of the throat swab of all patients was positive. The groups of COVID-19 patients was performed according to the following guideline: 1) Asymptomatic infection: SARS-CoV-2 virus detection or specific antibody positive but without clinical symptoms; 2) Mild: mild symptoms without pneumonia; 3) Moderate: fever or respiratory tract symptoms with pneumonia; 4) Severe (fulfill any of the three criteria): respiratory distress, respiratory rate =30 times/min; oxygen saturation =93% in resting-state; arterial blood oxygen partial pressure (PaO₂)/oxygen concentration (FiO₂) =300 mmHg; 5) Critical (fulfill any of the three criteria): respiratory failure and require mechanical ventilation; shock incidence; admission to ICU with other organ failures. The first (acute phase), second (progressive phase), and third (convalescent-phase) sample data were collected within one week after symptom onset, two to three weeks, and three to four weeks, respectively. All the clinical records and blood routines of patients were carefully preserved from admission to discharge.

Statistical Analysis

SPSS software version 23.0 was used for data statistics. Counts and percentages of categorical variables and continuous quantitative data were represented by median and interquartile ranges (IQR) since non-normally distributed. Proportions for categorical variables were compared using the χ^2 test, and the Fisher exact test was used when the data was limited. Mann–Whitney *U*-test was applied for comparison between two groups. Kruskal–Wallis *H* was used for multiple comparisons. ROC curves were constructed for neutrophil, lymphocyte, monocyte, NLR, and LMR during the course of the acute phase. AUC, sensitivity, specificity, positive predictive value, and negative predictive value were calculated and compared. Optimal cut-off values were determined by the Youden index. *P* value<0.05 was considered statistically significant.

Results

Presenting Characteristics

The study population included 78 laboratory-confirmed patients with COVID-19 in Chongqing. The median age was 45 years (IQR 34.0–55.8), 41 (52.6%) were female and 37 (47.4%) were male. The median days from onset/first nucleic acid positive to admission, admission to discharge, onset/first nucleic acid positive to discharge were 3 days (IQR 2.0–5.0), 21.5 days (IQR 14.3–29.0), 25.0 days (IQR 17.3–32.8),

respectively. The major clinical symptoms were fever (45 [57.7%]), cough (41[52.6%]), expectoration (24[30.8%]), fatigue (23[29.5%]), and less common symptoms were diarrhea, chest tightness, headache, pharyngalgia, and rash (6[7.7%]-19 [24.4%]). Digestive system diseases (9[11.5%]) and hypertension (7[9%]) were the most common basic diseases, while the respiratory system (20[25.6%]) and digestive system (11 [4.1%]) were more prone to have comorbidities (Table 1).

Compared with the non-severe group, severe patients were significantly older (median age, 59 years [IQR 51.0–68.0] vs 43 years [IQR 29.0–50.0]; $P<0.001$) and more likely to have potential complications, including respiratory system (15[88.2%] vs 5[8.2%]; $P<0.05$), immune system (3[17.6%] vs 1[1.6%]; $P<0.05$) and skin diseases (3[17.6%] vs 0[0.0%]; $P<0.05$). And the number of days from admission to discharge was also longer in the severe group (27 days [IQR 20.0–35.0] vs 20 days [IQR 13.0–27.0]; $P<0.05$). The proportion of symptoms such as headache, fatigue, and chest tightness were increased in severe cases compared with non-severe cases.

The severe patients exhibited lower lymphocyte (1.0 [IQR 0.8–1.3] vs 1.6[IQR 1.2–2.1]; $P<0.05$) but higher NLR (3.3[IQR 2.0–4.3] vs 2.1[1.5–3.0]; $P<0.05$). However, there were no significant differences in white blood cell, neutrophil, monocyte, and LMR between the severe and the non-severe group (Table 2).

The Dynamic Profile of Hematological Parameters

During hospitalization, obvious abnormalities of laboratory blood examinations were found. Lymphocyte and NLR of most patients changed significantly, and the severe group had lower lymphocyte ($P<0.01$) but higher NLR ($P<0.05$) in the acute, progressive, and convalescent-phase. There was a notable difference in the level of neutrophil between non-severe and severe patients in the progressive phase ($P<0.05$). And LMR distinguished the non-severe group from the severe group in progressive and convalescent-phase ($P<0.05$) (Figure 1).

ROC-Curve Analysis

To determine the diagnostic utility of hematological indexes within one week after symptom onset, we calculated sensitivity, specificity, positive predictive value, and negative predictive value between the two groups using the ROC curves (Table 3). Among the five parameters (lymphocyte, NLR, monocyte, LMR, and neutrophil), the

highest AUC was lymphocyte (0.74) with an optimal cut-off of 1.14, the sensitivity of 70.59%, specificity of 80.33%, the positive predictive value of 50.00%, and negative predictive value of 90.74%. At a cut-off of 2.36, the corresponding sensitivity, specificity, positive predictive value, negative predictive value, and AUC of the NLR were 76.47%, 67.21%, 39.39%, 91.11%, and 0.67. At a cut-off of 0.25, the sensitivity, specificity, positive predictive value, negative predictive value, and AUC of monocyte were 35.29%, 95.08%, 66.67%, 84.06%, and 0.65. However, the AUC of LMR and neutrophil were only 0.57 and 0.50, respectively (Figure 2).

Discussion

The human-to-human transmission of SARS-CoV-2 among close contacts was beyond imagination.²⁷ An in-depth understanding of the characteristics of COVID-19 is crucial for its early prevention and treatment. To explore the characteristics of COVID-19 patients during their hospitalization, 78 COVID-19 patients in Chongqing were included for further study.

The common symptoms of Chongqing COVID-19 on admission were fever, cough, expectoration, and fatigue. These performances are consistent with those reported in several studies.^{3,28,29} Nevertheless, fever, chills, malaise, and myalgia were major symptoms of SARS-CoV,³⁰ while the common symptoms of MERS-CoV were fever, cough, dyspnea, and chest pain.³¹ In this study, we discovered that digestive system diseases and high blood pressure were the most common underlying diseases, and the majority of complications tended to occur in the respiratory and digestive systems. In severe cases, age, as well as the proportion of underlying diseases, were higher than in non-severe cases coinciding with the results of a few studies,^{3,8,10} which means that age and comorbidities may be risk factors for adverse outcomes. However, there is no obvious difference between the sexes. This phenomenon was different from the recent report showing that COVID-19 was more likely to affect men.⁷ The possible explanation was that majority of the first batch of people who came into contact with the Seafood Wholesale Market in southern China were male workers.

The dynamic profile of hematological parameters was monitored in 78 COVID-19 patients. Hematological items of patients with different severity were compared, and five parameters (lymphocyte, NLR, monocyte, LMR, and neutrophil) were selected for the ROC analyzing. Asghar et al found an NLR value of 5.48 and LMR value of 2.85 admitted in an intensive care unit (ICU) as the potential markers for

Table 1 Clinical Characteristic of COVID-19 Patients in Chongqing

	Total (N=78)	Non-Severe (N=61)	Severe (N=17)	P value
Sex-n. (%)				
Male	37 (47.4)	27 (44.3)	10 (58.8)	0.288
Female	41 (52.6)	34 (55.7)	7 (41.2)	
Age-year	45.5 (34.0–55.8)	43.0 (29.0–50.0)	59.0 (51.0–68.0)	0.000
Smoke-no. (%)	17 (21.8)	13 (21.3)	4 (23.5)	0.845
Alcohol-no. (%)	21 (26.9)	14 (23.0)	7 (41.2)	0.234
Days from Onset/first nucleic acid positive to Admission	3.0 (2.0–5.0)	3.0 (2.0–4.0)	5.0 (4.0–6.0)	0.001
Days from Admission to Discharge	21.5 (14.3–29.0)	20.0 (13.0–27.0)	27.0 (20.0–35.0)	0.019
Days from Onset/first nucleic acid positive to Discharge	25.0 (17.3–32.8)	22.0 (17.0–29.0)	31.0 (26.0–37.0)	0.001
Acute Phase	4.0 (3.0–6.0)	4.0 (3.0–5.0)	7.0 (5.0–7.0)	0.000
Progressive Phase	11.0 (9.0–13.0)	11.0 (9.0–12.0)	13.0 (12.0–14.0)	0.002
Convalescent Phase	24.5 (17.0–29.0)	22.0 (16.0–29.0)	27.0 (25.0–29.0)	0.021
Symptom-no. (%)				
Fever	45 (57.7)	29 (47.5)	16 (94.1)	0.001
Cough	41 (52.6)	27 (44.3)	14 (82.4)	0.005
Expectoration	24 (30.8)	15 (24.6)	9 (52.9)	0.025
Pharyngalgia	11 (14.1)	10 (16.4)	1 (5.9)	0.479
Headache	15 (19.2)	7 (11.5)	8 (47.1)	0.003
Fatigue	23 (29.5)	10 (16.4)	13 (76.5)	0.000
Diarrhea	19 (24.4)	14 (23.0)	5 (29.4)	0.819
Chest tightness	16 (20.5)	7 (11.5)	9 (52.9)	0.001
Rash	6 (7.7)	3 (4.9)	3 (17.6)	0.220
Basic diseases-no. (%)				
Hypertension	7 (9.0)	5 (8.2)	2 (11.8)	1.000
Diabetes	5 (6.4)	0 (0.0)	5 (29.4)	0.000
Hematological System diseases	4 (5.1)	2 (3.3)	2 (11.8)	0.435
Digestive system diseases	9 (11.5)	6 (9.8)	3 (17.6)	0.644
Cardiovascular system diseases	3 (3.8)	1 (1.6)	2 (11.8)	0.228
Respiratory system diseases	1 (1.3)	0 (0.0)	1 (5.9)	0.492
Other Metabolic diseases	3 (3.8)	2 (3.3)	1 (5.9)	1.000
Comorbidity-no. (%)				
Respiratory system	20 (25.6)	5 (8.2)	15 (88.2)	0.000
Digestive system	11 (4.1)	7 (11.5)	4 (23.5)	0.385
Metabolic diseases	2 (2.6)	2 (3.3)	0 (0.0)	1.000
Hematological System	5 (6.4)	4 (6.6)	1 (5.9)	1.000
Immune system	4 (5.1)	1 (1.6)	3 (17.6)	0.043
Urinary system	1 (1.3)	0 (0.0)	1 (5.9)	0.492
Neuropsychological system	2 (2.6)	1 (1.6)	1 (5.9)	0.911
Skin diseases	3 (3.8)	0 (0.0)	3 (17.6)	0.008
Cardiovascular system	2 (2.6)	1 (1.6)	1 (5.9)	0.911
Other diseases	4 (5.1)	1 (1.6)	3 (17.6)	0.043
Chest CT-no. (%)				
Chest radiographs abnormalities	59 (75.6)	42 (68.9)	17 (100.0)	0.020

Table 2 The Correlation of Hematological Parameters During the Course of Acute Phase with the Severity of COVID-19 in Chongqing

Baseline Variables	Total (N=78)	Non-Severe (N=61)	Severe (N=17)	P value
WBC ($10^9/L$)	5.3 (4.2–6.7)	5.4 (4.2–6.8)	4.9 (3.9–5.9)	0.189
Neutrophil ($10^9/L$)	3.1 (2.4–4.4)	3.2 (2.2–4.4)	3.0 (2.7–4.4)	0.961
Lymphocyte ($10^9/L$)	1.4 (1.0–2.0)	1.6 (1.2–2.1)	1.0 (0.8–1.3)	0.003
Monocyte ($10^9/L$)	0.4 (0.3–0.5)	0.4 (0.3–0.5)	0.3 (0.2–0.5)	0.059
NLR	2.2 (1.6–3.3)	2.1 (1.5–3.0)	3.3 (2.0–4.3)	0.028
LMR	3.7 (2.6–4.8)	3.8 (2.7–5.4)	3.7 (2.5–4.3)	0.374

Abbreviations: NLR, neutrophil–lymphocyte ratio; LMR, lymphocyte–monocyte ratio.

severity of disease, with AUC of 0.841 and 0.227.³² In our study, we concluded that a slightly lower AUC of NLR was 0.67 at a cut-off value of 2.36 while a relatively higher AUC of LMR was 0.57 at a cut-off value of 4.75. The risk factors, age, and gender of the distinct populations included in the two studies were different, which may account for this phenomenon. And the AUC of lymphocyte, monocyte, and neutrophil were 0.74, 0.65, and 0.50, respectively, which were generally higher than that of another study.³³

Recent reports have shown that lymphocyte counts are normal in COVID-19 patients with mild disease. In contrast, 20–96.1% of severe diseases have lymphopenia.^{10,34} Similarly, we found that the severe group had progressively decreased

lymphocyte count during hospitalization. With the application of NLR to COVID-19, elevated NLR on admission was considered an independent risk factor for severe disease and poor clinical outcomes in COVID-19 patients.^{35,36} Similarly, the higher level of NLR during hospitalization in severe patients in this study also suggested an association of NLR with disease severity and clinical course. The result of the level of neutrophil in the progressive phase was higher but LMR was lower in the progressive and convalescent-phase in severe patients coincided with previous studies.^{32,37,38} In summary, lymphocyte, and NLR showed unexceptionable performance in patients' courses which could distinguish the severe group from the non-severe group.

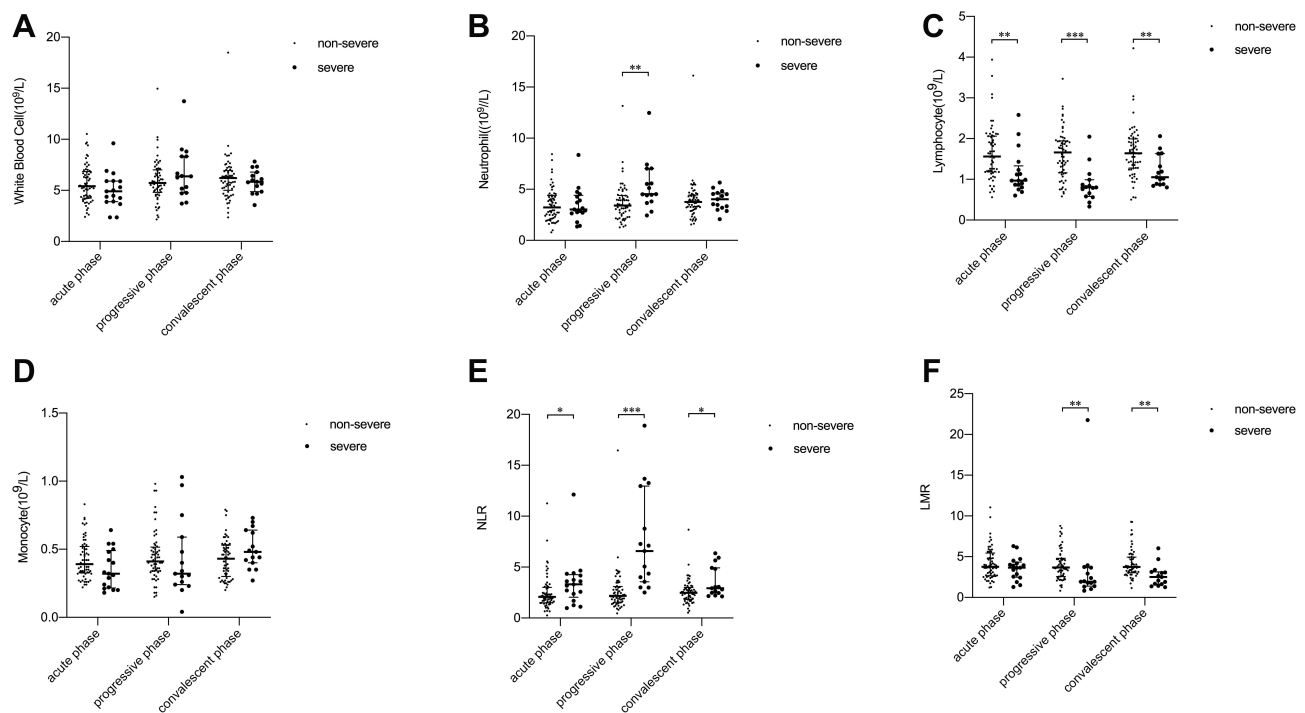


Figure 1 Dynamic changes of blood analyzing items of COVID-19 between the severe and non-severe groups (A–F). The levels of white blood cell (A), neutrophil (B), lymphocyte (C), monocyte (D), NLR (E), and LMR (F) on three different phases (the acute, progressive, and convalescent-phase) between the severe and non-severe group. *P<0.05, **P<0.01, ***P<0.001.

Table 3 The Value of Lymphocyte, NLR, Monocyte, LMR, and Neutrophil in the Diagnosis of COVID-19

Item	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Cut-off Value
Lymphocyte	70.59	80.33	50.00	90.74	1.14
NLR	76.47	67.21	39.39	91.11	2.36
Monocyte	35.29	95.08	66.67	84.06	0.25
LMR	88.24	32.79	26.79	90.91	4.75
Neutrophil	82.35	36.07	26.42	88.00	2.64

The purpose of our study is not only to provide hematological markers for reference but also to alert the clinicians to notice active surveillance for COVID-19 cases. And there were some limitations: as a single-center study, these results should be interpreted with caution owing to the small sample size of this observational study, bias and residual confusion may occur. Multi-center and large-scale researches are needed to further define the clinical implication of dynamic hematological parameters in COVID-19 cases.

Conclusion

In general, our results showed the hematological features of COVID-19 cases in Chongqing. There were remarkable differences in blood routine analyzing items including lymphocyte, neutrophil, LMR, and NLR in COVID-19 patients. And the dynamic changes of lymphocyte and neutrophil-lymphocyte ratio during the course of the disease may be useful for discriminating the severe group and non-severe group.

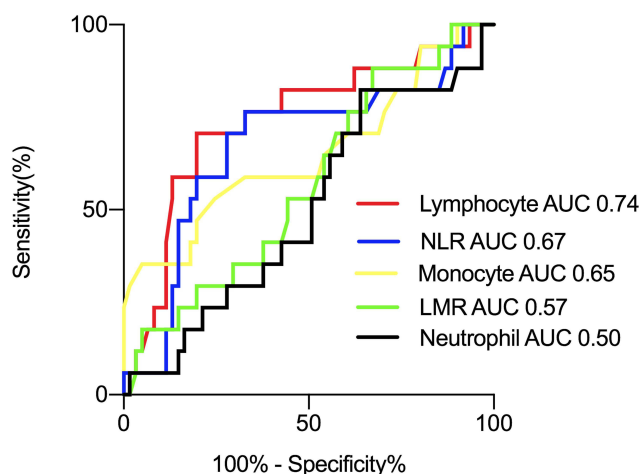


Figure 2 The receiver operation curves of hematological parameters for disease severity classification of COVID-19. ROC analysis of lymphocyte, monocyte, NLR, LMR, and neutrophil for discriminating 17 severe cases from 61 non-severe cases.

Ethical Approval

The study was approved by Chongqing General Hospital Ethics Committee [S2020-021-01]. Due to the nature of this retrospective study without any additional interventions, the need for consent was waived by the ethics committee. All personally identifiable records were kept confidential. The guidelines outlined in the Declaration of Helsinki were followed in this study.

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Disclosure

The authors declare that there is no conflict of interests.

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