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Hematological characteristics of COVID-19 patients with fever infected by the Omicron variant in Shanghai: A retrospective cohort study in China

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Abstract

Background: A wave of the Omicron variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has rapidly spread in Shanghai, China. Hematological abnormalities have been reported in coronavirus disease 2019 (COVID-19) patients; however, the difference in hematological parameters between COVID-19 patients with fever and patients who are febrile from other causes remains unexplored.

Methods: This retrospective cohort study enrolled 663 SARS-CoV-2 positive patients identified by RT-PCR. Clinical parameters, including age, sex, and threshold cycle values of all COVID-19 patients, and hematological parameters of COVID-19 patients in the fever clinic were abstracted for analysis.

Results: Overall, 60.8% of COVID-19 patients were male, and the median age was 45 years. Most of COVID-19 patients were asymptomatic, while 25.8% of patients showed fever and 10.9% of patients had other emergencies. COVID-19 patients with fever had significantly lower white blood cells (WBCs), neutrophils, lymphocytes, platelets and C-reactive protein (CRP), and significantly higher monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), mean platelet volume (MPV), and mean platelet volume-to-platelet ratio (MPR) levels, compared with those in SARS-CoV-2 negative patients with fever from other causes (p < 0.05). Neutrophil-to-lymphocyte ratio (NLR), PLR, and systemic inflammatory index (SII) levels were significantly higher in COVID-19 patients with emergencies (p < 0.05). WBCs showed the best performance with an area under the curve (0.756), followed by neutrophils (0.730) and lymphocytes (0.694) in the diagnosis of COVID-19 in the fever clinic.

Conclusion: WBCs, neutrophils, lymphocytes, platelets, CRP and MLR, PLR, and MPR may be useful in early diagnosis of COVID-19 in the fever clinic.

Tingting Wei, Jiangyan Li and Zhuo Cheng contributed equally to this work.

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KEYWORDS

coronavirus disease 2019, differential diagnosis, hematological parameters, inflammation, severe acute respiratory syndrome coronavirus 2

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread rapidly in more than 200 countries worldwide and has been announced as a public health emergency. The SARS-CoV-2 virus evolved continuously since its emergence. In November 2021, the B.1.1.529 variant of SARS-CoV-2 was first identified in South Africa and Botswana and named the Omicron variant by the World Health Organization (WHO).^{1,2}

The Omicron variant has a remarkable number of mutations, resulting in higher transmissibility than previous SARS-CoV-2 variants.³ Fortunately, the clinical symptoms of Omicron variant infection are mainly asymptomatic or mild, with a low risk of hospitalization and death.^{4,5} Currently, the Omicron variant of SARS-CoV-2 has overtaken other variants as the dominant transmission strain globally. In late February 2022, a wave of Omicron variant infection suddenly appeared in Shanghai, China. According to the Shanghai Municipal Health Commission, as of May 4, 2022, a total of 601,942 cases have been identified, including 547,056 asymptomatic carriers, and 503 people have died of causes associated with COVID-19.⁶

Hematological parameters play an important role in the early diagnosis of various inflammatory diseases, such as malignancies,^{7,8} metabolic disorder,⁹ and infection.¹⁰ Furthermore, COVID-19 is associated with increased inflammatory burden.¹¹ Therefore, hematological abnormalities might be associated with COVID-19 infection. Previous studies have reported hematological abnormalities in COVID-19 patients;^{12,13} however, information on the differences in hematological parameters between COVID-19 patients with fever and patients who are febrile from other causes remains limited. In addition, these differences in hematological parameters might be used to predict clinical manifestations of COVID-19 patients and aid in making informed clinical decisions and risk stratification for COVID-19 patients. Thus, this study aimed to investigate the clinical and hematological characteristics of COVID-19 patients infected the Omicron variant during the recent coronavirus outbreak in the city of Shanghai, China. We reported this study following the Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines.^{14,15}

2 | MATERIALS AND METHODS

2.1 | Subjects

In this retrospective and cross-sectional study, we consecutively enrolled a total of 663 COVID-19 infected patients at the Shanghai Changzheng Hospital, China, from March 1 to May 31, 2022. COVID-19 infection was diagnosed by real-time reverse transcription polymerase chain reaction (RT-PCR) in all cases. Clinical parameters including age, sex, cycle threshold (Ct) value and hematological parameters were abstracted from the electronic medical records. COVID-19 positive patients who lacked the complete blood count (CBC) test were excluded from subsequent comparisons. Patients with fever who were negative for SARS-CoV-2 by RT-PCR test were collected as a control group. This study was approved by the Ethics Board of the hospital and conducted in accordance with the Declaration of Helsinki. This study had no effect on the subsequent management of patients. There were no adverse events during the study.

2.2 | Laboratory tests

Hematological parameters were detected using a Sysmex XN-9000 automated hematology analyzers (Sysmex Corp., Kobe, Japan). Ratios were calculated as follows: NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-tolymphocyte ratio; MPR, mean platelet volume-to-platelet ratio; and systemic inflammatory index (SII), thrombocyte count × neutrophil count/lymphocyte count.

Nasopharyngeal swabs were taken from all specimens for Ct value analysis. Detection was performed by RT-PCR with the SARS-CoV-2 nucleic acid detection kit (Shanghai Zhijiang Biotechnology Co., Ltd.) following the manufacturer's instructions.

2.3 | Statistical analysis

The Kolmogorov–Smirnov test was performed to evaluate variable distribution. Continuous variables were presented as median (interquartile range, IQR) and analyzed by nonparametric Mann–Whitney or Kruskal–Wallis test as appropriate.¹⁶ Categorical variables were analyzed by Fisher's exact test or Chi-square test. The receiver-operating characteristic (ROC) analysis was performed, and the area under the curve (AUC) was calculated. Optimal cut-off value, sensitivity and specificity were estimated according to the Youden index. All analyses were performed using SPSS 21.0 software (SPSS Inc., Chicago, IL, USA) and MedCalc 19.7.2 software (MedCalc Software, Ostend, Belgium). A *p* value less than 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Clinical characteristics of patients infected by the Omicron variant of SARS-CoV-2

The flow chart of COVID-19 patient selection and study design was presented in Figure 1. A total of 663 COVID-19 patients from March 1 to May 31, 2022 were included, and the demographic and clinical



FIGURE 1 Flow chart of COVID-19 patient selection.

characteristics of all patients were summarized in Table 1. The majority of patients (465/663, 70%) were diagnosed in April, and 403 patients (60.8%) were male. The median age was 45 years (IQR: 31–62 years); 10 patients (1.5%) were children aged <18 years, and 42 patients (6.3%) were aged ≥80 years. Of 663 patients, 31 patients were hemodialysis patients.

We further divided all COVID-19 patients into three subgroups: outpatients, patients with fever, and patients with other emergencies. 420 patients (63.4%) were COVID-19 outpatients who tested positive for SARS-CoV-2 by RT-PCR tests, and most of them were asymptomatic. There were 171 COVID-19 patients with a symptom of fever (25.8%) and 72 COVID-19 patients (10.9%) presented to the emergency department with other emergencies. Significant differences were observed in the gender and age makeup of the three COVID-19 subgroups (p < 0.001): in COVID-19 patients with fever, 43.9% were male, and the median age was 59 years; while in COVID-19 patients with other emergencies, 44.4% were male, and the median age was 66 years. Compared with COVID-19 outpatients (median age 40 years), COVID-19 patients with fever or other emergencies were older (median ages 59 and 66 years, respectively, p < 0.001). The Ct values of SARS-CoV-2 gene of COVID-19 patients with fever (25.5 and 24.0) were lower than those of outpatients (28.3 and 27.7, p < 0.01) and patients with other emergencies (27.5 and 26.3, p < 0.05).

3.2 | Hematological parameters of patients infected by the Omicron variant of SARS-CoV-2

A total of 190 patients with fever who were negative for SARS-CoV-2 were collected as a control group. Hematology parameters in each subgroup of COVID-19 patients and the control group were analyzed. As shown in Table 2, no statistically significant difference was found in gender or age between the control group and

COVID-19 patients with fever (p > 0.05). Compared with the control group, the counts of white blood cells (WBCs), neutrophils, lymphocytes, platelets, and C-reactive protein (CRP) were significantly lower in COVID-19 patients with fever (p < 0.01); MLR, PLR, mean platelet volume (MPV), and MPR levels were significantly higher in COVID-19 patients with fever (p < 0.05). No significant difference was found in red blood cells, hemoglobin levels, or hematocrit between the two groups (p > 0.05), and these parameters were within the normal range, indicating that anemia is not a significant factor in most COVID-19 patients. Additional comparisons showed that NLR, PLR, and SII levels were significantly higher in COVID-19 patients with other emergencies, compared with those in COVID-19 patients with fever (p < 0.05).

3.3 | Performance of hematological parameters in the diagnosis of patients infected by the Omicron variant of SARS-CoV-2 in the fever clinic

Since the hematological analysis revealed significant differences between COVID-19 patients with fever and those with fever from other causes, ROC analysis was then performed. The subgroup of COVID-19 patients with fever was set as the positive group, and the patients with fever from other causes was set as the negative group. ROC curve was established to analyze the efficacy of various hematological parameters for the diagnosis of COVID-19 in the fever clinic. As shown in Table 3, the AUC of WBCs was 0.756 (95% confidence interval (CI): 0.706–0.805; p < 0.001); the AUC of neutrophils was 0.730 (95% CI: 0.678-0.782; p < 0.001); the AUC of lymphocytes was 0.694 (95% CI: 0.640-0.749; p < 0.001); the AUC of platelets was 0.581 (95% CI: 0.522-0.640; p = 0.008); the AUC of MPV was 0.574 (95% CI: 0.515-0.633; p = 0.016); the AUC of MLR was 0.660 (95% CI: 0.603-0.716; p<0.001); the AUC of PLR was 0.643 (95% CI: 0.586-0.700; p <0.001); and the AUC of CRP was 0.672 (95% CI: 0.615-0.728; p < 0.001). The difference between the AUCs for WBCs and neutrophils was statistically significant (p = 0.0028) (Figure 2). WBCs showed the largest AUC, followed by neutrophils and lymphocytes, indicating that WBCs is the most discriminative hematological parameter for clinical diagnosis of COVID-19 with fever.

4 | DISCUSSION

COVID-19 is a global pandemic that poses a serious threat to human life and health, particularly for people with underlying diseases and the elderly. Hematological abnormalities have been reported in COVID-19 patients in some previous studies;¹² however, few studies have compared hematological parameters in COVID-19 patients with fever versus those with fever from other causes. Given the rapid onset and spread of COVID-19, early and effective differential diagnosis is critical.

Previous studies have shown that the pathogenicity, severity, and mortality of COVID-19 decreased during the wide spread WILEY

Characteristic	Total patients	COVID-19 outpatients	COVID-19 with fever	COVID-19 with emergencies	p-Value ^a
No. (%)	663	420 (63.4)	171 (25.8)	72 (10.9)	
Distribution, n (%)					
March	112 (16.9%)	94 (22.4%)	18 (10.5%)	0 (0)	
April	465 (70.1%)	297 (70.7%)	108 (63.2%)	60 (83.3%)	
May	86 (13.0%)	29 (6.9%)	45 (26.3%)	12 (16.7%)	
Sex, n (%)					
Male	403 (60.8%)	296 (70.5%)	75 (43.9%)	32 (44.4%)	<0.001
Female	260 (39.2%)	124 (29.5%)	96 (56.1%)	40 (55.6%)	
Age, year	45 (31–62)	40 (30–52)	59 (37–71)	66 (48–75)	<0.001
Age groups, n (%)					
<18 years	10 (1.5%)	3 (0.7%)	6 (3.5%)	1 (1.4%)	
18–49 years	363 (54.8%)	291(69.3%)	54 (31.6%)	18 (25.0%)	
50–79 years	248 (37.4%)	121 (28.8%)	89 (52.0%)	38 (52.8%)	
≥80 years	42 (6.3%)	5 (1.2%)	22 (12.9%)	15 (20.8%)	
RT-PCR Ct value					
ORF1ab gene	27.4 (23.1-32.1)	28.3 (23.5-32.7)	25.5 (22.4-29.4)	27.5 (23.2-32.8)	<0.001
N gene	26.3 (21.8-32.2)	27.7 (22.5-33.1)	24.0 (20.6-29.2)	26.3 (22.1-32.9)	< 0.001

^aComparison of three subgroups. Data are shown as number (%) or median (interquartile range). RT-PCR, reverse transcription polymerase chain reaction; Ct, cycle threshold.

of the Omicron variant.¹⁷ In this study, a total of 663 SARS-CoV-2 positive patients were included, most of whom were asymptomatic. Furthermore, asymptomatic patients were more likely to be males and middle-aged adults, while COVID-19 patients with fever or other emergencies were more likely to be females and elderly. In addition, comparison of Ct values by RT-PCR showed that the viral load of COVID-19 patients with fever was higher than those of other subgroups.

In line with other studies,^{13,18,19} we observed that COVID-19 patients with fever had lower leukocytes, neutrophils, lymphocytes, and platelets and CRP levels compared with those in patients who were febrile from other causes. This might be related to the pathological effects of SARS-CoV-2 on the hematological and immune system.²⁰ Lymphopenia is the most common hematological abnormality in patients with COVID-19 infection, which is generally considered to be a defective immune response to viral infection.¹¹ Lymphopenia observed in COVID-19 may be related to the virus's ability to infect lymphocytes via angiotensin-converting enzyme 2 (ACE2) receptors, leading to the apoptosis of lymphocytes, and enhanced immune escape ultimately.^{21,22} The presence of thrombocytopenia has been reported to be associated with the severity of the COVID-19 and organ failure, and the mechanistic study suggested that platelets take up SARS-CoV-2 mRNA might be independent of ACE2.²³

Not only do lymphocytes and platelets played an important role in regulating various inflammatory processes but their ratio may also be an indicator of early inflammation.²⁴ MLR, PLR, and MPR have been reported as significant predictors for the severity and mortality of COVID-19.²⁵⁻²⁷ In the present study, among patients with fever, MLR, PLR, and MPR levels were significantly higher in COVID-19 patients than those in patients who were febrile from other causes. These inflammatory indices have been considered as indicators for the diagnosis and progression assessment of various diseases, especially inflammatory diseases. Elevated MLR has been reported to be a feature not only of COVID-19 infection but also of diabetic kidney injury.²⁸ non-alcoholic fatty liver disease (NAFLD).²⁹ and cancer.^{30,31} Raised PLR has been also reported in other inflammatory conditions including liver fibrosis,³² thyroid conditions,^{33,34} diabetes mellitus,³⁵ and systemic lupus erythematosus.³⁶ Increased MPR has been shown to be associated with hepatitis B-related liver fibrosis,³² sepsis,³⁷ and cancer.³⁸ MPR reflects the proliferation of megakaryocytes and platelet production in the bone marrow.³⁹ Inflammation in COVID-19 leads to a decrease in platelet counts, inducing the production of thrombopoietin, which in turn accelerates platelets production. Young platelets released from the bone marrow are usually larger, performed as increased MPV, which in combination with thrombocytopenia, leads to an increase in MPR.^{39,40}

NLR is also known as an inflammatory marker in inflammatory diseases such as inflammatory bowel disease,⁴¹ diabetes mellitus,^{42,43} cardiac conditions,⁴⁴ and thyroiditis.⁴⁵ In addition, elevated NLR has been reported to be associated with the severity of COVID-19.^{26,46} SII, which relies on thrombocytes, neutrophils and lymphocytes, has been used to define the inflammatory response and predict in-hospital mortality in COVID-19 patients.⁴⁷ However, in our study, no statistically significant difference was found in NLR or SII between COVID-19 patients with fever and those with fever from other causes, while a significant increase was found in NLR and SII in COVID-19 patients with other emergencies. This difference in results might be related to the immune status of the enrolled TABLE 2 The hematological profiles of COVID-19 patients infected by the Omicron variant and control group as indicated

	Control group (1)	COVID-19 with fever (2)	COVID-19 with emergences (3)	p-Value	
Variable	(<i>n</i> = 190)	(n = 170)	(n = 46)	1 vs. 2	2 vs. 3
Male/Female	101/89	75/95	22/24	0.092	0.739
Age, year	57 (34–73)	59 (37–71)	68 (57–80)	0.603	0.024
WBC, ×10 ⁹ /L	9.6 (7.3-12.35)	6.40 (4.80-8.30)	6.75 (5.68-9.45)	<0.001	0.213
Neutrophils, ×10 ⁹ /L	7.21 (5.00-9.71)	4.67 (3.28-6.10)	4.96 (3.63-8.43)	<0.001	0.081
Lymphocytes, ×10 ⁹ /L	1.44 (0.94-2.04)	0.93 (0.60-1.40)	0.77 (0.42-1.25)	<0.001	0.086
Monocytes, ×10 ⁹ /L	0.7 (0.48-1.0)	0.67 (0.48-0.88)	0.63 (0.45-0.89)	0.354	0.613
NLR	4.6 (2.90-8.57)	4.96 (2.78-8.10)	6.99 (3.71-12.83)	0.571	0.008
MLR	0.49 (0.31-0.75)	0.72 (0.47-1.09)	0.82 (0.44-1.62)	<0.001	0.194
RBC, ×10 ¹² /L	4.65 (4.14-5.06)	4.58 (4.18-4.99)	4.41 (4.00-4.70)	0.647	0.03
Hemoglobin, g/L	138 (125–152)	136 (123–148)	136 (123–142)	0.225	0.526
Hematocrit, %	41.6 (38.05-45.00)	40.50 (37.20-44.25)	40.00 (36.73-42.93)	0.193	0.206
MCV, fL	89.9 (87.3-92.9)	89.10 (86.30-91.33)	90.65 (87.65-93.80)	0.033	0.033
MCHC, gL	334 (326-342)	333 (323–341)	334 (329–345)	0.348	0.078
MCH, pg	29.9 (29.2-31.0)	29.70 (28.50-30.80)	30.50 (29.45-31.53)	0.055	0.001
RDW, %	12.4 (11.9–13.2)	12.30 (11.90–13.20)	12.25 (11.90-13.03)	0.513	0.846
Platelets, $\times 10^{9}/L$	200 (158–259)	176 (145–227)	202 (153–247)	0.008	0.165
PLR	140.21 (105.34–204.43)	184.12 (130.94–293.99)	258.57 (157.59-449.65)	<0.001	0.018
MPV, fL	9.60 (8.90–10.30)	9.80 (9.20-10.40)	10.10 (9.60–10.60)	0.016	0.157
MPR	0.048 (0.036-0.065)	0.053 (0.042-0.069)	0.050 (0.038-0.067)	0.013	0.272
CRP, mg/L	24.19 (2.19-66.24)	5.53 (0.98–13.29)	4.67 (2.76-25.46)	<0.001	0.112
SII	998.35 (593.23-1868.21)	823.38 (472.68-1702.68)	1368.57 (682.35-2411.92)	0.091	0.006

Note: Values are presented as median (interquartile range) for continuous variables. p-values with statistical differences were shown in bold. Abbreviations: WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; RBC, red blood cell; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red blood cell width distribution; PLR, platelet-to-lymphocyte ratio; MPV, mean platelet volume; MPR, mean platelet volume-to-platelet ratio; CRP, C-reactive protein; SII, systemic inflammatory index.

patients or the excessive inflammatory response caused by complications associated with emergency patients.

In the present study, ROC curve comparison showed that WBCs might be the most valuable hematological parameter for clinical diagnosis of COVID-19 with fever. Low WBC, neutrophil, and lymphocyte counts, readily available and cost-effective hematological parameters, could assist clinicians in the early differential diagnosis of COVID-19 infection in fever clinic. In 2020, some studies have explored machine learning models to predict SARS-CoV-2 infection⁴⁸ and mortality risk⁴⁹ of COVID-19 based on clinical data. However, these models were trained in moderate or life-threatening inpatients, which were not applicable to asymptomatic or mild COVID-19 cases. In the outbreak of COVID-19 in Shanghai in 2022, most patients with the Omicron variant were asymptomatic or mild with a low risk of hospitalization, leading to little data from CBC testing and other laboratory tests that could be collected. Therefore, it was difficult to perform a machine learning model to predict the infection of Omicron variant based on available laboratory data.

This study had some limitations. Because this was a single-center retrospective study, the number of COVID-19 patients in different subgroups was small, so some bias might have occurred. Second, as our hospital was not a designated isolation hospital, this study could only analyze the initial hematological parameters in COVID-19 patients and could not conduct continuous monitoring of patients during hospitalization or predict the mortality risk stratification. Therefore, further prospective and multi-center studies are needed to evaluate the prognostic value of these indicators in COVID-19.

5 | CONCLUSIONS

This retrospective study showed that most of COVID-19 patients infected by the Omicron variant in Shanghai were asymptomatic. Among the COVID-19 patients with fever, most of them were female, with an older median age and a lower median Ct value. Low leukocytes, neutrophils, platelets, and CRP as well as high MLR, PLR,

Variable	AUC	Cut off	Sensitivity (%)	Specificity (%)	95% CI	p-Value
WBCs, ×10 ⁹ /L	0.756	≤7.25	62.9	76.7	0.706- 0.805	<0.001
Neutrophils, ×10 ⁹ /L	0.730	≤5.07	62.4	74.6	0.678- 0.782	<0.001
Lymphocytes, ×10 ⁹ /L	0.694	≤1.26	72.4	62.4	0.640- 0.749	<0.001
Platelets, ×10 ⁹ /L	0.581	≤242	83.5	31.7	0.522- 0.640	0.008
MPV, fL	0.574	>8.95	86.6	26.5	0.515- 0.633	0.016
MLR	0.660	>0.605	64.1	64.2	0.603- 0.716	<0.001
PLR	0.643	>144	71.2	52.6	0.586- 0.700	<0.001
MPR	0.576	>0.036	88.2	26.8	0.517- 0.635	0.013
CRP, mg/L	0.672	≤13.37	75.9	59.7	0.615- 0.728	<0.001

Abbreviations: AUC, area under the curve; CI, confidence intervals; WBC, white blood cell; MPV, mean platelet volume; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MPR, mean platelet volume-to-platelet ratio; CRP, C-reactive protein.



FIGURE 2 The receiver operating characteristic (ROC) curves of hematological parameters in diagnosis of COVID-19 patients in the fever clinic. WBC, white blood cell; MLR, monocyte-to-lymphocyte ratio; N, neutrophils; L, lymphocytes; PLT, platelets; PLR, plateletto-lymphocyte ratio.

MPV, and MPR levels were valuable for the differential diagnosis of COVID-19 patients in the fever clinic. In addition, high NLR and SII values might indicate a high inflammatory status in COVID-19 patients with other emergency conditions.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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TABLE 3 The value of hematological parameters in diagnosis of COVID-19 patients in the fever clinic

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