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ORIGINAL RESEARCH

Value of Laboratory Indicators in Predicting Pneumonia in Symptomatic COVID-19 Patients Infected with the SARS-CoV-2 Omicron Variant

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Background: The pathogenicity of Omicron is different from that of the previous strains. The value of hematological indicators in patients at high risk of Omicron infection remains unclear. We need rapid, inexpensive and widely available biomarkers to guide the early detection of people at risk of pneumonia and to provide early intervention. We aimed to assess the value of hematological indicators as risk factors for pneumonia in symptomatic COVID-19 patients infected with the SARS-CoV-2 Omicron variant.

Patients and Methods: The study enrolled 144 symptomatic COVID-19 patients with Omicron infection. We collected available clinical details, including laboratory tests and CT examinations. Univariate and multivariate logistic analyses and receiver operating characteristic (ROC) curve analyses were used to assess the value of laboratory markers in predicting the development of pneumonia.

Results: Among the 144 patients, 50 (34.7%) had pneumonia. The ROC analysis revealed that the areas under the ROC curve (AUC) for leukocytes, lymphocytes, neutrophils, and fibrinogen were 0.603 (95% confidence interval (CI): 0.501–0.704, P=0.043), 0.615 (95% CI: 0.517–0.712, P=0.024), 0.632 (95% CI: 0.534–0.730, P=0.009) and 0.635 (95% CI: 0.539–0.730, P=0.008), respectively. The AUC for neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), fibrinogen to lymphocyte ratio (FLR), and fibrinogen to D-dimer ratio (FDR) were 0.670 (95% CI: 0.580–0.760, P=0.001), 0.632 (95% CI: 0.535–0.728, P=0.009), 0.669 (95% CI: 0.575–0.763, P=0.001) and 0.615 (95% CI: 0.510–0.721, P=0.023), respectively. Univariate analysis showed that elevated levels of NLR (odds ratio (OR): 1.219, 95% CI: 1.046–1.421, P=0.011), FLR (OR: 1.170, 95% CI: 1.014–1.349, P=0.031) and FDR (OR: 1.131, 95% CI: 1.039–1.231, P=0.005) were significantly correlated with the presence of pneumonia. Multivariate analysis indicated elevated NLR (OR: 1.248, 95% CI: 1.068–1.459, P=0.005) and FDR (OR: 1.160, 95% CI: 1.054–1.276, P=0.002) levels were associated with the existence of pneumonia. The AUC for the combination of NLR and FDR was 0.701 (95% CI: 0.606–0.796, P<0.001, sensitivity 56.0%, specificity 83.0%).

Conclusion: NLR and FDR can predict the presence of pneumonia in symptomatic COVID-19 patients infected with the SARS-CoV -2 Omicron variant.

Keywords: COVID-19, Omicron, pneumonia, neutrophil to lymphocyte ratio, fibrinogen, D-dimer

Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global public health concern since December 2019.[1,2] In late February 2022, a wave of SARS-CoV-2 Omicron variant infections rapidly emerged in Shanghai, China. Phylogenetic characterization of SARS-CoV-2 viral genomes from 129 patients in Shanghai indicated that all new viral genomes clustered in the SARS-CoV-2 BA.2.2 sublineage. The Omicron variant of SARS-CoV-2 emerged in South Africa in 2021, spreading more readily than other variants.[3]

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Therefore, Omicron rapidly replaced other variants as the dominant variant worldwide.[4] However, Omicron is less virulent and thus less pathogenic, resulting in a lower risk of hospitalization and a lower prevalence of pneumonia.[5–7]

Pneumonia is a common cause of hospitalization and death in COVID-19 patients, and computed tomography (CT) images play a vital role in determining the severity and extent of the disease.[8–12] However, the incidence of pneumonia in Omicron itself is low, not all patients can receive immediate CT screening during a pandemic, and it is not necessary to perform CT scans on all Omicron-infected patients. In addition, the CT suites are high-risk areas for hospital-related transmission of COVID-19 and require infection control.[13] Male gender, increasing age, smoking and chronic comorbidities are associated with a higher risk of pneumonia following Omicron infection.[14–18] COVID-19 vaccine is less effective against symptomatic Omicron infection but provides strong protection against pneumonia, hospitalization and death associated with COVID-19.[16,19–21]

Dysregulation of immune response is present in COVID-19 patients[22] and hematological indicators such as neutrophil to lymphocyte ratio (NLR) are independent predictors of disease progression and mortality in patients with COVID-19.[23–28] Hypercoagulable states and elevated levels of D-dimer have been proven in COVID-19 patients. D-dimer levels are valuable predictors of severity and mortality and may be associated with inflammation in SARS-COV-2 pneumonia prior to coagulopathy/thrombosis.[28–31]

However, the pathogenicity of Omicron is different from that of the previous strains.[3,5–7] Omicron is less virulent. The infectivity of the SARS-CoV-2 Omicron variant is more than Alpha, but Omicron patients are less likely to be admitted to ICU. Are the previous hematological indicators still valuable in the Omicron era? The value and threshold of these indicators could be more precise. In the Omicron era, we have also focused on symptomatic, elderly patients with comorbidities. The value of these indicators in patients at high risk of Omicron infection remains unclear. A previous study found that only aging was associated with pneumonia.[15] We need rapid, inexpensive and widely available biomarkers to guide the early detection of people at risk of pneumonia and to provide early intervention. Therefore, further studies of hematological indicators associated with pneumonia in COVID-19 patients infected by Omicron are needed and may improve patients' clinical management in the Omicron era. In the present study, we aimed to assess the value of hematological indicators as risk factors for pneumonia in symptomatic COVID-19 patients infected with the SARS-CoV-2 Omicron variant.

Materials and Methods

Study Design and Participants

This retrospective cohort study enrolled patients with a confirmed diagnosis of COVID-19 admitted to Shanghai Lingang Shelter Hospital in China between April 21, 2022 and May 20, 2022. Symptomatic COVID-19 patients aged 18 years or older with complete clinical data, blood and CT examinations were included. Patients were excluded if they met one of the following criteria: 1) past or existing history of chronic medical conditions affecting inflammatory markers, such as autoimmune disease, chronic inflammatory disease, malignancy under treatment, gastrointestinal bleeding, chronic hematological disease, recent acute myocardial damage, recent surgery, HIV infection and cirrhosis of the liver; 2) recent disease affecting the coagulation system, such as acute pulmonary embolism, lower limb deep vein thrombosis, hematological disorders, prior to COVID-19 infection; 3) during pregnancy and lactating women; 4) ongoing treatment with drugs that affect indicators of inflammation and coagulation system, such as corticosteroids and anticoagulants. This study was authorized by the Ethics Commission for Clinical Research of Zhongda Hospital, affiliated to Southeast University. Informed consent was waived due to the nature of the study as a retrospective study. The study was conducted in accordance with the principles described in the Declaration of Helsinki and the confidentiality of patients was guaranteed.

Data Collection

Health information stored in the electronic medical record system was analyzed. We collected available clinical details, including demographic characteristics, vaccination status, comorbidities, nucleic acid test results, laboratory tests and CT examinations. Comorbidities included hypertension, diabetes mellitus, cardiovascular disease, chronic respiratory disease (asthma, chronic obstructive pulmonary disease or interstitial lung disease) and chronic kidney disease. Laboratory indicators were collected, including leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, platelets, hemoglobin, aspartate aminotransferase, alanine aminotransferase, total bilirubin, direct bilirubin, blood urea nitrogen, serum

creatinine, fibrinogen and D-dimer. This study also calculated and collected derived hematological indicators, including NLR, monocyte to lymphocyte ratio (MLR), eosinophil to lymphocyte ratio (ELR), platelet to lymphocyte ratio (PLR), fibrinogen to lymphocyte ratio (FLR), fibrinogen to D-dimer ratio (FDR). Nasopharyngeal swab specimens were collected daily from each patient during hospitalization. The criterion for negative conversion was two consecutive negative nucleic acid tests within a 24-hour minimum sampling interval. The date of the first two consecutive negative nucleic acid tests after admission to the hospital was defined as the date of nucleic acid negativity. The nucleic acid negative conversion time (NCT) was calculated as the number of days between the date of positive nucleic acid on the pre-admission community screen and the date of negative nucleic acid after admission.[32,33]

Statistical Analysis

Categorical variables are presented as the number and percentage of the total. Continuous variables are shown as the median (Quartile 25%, 75%). The distribution of continuous variables was assessed using the Shapiro–Wilk test. The chi-squared test or Fisher's exact test was used to compare the significance of the differences between categorical variables. We compared continuous variables between different groups using the Student's *t*-test or Mann–Whitney *U*-test as appropriate. Univariate and forward stepwise multivariate logistic analyses were conducted to examine risk factors for the presence of pneumonia. Receiver operating characteristic (ROC) curve analysis was used to assess the value of laboratory markers in predicting the development of pneumonia. Optimal cut-off levels were determined and their sensitivities and specificities were calculated. All analyses were performed using SPSS 25.0 software (SPSS Inc, Chicago, IL). Two-tailed P values of <0.05 were considered statistically significant.

Results

Clinical Characteristics

151 symptomatic COVID-19 patients aged 18 years or older with complete clinical data, blood tests and CT examinations met the inclusion criteria. Of these, 3 patients were excluded from the study due to autoimmune diseases. In addition, 2 patients were ruled out due to ongoing treatment for malignancy. Furthermore, 2 patients were excluded because they were being treated with anticoagulants for a recent thrombotic disease. The study ultimately enrolled 144 symptomatic COVID-19 patients with Omicron infection (Figure 1). Asymptomatic infected individuals were not included in this study.

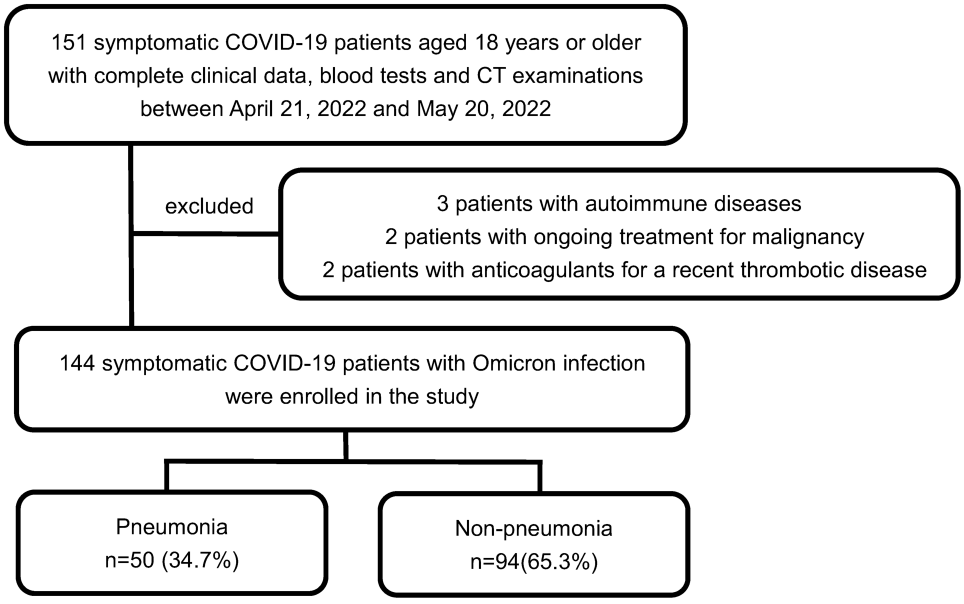

Figure 1 The flowchart of patients according to inclusion and exclusion criteria.

Table 1 Clinical Characteristics of Symptomatic COVID-19 Patients Infected by SARS-CoV-2 Omicron Variant

Variables	Total (n=144)	Non-Pneumonia (n=94)	Pneumonia (n=50)	*P* value
Age, years	66(51, 74)	66(50,73)	69(53,76)	0.481
Male	79(54.9%)	49(52.1%)	30(60.0%)	0.366
Hypertension	51(35.4%)	36(38.3%)	15(30.0%)	0.322
Diabetes	24(16.7%)	19(20.2%)	5(10.0%)	0.117
Cardiovascular diseases	6(4.2%)	4(4.3%)	2(4.0%)	1.000
Chronic respiratory diseases	4(2.8%)	1(1.1%)	3(6.0%)	0.121
Chronic kidney disease	9(6.3%)	6(6.4%)	3(6.0%)	1.000
Vaccination				0.140
0 dose	64(44.4%)	38(40.4%)	26(52.0%)	
1 dose	4(2.8%)	3(3.2%)	1(2.0%)	
2 doses	34(23.6%)	22(23.4%)	12(24.0%)	
3 doses	42(29.2%)	31(33.0%)	11(22.0%)	
NCT, days	8(5,10)	7(5,10)	9(5,13)	0.040

Note: Data are presented as median (Quartile 25th–75th) for continuous variables and as number with percentage for categorical variables.
Abbreviation: NCT, negative conversion time.

Table 1 shows the clinical characteristics of symptomatic COVID-19 patients infected with Omicron by pneumonia status classification. The median age of the patients was 66 years, and the majority of patients were elderly. 50 patients (34.7%) had pneumonia, and 79 (54.9%) were male. Figure 2 shows common CT findings in pneumonia COVID-19 patients infected by the SARS-CoV-2 Omicron variant. Comorbidities were common in these patients, including 51 patients (35.4%) with hypertension, 24 (16.7%) with diabetes, 6 (4.2%) with cardiovascular disease, 4 (2.8%) with chronic respiratory diseases and 9 (6.3%) with chronic kidney disease. 80 patients (64.2%) received at least one dose of the inactivated vaccine (vero cell), of which 42 patients (29.2%) received a third (booster) dose. Only 4 patients (2.8%) received one dose of the inactivated vaccine, and 34 patients (23.6%) got two doses of the inactivated vaccine. There were still 64 patients in this study who did not receive any vaccination. None of the patients had a history of COVID-19 infection. The median time to NCT of nucleic acids was 8 (5,10) days. The clinical data were compared according to the presence or absence of pneumonia. Age, gender, comorbidities and doses of the vaccine showed no significant differences between the two groups of pneumonia patients and non-pneumonia patients (all $P>0.05$). The median time to NCT of nucleic acid was longer in patients with pneumonia than those without pneumonia, with 9 and 7 days in the two groups, respectively ($P=0.040$). 2 patients in the pneumonia group were admitted to ICU, and these two patients were not vaccinated. In this study, no patients had secondary complications or died.

Laboratory Results

Table 2 shows the laboratory results of symptomatic COVID-19 patients infected by the SARS-CoV-2 Omicron variant classified by pneumonia status. Patients with pneumonic COVID-19 had higher levels of leukocytes ($P=0.043$), neutrophils ($P=0.009$), fibrinogen ($P=0.008$), and lower levels of lymphocytes ($P=0.048$) compared to those with non-pneumonic COVID-19 infection. In contrast, values for platelets, hemoglobin, ALT, AST, total bilirubin, direct bilirubin, total protein, albumin, blood urea nitrogen, serum creatinine and D-dimer were similar between the two groups (all $P>0.05$). Derived hematological parameters of symptomatic COVID-19 patients with the SARS-CoV-2 Omicron variant are shown in Table 3. NLR ($P=0.001$), MLR ($P=0.009$), FLR ($P=0.001$) and FDR ($P=0.023$) were all significantly higher in the pneumonia group than in the non-pneumonia group, while ELR and PLR were statistically indistinguishable ($P>0.05$).

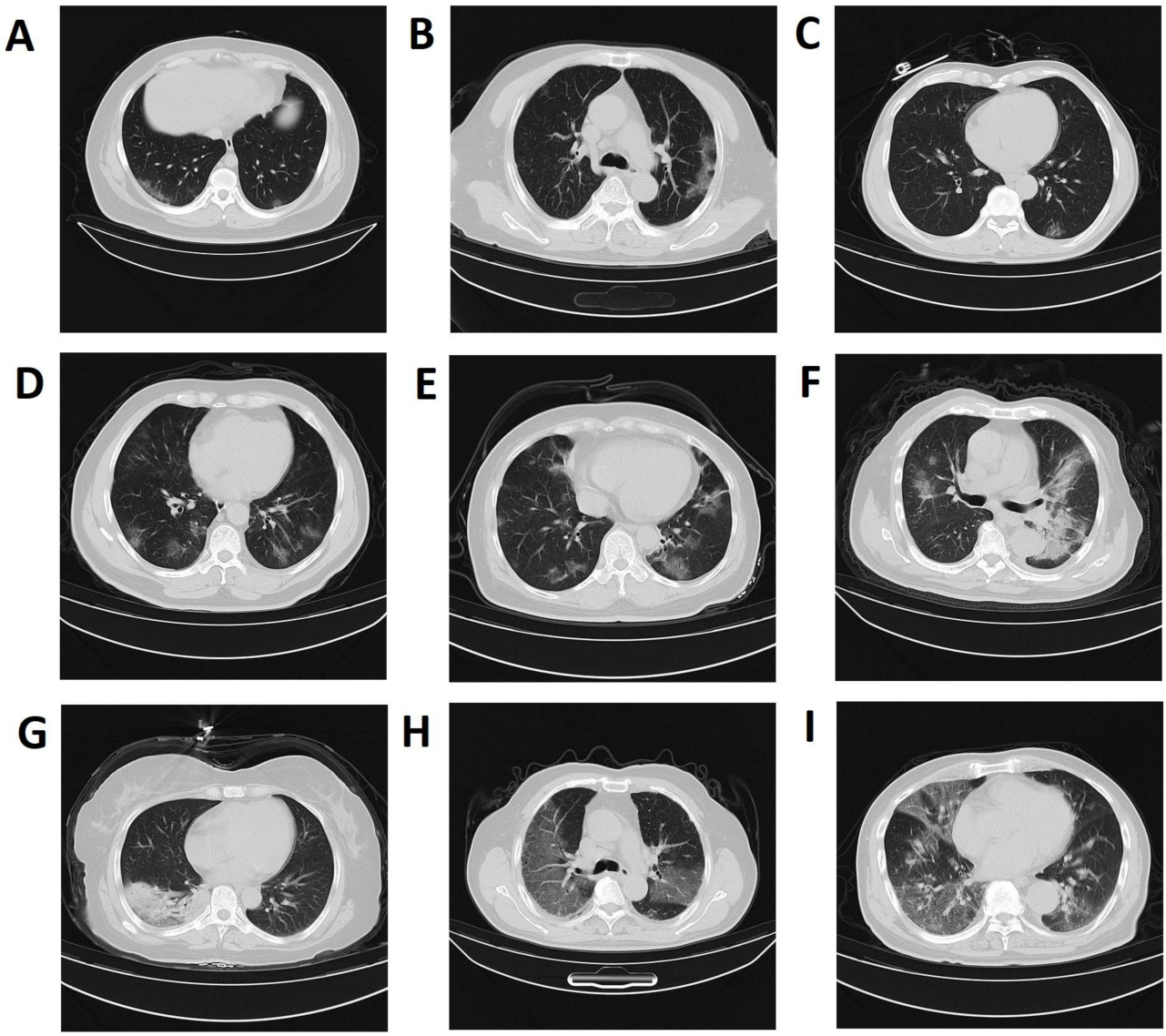

Figure 2 CT images in pneumonia COVID-19 patients infected by SARS-CoV-2 Omicron variant. (**A**–**C**), peripheral ground glass lesions. (**D** and **E**), scattered ground-glass lesions in both lungs. (**F** and **G**), local consolidation.(**H** and **I**), diffuse ground glass lesions in both lungs.

Risk Factors for Pneumonia

ROC curve analyses based on the presence of pneumonia in patients with symptomatic COVID-19 infected by the SARS-CoV -2 Omicron variant were performed to compare the predictive performance of blood parameters (Figure 3). As presented in Table 4, cut-off values and the area under the ROC curve (AUC) also were calculated. The AUC for leukocytes, lymphocytes, neutrophils and fibrinogen were 0.603 (95%confidence interval(CI): 0.501–0.704, *P*=0.043), 0.615 (95% CI:0.517–0.712, *P*=0.024), 0.632 (95% CI:0.534–0.730, *P*=0.009) and 0.635 (95% CI:0.539–0.730, *P*=0.008), respectively. In contrast, the AUC for monocytes, eosinophils, platelets, hemoglobin and D-dimer were insignificant (all *P*>0.05). ROC curve analyses also revealed the cut-off levels of leukocytes (cut-off:6.345×109/L, sensitivity 46.0%, specificity 74.5%), lymphocytes (cut-off :1.340×109/L, sensitivity 60.0%, specificity 63.8%), neutrophils (cut-off:2.945×109/L, sensitivity 72.0%, specificity 50.0%) and fibrinogen (cut-off:3.99g/L, sensitivity 40.0%, specificity 83.0%).

Then, ROC curve analyses were performed to compare the predictive performances among derived hematological indicators according to pneumonia in symptomatic Omicron patients (Figure 4A). As shown in Table 5, the AUC for NLR, MLR, FLR and FDR were 0.670 (95% CI:0.580–0.760, *P*=0.001), 0.632 (95% CI:0.535–0.728, *P*=0.009), 0.669 (95%

Table 2 Laboratory Findings of Symptomatic COVID-19 Patients Infected by SARS-CoV-2 Omicron Variant

Variables	Total (n=144)	Non-Pneumonia (n=94)	Pneumonia (n=50)	*P* value
Leukocytes, $\times10^9$/L	5.41(4.18,6.71)	5.23(4.02,6.48)	5.92(4.50,7.74)	0.043
Lymphocytes, $\times10^9$/L	1.45(1.06,1.91)	1.60(1.14,1.95)	1.25(0.87,1.77)	0.048
Neutrophils, $\times10^9$/L	3.16(2.28,4.50)	2.95(2.17,4.23)	3.68(2.77,5.13)	0.009
Monocytes, $\times10^9$/L	0.40(0.31,0.53)	0.40(0.30,0.49)	0.42(0.33,0.56)	0.136
Eosinophils, $\times10^9$/L	0.06(0.02,0.14)	0.07(0.03,0.14)	0.06(0.02,0.13)	0.424
Platelets, $\times10^9$/L	200(151,247)	199(157,249)	211(144,243)	0.985
Hemoglobin, g/L	132(116,141)	132(118,143)	131(114,140)	0.685
ALT, U/L	19.0(13.0,30.5)	19.0(12.8,28.3)	21.0(13.0,34.0)	0.281
AST, U/L	22.0(17.0,27.0)	21.0(17.8,26.0)	23.0(16.0,31.0)	0.522
Total Bilirubin, umol/L	8.0(6.4,12.4)	7.8(6.0,12.7)	8.3(6.8,11.9)	0.536
Direct bilirubin, umol/L	3.0(2.1,4.7)	2.9(2.0,4.8)	3.2(2.4,4.3)	0.498
Total protein, g/L	65.5(63.2,69.9)	65.4(62.4,70.6)	65.9(63.7,68.7)	0.993
Albumin, g/L	40.4(38.2,43.3)	40.4(37.8,43.3)	40.5(38.5,43.2)	0.575
Blood urea nitrogen, mmol/L	4.45(3.78,5.86)	4.51(3.78,5.90)	4.41(3.78,5.85)	0.939
Serum creatinine, umol/L	67.5(59.0,76.0)	69.0(59.0,77.3)	66.5(55.3,74.8)	0.310
Fibrinogen, g/L	3.21(2.76,4.00)	3.11(2.60,3.75)	3.68(2.82,4.45)	0.008
D-dimer, ug/mL	0.45(0.32,0.75)	0.45(0.33,0.76)	0.42(0.29,0.88)	0.374

Note: Data are presented as median (Quartile 25th–75th) for continuous variables.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 3 Derived Hematological Indicators of Symptomatic COVID-19 Patients Infected by SARS-CoV-2 Omicron Variant

Variables	Total (n=144)	Non-Pneumonia (n=94)	Pneumonia (n=50)	*P* value
NLR	2.16(1.45,3.05)	2.00(1.26,2.86)	2.60(1.82,4.90)	0.001
MLR	0.27(0.20,0.44)	0.25(0.18,0.36)	0.35(0.22,0.52)	0.009
ELR	0.046(0.016,0.102)	0.046(0.016,0.083)	0.043(0.019,0.109)	0.613
PLR	144.11(104.89,174.90)	139.40(99.08,170.69)	150.32(120.96,218.89)	0.140
FLR	2.26(1.67,3.19)	2.07(1.60,2.91)	2.76(2.05,4.21)	0.001
FDR	7.18(4.54,10.11)	6.77(4.24,9.44)	9.24(5.0,12.30)	0.023

Note: Data are presented as median (Quartile 25th–75th) for continuous variables.
Abbreviations: NLR, neutrophil to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; ELR, eosinophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; FLR, fibrinogen to lymphocyte ratio; FDR, fibrinogen to D-dimer ratio.

CI:0.575–0.763, *P*=0.001) and 0.615 (95% CI:0.510–0.721, *P*=0.023), respectively. However, ELR and PLR had no statistical differences (*P*>0.05), and the AUC was relatively small (0.526 and 0.575). The cut-off levels of NLR (cut-off:2.23, sensitivity 62.0%, specificity 62.8%), MLR (cut-off:0.34, sensitivity 54.0%, specificity 74.5%), FLR (cut-off:2.21, sensitivity 70.0%, specificity 57.4%) and FDR (cut-off:10.43, sensitivity 40.0%, specificity 87.2%) were also provided by the analyses.

By applying logistic regression analysis, we aimed to determine the effect of derived hematological indicators on pneumonia in patients with symptomatic COVID-19 infected by the SARS-CoV-2 Omicron variant. Table 6 summarizes the results of the univariate analysis. As for the derived hematological indicators, elevated levels of NLR (OR:1.219, 95% CI:1.046–1.421, *P*=0.011), FLR (OR:1.170, 95% CI:1.014–1.349, *P*=0.031) and FDR (OR:1.131, 95% CI:1.039–1.231, *P*=0.005) were significantly correlated with an increased risk of pneumonia. In order to find the ideal model, forward stepwise multivariate logistic regression was performed. Ultimately elevated levels of NLR (OR:1.248, 95% CI:1.068–1.459, *P*=0.005) and FDR (OR:1.160, 95% CI:1.054–1.276, *P*=0.002) were associated with the development of pneumonia (Table 6).

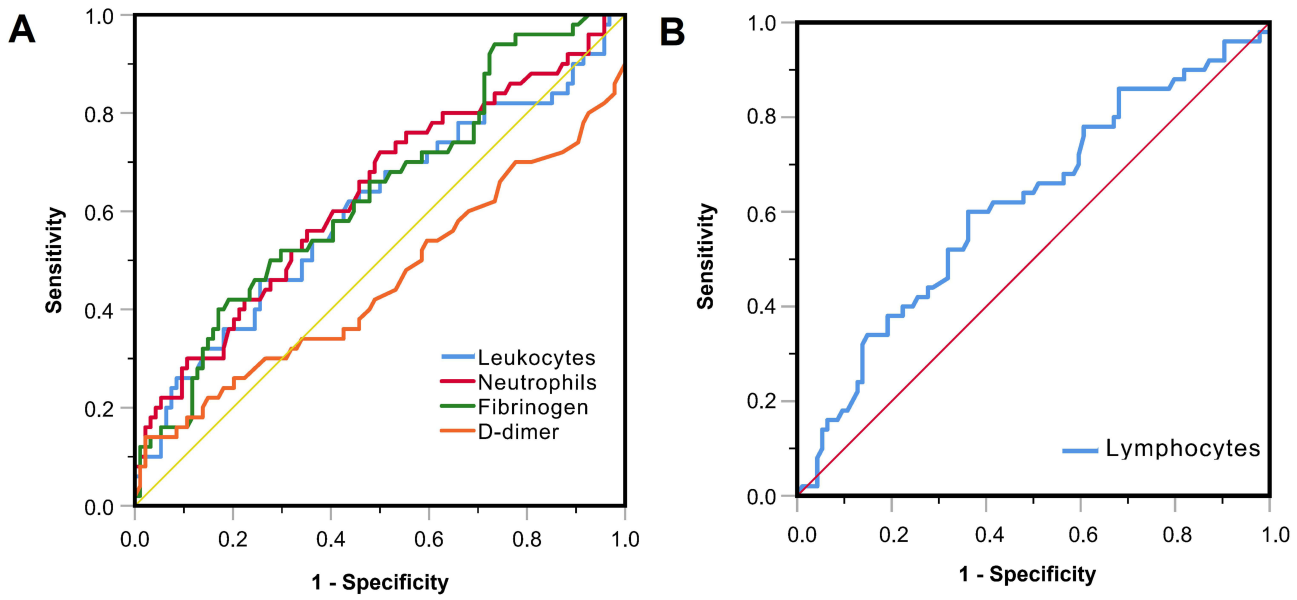

Figure 3 Receiver operating characteristic (ROC) curve for the blood parameters according to the presence of pneumonia in symptomatic COVID-19 patients infected by SARS-CoV-2 Omicron variant. (**A**), ROC curve for leukocytes, neutrophils, fibrinogen and D-dimer. (**B**), ROC curve for lymphocytes.

Finally, we performed ROC curve analysis to evaluate the value of the combined NLR and FDR indicator for pneumonia. The combined NLR and FDR indicators could also predict pneumonia in symptomatic COVID-19 patients infected by the SARS-CoV-2 Omicron variant, with an AUC of 0.701 (95% CI:0.606–0.796, $P<0.001$, sensitivity 56.0%, specificity 83.0%) (Figure 4B, Table 5).

Discussion

The study ultimately included 144 patients with symptomatic Omicron infection, 50 of whom had pneumonia. Patients with COVID-19 who had pneumonia had higher levels of leukocytes, neutrophils, fibrinogen, and lower levels of lymphocytes compared to patients without pneumonic Omicron infection. The derived hematological indices NLR, MLR, FLR and FDR were significantly higher in the pneumonia group than in the non-pneumonia group. When ROC analysis was performed, these derived indicators had better results than the original hematological indicators. Univariate analysis of these derived hematological indicators also confirmed that NLR, FLR, and FDR were significantly associated with an increased risk of pneumonia. Furthermore, multivariate analysis showed statistically significant results for NLR

Table 4 The Area Under the ROC Curve and Optimal Cut-Off Values for the Blood Parameters Based on the Presence of Pneumonia in Symptomatic COVID-19 Patients Infected by SARS-CoV-2 Omicron Variant

Variables	AUC (95% CI)	*P* value	Cut-Off Level	Sensitivity	Specificity	Youden Index
Leukocytes	0.603(0.501–0.704)	0.043	≥6.345×10^9/L	46.0%	74.5%	0.205
Lymphocytes	0.615(0.517–0.712)	0.024	≤1.340×10^9/L	60.0%	63.8%	0.238
Neutrophils	0.632(0.534–0.730)	0.009	≥2.945×10^9/L	72.0%	50.0%	0.22
Monocytes	0.576(0.478–0.674)	0.136	≥0.525×10^9/L	36.0%	80.9%	0.169
Eosinophils	0.520(0.419–0.621)	0.696	≤0.075×10^9/L	60.0%	47.9%	0.079
Platelets	0.504(0.403–0.606)	0.935	≤150.5×10^9/L	30.0%	78.7%	0.087
Hemoglobin	0.528(0.427–0.628)	0.585	≤123.5g/L	40.0%	70.2%	0.102
Fibrinogen	0.635(0.539–0.730)	0.008	≥3.99g/L	40.0%	83.0%	0.230
D-dimer	0.455(0.348–0.562)	0.374	≥1.93ug/mL	14.0%	97.9%	0.119

Note: The optimal discriminating cut-off values were obtained by calculating the Youden index.
Abbreviations: AUC, area under the ROC curve; CI, confidence interval; ROC curve, receiver operating characteristic curve.

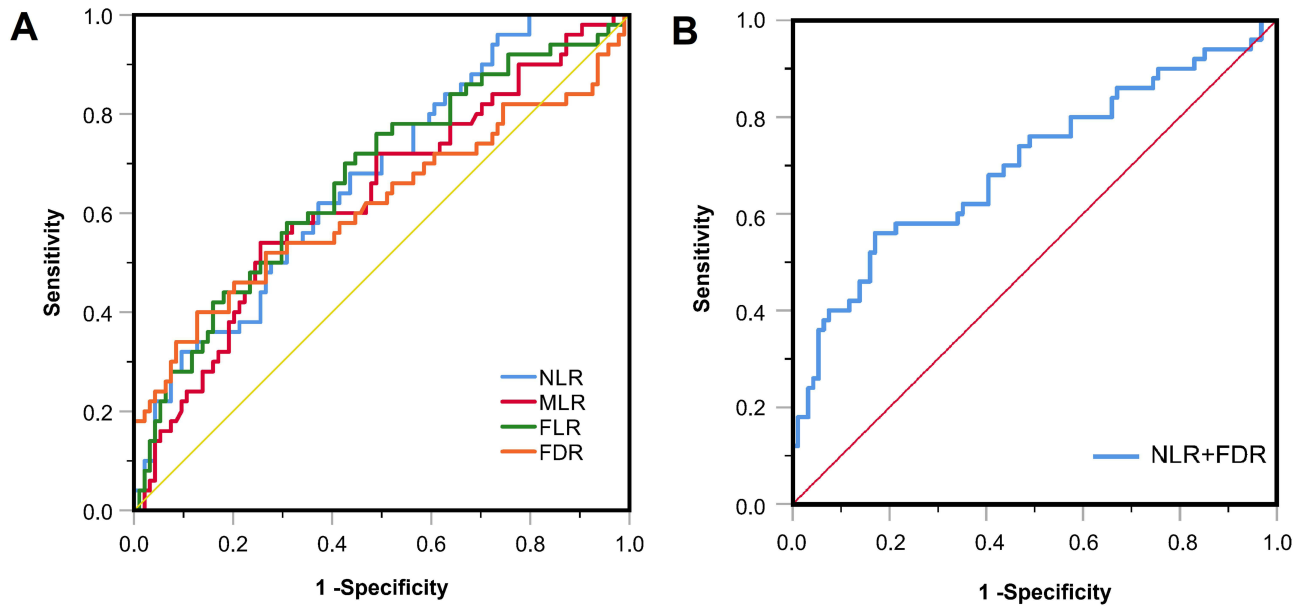

Figure 4 Receiver operating characteristic (ROC) curve for the derived hematological indicators according to the presence of pneumonia in symptomatic COVID-19 patients infected by SARS-CoV-2 Omicron variant. (**A**), ROC curve for NLR, MLR, FLR and FDR. (**B**), ROC curve for NLR+FDR.
Abbreviations: NLR, neutrophil to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; FLR, fibrinogen to lymphocyte ratio; FDR, fibrinogen to D-dimer ratio.

and FDR. Ultimately, the ROC analysis suggested that the combination of NLR and FDR was more helpful than other indicators in identifying pneumonia in symptomatic COVID-19 patients infected by Omicron.

Previous studies have identified age and comorbidities as independent risk factors for pneumonia due to Omicron infection.[14–16] However, in this study, there was no distinction in age and comorbidity between pneumonia and non-pneumonia groups. It may be due to the advanced age and the high incidence of comorbidities in the enrolled patients. More than half of the patients were elderly with comorbidities. Breakthrough infection with pneumonia has been reported.[34] The Omicron variant may evade immunization from previous vaccines or infections,[35–37] but vaccination can protect against hospitalization and death.[19–21] In this study, the vaccination rate of the pneumonia group is lower than that of the non-pneumonia group, which is not statistically significant. However, this may be limited to the sample size, so it cannot reflect the protective effect of the vaccines on pneumonia. Although the data is limited, there is no evidence that the treatment of breakthrough infection should differ from the treatment used at the time of initial infection. This study also found that the nucleic acid NCT was longer in the pneumonia group, suggesting that patients with lower

Table 5 The Area Under the ROC Curve and Optimal Cut-Off Values for the Derived Haematological Indicators Based on the Presence of Pneumonia in Symptomatic COVID-19 Patients Infected by SARS-CoV-2 Omicron Variant

Variables	AUC (95% CI)	*P* value	Cut-Off Level	Sensitivity	Specificity	Youden Index
NLR	0.670(0.580–0.760)	0.001	≥2.23	62.0%	62.8%	0.248
MLR	0.632(0.535–0.728)	0.009	≥0.34	54.0%	74.5%	0.285
ELR	0.526(0.424–0.627)	0.613	≥0.09	36.0%	78.7%	0.147
PLR	0.575(0.474–0.676)	0.140	≥268.24	22.0%	96.8%	0.188
FLR	0.669(0.575–0.763)	0.001	≥2.21	70.0%	57.4%	0.274
FDR	0.615(0.510–0.721)	0.023	≥10.43	40.0%	87.2%	0.272
NLR+FDR	0.701(0.606–0.796)	<0.001	–	56.0%	83.0%	–

Note: The optimal discriminating cut-off values were obtained by calculating the Youden index.
Abbreviations: AUC, area under the ROC curve; CI, confidence interval; ROC curve, receiver operating characteristic curve; NLR, neutrophil to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; ELR, eosinophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; FLR, fibrinogen to lymphocyte ratio; FDR, fibrinogen to D-dimer ratio.

Table 6 Univariate and Multivariate Logistic Analyses for Determining Risk Factors for Pneumonia in Symptomatic COVID-19 Patients Infected by SARS-CoV-2 Omicron Variant

Variables	Univariate Analysis			Multivariate Analysis		
	B	OR(95% CI)	*P* value	B	OR(95% CI)	*P* value
NLR	0.198	1.219(95% CI:1.046–1.421)	0.011	0.222	1.248(95% CI:1.068–1.459)	0.005
MLR	1.356	3.880(95% CI:0.946–15.91)	0.06	–	–	–
ELR	0.876	2.402(95% CI:0.437–13.212)	0.314	–	–	–
PLR	0.003	1.003(95% CI:1.000–1.007)	0.056	–	–	–
FLR	0.157	1.170(95% CI:1.014–1.349)	0.031	–	–	–
FDR	0.123	1.131(95% CI:1.039–1.231)	0.005	0.148	1.160(95% CI:1.054–1.276)	0.002

Abbreviations: OR, odds ratio; CI, confidence interval; NLR, neutrophil to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; ELR, eosinophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; FLR, fibrinogen to lymphocyte ratio; FDR, fibrinogen to D-dimer ratio.

respiratory tract involvement might carry the virus for a longer time and have a longer duration of illness. This result also prompts that it is more important to investigate the risk factors for pneumonia and identify relevant indicators.

Inflammatory indicators have been studied extensively as reliable predictors of the progression and severity of COVID-19.[25–27,38,39] In our study, we found elevated levels of leukocytes and neutrophils with decreased levels of lymphocytes in patients with Omicron-induced pneumonia compared to those with non-pneumonic Omicron infection, resulting in elevated NLR and MLR, the derived hematological indicators in the pneumonia group. Furthermore, the derived indicators NLR and MLR were superior to the original hematological inflammatory indicators in the ROC analysis. However, unlike the results of previous non-Omicron studies,[40] other inflammatory indicators such as MLR, PLR and ELR were not statistically significant in the univariate analysis. Ultimately only NLR entered the model with statistical significance in multivariate logistic analysis.

Fibrinogen and D-dimer are traditional indicators for coagulation, while some studies have reported that they can also be indicators of inflammation rather than coagulation alone.[41,42] Interestingly, there was no difference in D-dimer levels between the pneumonia group and the non-pneumonia group due to Omicron infection during the comparison of coagulation indicators in this study. In contrast, fibrinogen was significantly higher in the Omicron pneumonia group, and the derived indicators FLR and FDR were higher than their levels in the non-pneumonia group. Some studies have found that fibrinogen needs to be together with D-dimer for a more appropriate predictive role.[43,44] Predictably, this study also found that FLR and FDR levels were significantly higher in the pneumonia group than in the non-pneumonia group and that the multifactorial analysis of FDR together with NLR was significant. Ultimately, the ROC analysis also confirmed that the combination of FDR and NLR was effective.

This study has several limitations. As a retrospective study, the study only involved symptomatic COVID-19 cases infected by Omicron, so the conclusions cannot be applied to asymptomatic Omicron cases. Only hematological indicators were discussed, and this study did not compare the symptoms of COVID-19 patients infected with Omicron. There was also no comparative analysis of specific CT manifestations of pulmonary involvement in the study. Undoubtedly NLR and FDR are traditional markers, but they are cheap, convenient, and a better choice. Moreover, due to the limited sample size, the protective effect of different vaccine statuses also requires further expansion of the sample size. The impact of different CT manifestations, symptoms, and vaccine status on the occurrence of pneumonia needs to be studied with a larger sample size.

Conclusion

In conclusion, the current study suggests that NLR and FDR can predict the presence of pneumonia in symptomatic COVID-19 patients infected with the SARS-CoV-2 Omicron variant.

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author.

Ethical Approval and Consent to Participate

This study was authorized by the Ethics Commission for Clinical Research of Zhongda Hospital, affiliated to Southeast University. Informed consent was waived due to the nature of the study as a retrospective study. The study was conducted in accordance with the principles described in the Declaration of Helsinki and confidentiality of patients was guaranteed.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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