

RESEARCH ARTICLE

Diagnostic value of peripheral hematologic markers for coronavirus disease 2019 (COVID-19): A multicenter, cross-sectional study

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Abstract

Background: To determine the diagnostic value of hematologic markers for coronavirus disease 2019 (COVID-19) and explore their relationship with disease severity.

Methods: Subjects included 190 COVID-19 patients, 190 healthy subjects, and 105 influenza pneumonia (IP) patients. COVID-19 patients were divided into the ARDS and non-ARDS groups. Routine blood examination, biochemistry indicator, days in hospital, body temperature, pneumonia severity index (PSI), CURB-65, and MuLBSTA were recorded. Correlations between variables were assessed using Spearman's correlation analysis. Receiver operating characteristic (ROC) curves were used to study the accuracy of the various diagnostic tests.

Results: Compared with healthy subjects, COVID-19 patients had lower white blood cell (WBC), lymphocyte, platelet, and hemoglobin levels; higher percentages of neutrophils and monocytes; lower percentages of lymphocytes and higher neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) values ($P < .05$). COVID-19 patients had higher WBC and neutrophil levels and lower percentages of lymphocytes compared to IP ($P < .05$). ROC curve analysis revealed that MLR had a high diagnostic value in differentiating COVID-19 patients from healthy subjects, but not from IP patients. NLR showed significant positive correlations with PSI, CURB-65, and MuLBSTA. Lymphocyte count was lower in the ARDS group and yielded a higher diagnostic value than the other variables.

Conclusions: Monocyte-to-lymphocyte ratio showed an acceptable efficiency to separate COVID-19 patients from healthy subjects, but failed to rule out IP patients. NLR may be a reliable marker to evaluate the disease severity of COVID-19.

Abbreviations: ALT, alanine aminotransferase;; ARDS, acute respiratory distress syndrome;; AST, aspartate aminotransferase;; AUC, area under the curve;; CI, confidence interval;; CKMB, creatine kinase isoenzyme;; COVID-19, coronavirus disease 2019;; CREA, creatinine;; CRP, C-reactive protein;; CT, computerized tomography;; ESR, erythrocyte sedimentation rate;; HGB, hemoglobin;; IP, influenza pneumonia;; LHS, length of hospital stay;; MERS-CoV, middle east respiratory syndrome coronavirus;; MLR, monocyte-to-lymphocyte ratio;; NLR, neutrophil-to-lymphocyte ratio;; PCT, procalcitonin;; PLR, platelet-to-lymphocyte ratio;; PSI, pneumonia severity index;; ROC, receiver operating characteristic;; RT-PCT, real-time reverse transcription polymerase chain reaction;; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2;; SE, standard error;; WBC, white blood cell;; WHO, World Health Organization.

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Lymphocyte count may be useful to establish the early diagnosis of ARDS in the COVID-19 patients.

KEYWORDS

coronavirus disease 2019, diagnostic value, lymphocyte, monocyte-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease it causes, coronavirus disease 2019 (COVID-19), were first reported in Wuhan, the capital of Hubei Province, and have quickly spread to different regions of China and other countries, including the United States, Japan, South Korea, and Thailand.^{1,2} The World Health Organization (WHO) has declared that the outbreak of SARS-CoV-2 can be characterized as a global pandemic, and as of May 5, 2020, the number of confirmed COVID-19 cases surged above 3 570 000, with nearly 250 000 deaths.³ Several published reports of early clinical descriptions of COVID-19 found that 26%-33% of patients required intensive care and 4%-15% died.^{1,4-6} Subsequently, a report of 72 314 cases estimated that approximately 19% of people with COVID-19 have severe or critical disease, with a case fatality rate of 2.3%.⁷ Early identification and management are the most effective ways to improve the curative efficacy, which is a challenging task for physicians in clinical practice.

Currently, a positive result on high-throughput sequencing or real-time reverse transcription polymerase chain reaction (RT-PCR) of nasal and pharyngeal swab specimens is considered an optimal standard of COVID-19. Chest computerized tomography (CT) is widely used as an important diagnostic tool of COVID-19, and some CT manifestations may be associated with the progression and prognosis of COVID-19.⁸ However, their clinical application is restricted by many factors, such as limited medical resources and high examination costs. Thus, convenient and cost-effective indicators are urgently required to simplify the diagnostic process and evaluate the disease severity.

Hematologic markers, including neutrophils, lymphocytes, monocytes, platelets, neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR), have been proposed as indicators to assist in the diagnosis, early warning, and risk stratification of infectious diseases.⁹ NLR has been demonstrated as an informative biomarker of diagnosis and disease severity in community-acquired pneumonia and bacteremia.^{10,11} MLR and PLR have also been recognized as a surrogate biological marker for the diagnosis of influenza virus infection in patients with respiratory tract infection.¹²⁻¹⁴ However, few studies have focused on the diagnostic value of hematologic markers for COVID-19.

Therefore, this study aimed to examine neutrophils, lymphocytes, monocytes, platelets, NLR, MLR, and PLR in COVID-19

patients, determine their diagnostic value for COVID-19, and explore their relationship with disease severity.

2 | MATERIALS AND METHODS

2.1 | Study design and participant characteristics

This multicenter cross-sectional study was conducted in three hospitals (the Second Affiliated Hospital of Chongqing Medical University, Chongqing Public Health Medical Center and Qianjiang Central Hospital of Chongqing) in Chongqing Province municipality from January 19 to March 25, 2020. According to the World Health Organization interim guidance,¹⁵ the diagnostic criteria of COVID-19 were based on virus RNA detection, clinical characteristics, chest imaging, and ruling out of common pathogens. Patients who had been treated with antibiotics or glucocorticoids before admission and had other kinds of disease, such as renal or liver failure, malignant tumors, active infection, hypertension, diabetes mellitus, or coronary heart disease, were excluded from the study. A same number of healthy controls were recruited from the clinical database of health examine center after matching for age and gender. In addition, with the same exclusion criteria, patients who had positive influenza virus RT-PCR results or influenza virus-specific IgM antibody and CT manifestations of viral pneumonia were included from January 2018 to March 2020. Finally, a total of 190 confirmed cases with COVID-19, 190 healthy subjects, and 105 influenza pneumonia (IP) patients were enrolled in the study.

This study was approved by the institutional ethics board of the Second Affiliated Hospital of Chongqing Medical University (No. 2020-09), Chongqing Public Health Medical Center (No. 2020-015-01-KY), and Qianjiang Central Hospital of Chongqing (No. 2020-07) and was in accordance with the Declaration of Helsinki. Due to the retrospective nature of the study design, informed consent was waived.

2.2 | Data collection

Data including demographic information, medical history, clinical manifestations, laboratory findings, radiologic images, and days in hospital were collected from the patients' medical and nursing records. Laboratory results included WBCs, neutrophils, lymphocytes, monocytes, platelets, hemoglobin (HGB), C-reactive protein (CRP),

erythrocyte sedimentation rate (ESR), procalcitonin (PCT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (CREA), and creatine kinase isoenzyme (CKMB). NLR, MLR, and PLR were calculated by dividing the absolute neutrophil, monocyte, and platelet counts by the absolute lymphocyte counts. The pneumonia severity index (PSI), CURB-65, and MuLBSTA¹⁶ were determined within 24 hours after admission by standardized forms. The diagnosis of acute respiratory distress syndrome (ARDS) was based on the Berlin definition.¹⁷ Two senior physicians independently reviewed the data.

2.3 | Statistical analysis

Continuous variables are presented as the mean \pm standard deviation (SD), and categorical variables are indicated as numbers (n) and percentages (%). The normal distribution test was conducted in the variables by Kolmogorov-Smirnov test. Groups were compared using Student's *t* tests for parametric continuous variables or Mann-Whitney *U* tests for non-parametric continuous variables. Proportions for categorical variables were compared using the chi-square test. Correlations between variables were assessed using Spearman's correlation analysis. Receiver operating characteristic (ROC) curves were used to study the accuracy of the various diagnostic tests. All statistical analyses were performed using SPSS 22.0 software, and pictures were drawn by GraphPad Prism 8.0 software. A two-sided *P*-value of $<.05$ was considered significant.

3 | RESULTS

3.1 | Demographics and baseline characteristics

A total of 190 COVID-19 patients, 190 healthy subjects, and 105 IP patients were enrolled in the study. Age and gender distribution were similar among the three groups. Compared with healthy subjects, COVID-19 patients had lower WBC counts (5.45 ± 2.16 vs $5.89 \pm 1.07 \times 10^9/L$, $P < .001$), lymphocyte counts (1.30 ± 0.57 vs $2.00 \pm 0.41 \times 10^9/L$, $P < .001$), platelet counts (193.71 ± 84.28 vs $205.03 \pm 47.12 \times 10^9/L$, $P < .001$), and hemoglobin levels (135.18 ± 16.66 vs 146.98 ± 13.55 g/dL, $P < .001$); higher percentages of neutrophils (3.53 ± 1.97 vs $3.41 \pm 0.85\%$, $P < .001$) and monocytes (7.71 ± 2.61 vs $5.79 \pm 1.26\%$, $P < .001$); lower percentages of lymphocytes (1.30 ± 0.57 vs $2.00 \pm 0.41\%$, $P < .001$); and higher NLR (3.29 ± 2.76 vs 1.77 ± 0.58 , $P < .001$), MLR (0.34 ± 0.17 vs 0.17 ± 0.05 , $P < .001$), and PLR (169.51 ± 97.51 vs 105.87 ± 30.54 , $P < .001$). The ESR was 32.76 ± 20.41 mm/h (normal range: <20.00 mm/h), CRP was 29.12 ± 31.21 mg/L (normal range < 10.00 mg/L), and PCT was 0.057 ± 0.055 ng/mL (normal range < 0.050 ng/mL) in the COVID-19 patients. In addition, the length of hospital stay was 13.91 ± 1.84 days, the body temperature was $37.38 \pm 0.87^\circ\text{C}$, ALT was 28.77 ± 24.87 U/L (normal range: $7.00-40.00$ U/L), AST was 27.82 ± 18.28 U/L (normal

range: $13.00-35.00$ U/L), CREA was 68.93 ± 19.10 $\mu\text{mol/L}$ (normal range: $41.00-81.00$ $\mu\text{mol/L}$), CKMB was 11.59 ± 16.74 ng/mL (normal range: <5.00 ng/mL), PSI was 61.77 ± 27.03 , CURB-65 was 0.51 ± 0.62 , and MuLBSTA was 7.09 ± 2.50 in the COVID-19 group. There were no statistical differences in laboratory findings between COVID-19 and IP groups except for the WBC counts (5.45 ± 2.16 vs $6.04 \pm 2.31 \times 10^9/L$, $P = .013$), neutrophil counts (3.53 ± 1.97 vs $3.97 \pm 2.16 \times 10^9/L$, $P = .043$), and the percentages of lymphocytes (25.52 ± 10.31 vs $23.07 \pm 11.58\%$, $P = .032$; Table 1).

3.2 | Monocyte-to-lymphocyte ratio has a high diagnostic value in differentiating COVID-19 patients from healthy subjects

Receiver operating characteristic curves for the concentrations of hematologic markers were computed for the prediction of COVID-19. When comparing COVID-19 patients with healthy subjects, the area under the curve (AUC) for neutrophils was 0.546 (95% CI: 0.495-0.597), for lymphocytes was 0.847 (95% CI: 0.806-0.881), for monocytes was 0.513 (95% CI: 0.462-0.564), for platelets was 0.605 (95% CI: 0.554-0.655), for NLR was 0.722 (95% CI: 0.674-0.766), for MLR was 0.892 (95% CI: 0.856-0.921), and for PLR was 0.748 (95% CI: 0.702-0.791). ROC curve analysis revealed that MLR had a higher diagnostic value than neutrophils, lymphocytes, monocytes, platelets, NLR, and PLR. In addition, the results showed that an MLR level with a threshold of 0.23 could discriminate COVID-19 patients from healthy subjects with 90.00% specificity and 75.79% sensitivity. However, when comparing patients with COVID-19 to those with IP, the AUC was lower than 0.600 in all the hematologic markers examined (Figure 1 and Table 2).

3.3 | Correlation between the variables

Neutrophils were positively correlated with CRP ($r = .345$, $P < .001$), hospital stay ($r = .148$, $P = 0.042$), ALT ($r = .216$, $P = .003$), and PSI ($r = .228$, $P = .002$). Lymphocytes were negatively correlated with the ESR ($r = -.050$, $P = .023$), PCT ($r = -.263$, $P < .001$), body temperature ($r = -.243$, $P = .001$), AST ($r = -.226$, $P = .002$), PSI ($r = -.255$, $P < .001$), and MuLBSTA ($r = -.175$, $P = .016$). Platelets were negatively correlated with PCT ($r = -.213$, $P = .003$), body temperature ($r = -.189$, $P = .009$), AST ($r = -.233$, $P = .001$), and PSI ($r = -.147$, $P = .043$). Monocytes were negatively correlated with AST ($r = -.275$, $P < .001$) but positively correlated with CREA ($r = .147$, $P = .042$). NLR was positively correlated with CRP ($r = .272$, $P < .001$), PCT ($r = .152$, $P = .036$), hospital stay ($r = .216$, $P = .003$), ALT ($r = .213$, $P = .003$), PSI ($r = .332$, $P < .001$), CURB-65 ($r = .144$, $P = .047$), and MuLBSTA ($r = .203$, $P = .005$). MLR was positively correlated with body temperature ($r = .193$, $P = .008$). PLR was positively correlated with PCT ($r = .285$, $P < .001$). These results suggested that there were significant positive correlations between NLR and disease severity of COVID-19 (Table 3).

TABLE 1 Demographic features and laboratory findings of the participants

	Healthy subject (n = 190)	COVID-19 (n = 190)	IP (n = 105)	P ₁	P ₂
Age (years)	46.44 ± 14.48	46.35 ± 15.07	47.52 ± 17.13	.956	.569
Male (%)	90 (47.3%)	90 (47.3%)	56 (53.33%)	1.000	.327
WBCs (×10 ⁹ /L)	5.89 ± 1.07	5.45 ± 2.16	6.04 ± 2.31	<.001	.013
Neutrophils (×10 ⁹ /L)	3.41 ± 0.85	3.53 ± 1.97	3.97 ± 2.16	.118	.043
Neutrophil percentage, %	57.57 ± 6.96	62.31 ± 12.43	62.60 ± 15.89	<.001	.298
Lymphocytes (×10 ⁹ /L)	2.00 ± 0.41	1.30 ± 0.57	1.26 ± 0.56	<.001	.595
Lymphocyte percentage, %	34.41 ± 6.40	25.52 ± 10.31	23.07 ± 11.58	<.001	.032
Monocytes (×10 ⁹ /L)	0.39 ± 0.08	0.40 ± 0.15	0.46 ± 0.40	.659	.534
Monocyte percentage, %	5.79 ± 1.26	7.71 ± 2.61	7.55 ± 4.01	<.001	.210
Platelets (×10 ⁹ /L)	205.03 ± 47.12	193.71 ± 84.28	203.19 ± 108.22	<.001	.796
Hemoglobin (g/dL)	146.98 ± 13.55	135.18 ± 16.66	135.52 ± 22.40	<.001	.526
NLR	1.77 ± 0.58	3.29 ± 2.76	4.08 ± 3.76	<.001	.090
MLR	0.17 ± 0.05	0.34 ± 0.17	0.42 ± 0.34	<.001	.256
PLR	105.87 ± 30.54	169.51 ± 97.51	180.54 ± 105.40	<.001	.745
ESR (mm/h)	–	32.76 ± 20.41	35.75 ± 22.07	–	.221
CRP (mg/L)	–	29.12 ± 31.21	25.73 ± 25.20	–	.712
PCT (ng/mL)	–	0.057 ± 0.055	0.057 ± 0.046	–	.429
Body temperature (°C)	–	37.38 ± 0.87	37.46 ± 0.95	–	.495
Hospital stay (days)	–	13.91 ± 1.84	13.83 ± 2.13	–	.214
ALT (U/L)	–	28.77 ± 24.87	28.17 ± 19.32	–	.784
AST (U/L)	–	27.82 ± 18.28	28.14 ± 15.62	–	.780
CREA (ng/mL)	–	68.93 ± 19.10	69.87 ± 20.70	–	.638
CKMB (μmol/L)	–	11.59 ± 16.74	10.95 ± 11.02	–	.452
PSI	–	61.77 ± 27.03	63.15 ± 17.86	–	.372
CURB-65	–	0.51 ± 0.62	0.53 ± 0.76	–	.701
MuLBSTA	–	7.09 ± 2.50	7.00 ± 2.72	–	.460

Note: Data are presented as mean ± standard deviation (SD) and n (%). P₁: Compared between COVID-19 and healthy subjects; P₂: Compared between COVID-19 and IP.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKMB, creatine kinase isoenzyme; COVID-19, coronavirus disease 2019; CREA, creatinine; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IP, influenza pneumonia; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PCT, procalcitonin; PLR, platelet-to-lymphocyte ratio; PSI, pneumonia severity index; WBC, white blood cell.

3.4 | Comparison between the non-ARDS and ARDS groups

According to the Berlin definition,¹⁷ COVID-19 patients were divided into the non-ARDS (n = 159) and ARDS (n = 31) groups, and the differences between the two groups were analyzed. There were no significant differences of age and gender between the two groups. The results showed that when compared with those of the non-ARDS group, the lymphocyte and platelet counts were markedly decreased (0.83 ± 0.35 vs 1.40 ± 0.55 × 10⁹/L, *P* < .001; 147.23 ± 51.96 vs 202.77 ± 86.47, *P* < .001), while NLR, MLR, CRP, PCT, PSI, CURB-65, and MuLBSTA were markedly elevated in the ARDS patients (NLR: 5.08 ± 4.48 vs 2.95 ± 2.13, *P* < .001; MLR: 0.49 ± 0.22 vs 0.32 ± 0.14, *P* < .001; CRP: 48.14 ± 34.56 vs 25.41 ± 29.22 mg/L, *P* < .001; PCT: 0.09 ± 0.06 vs 0.05 ± 0.05 ng/

mL, *P* < .001; PSI: 88.65 ± 29.13 vs 56.53 ± 23.32, *P* < .001; CURB-65: 0.97 ± 0.87 vs 0.42 ± 0.52, *P* = .001; MuLBSTA: 8.94 ± 2.69 vs 6.73 ± 2.29, *P* < .001; Table 4).

3.5 | Lymphocytes have a high diagnostic value for ARDS

Receiver operating characteristic curve analysis was carried out to evaluate the accuracy, specificity, and sensitivity of the hematologic markers, PSI, CURB-65, and MuLBSTA for the diagnosis of ARDS in the COVID-19 patients. The results showed that a lymphocyte level <0.87 × 10⁹/L was an optimal cutoff for predicting ARDS in COVID-19 patients with 88.05% specificity and 70.97% sensitivity, which was higher than that of other variables (Table 5 and Figure 2).

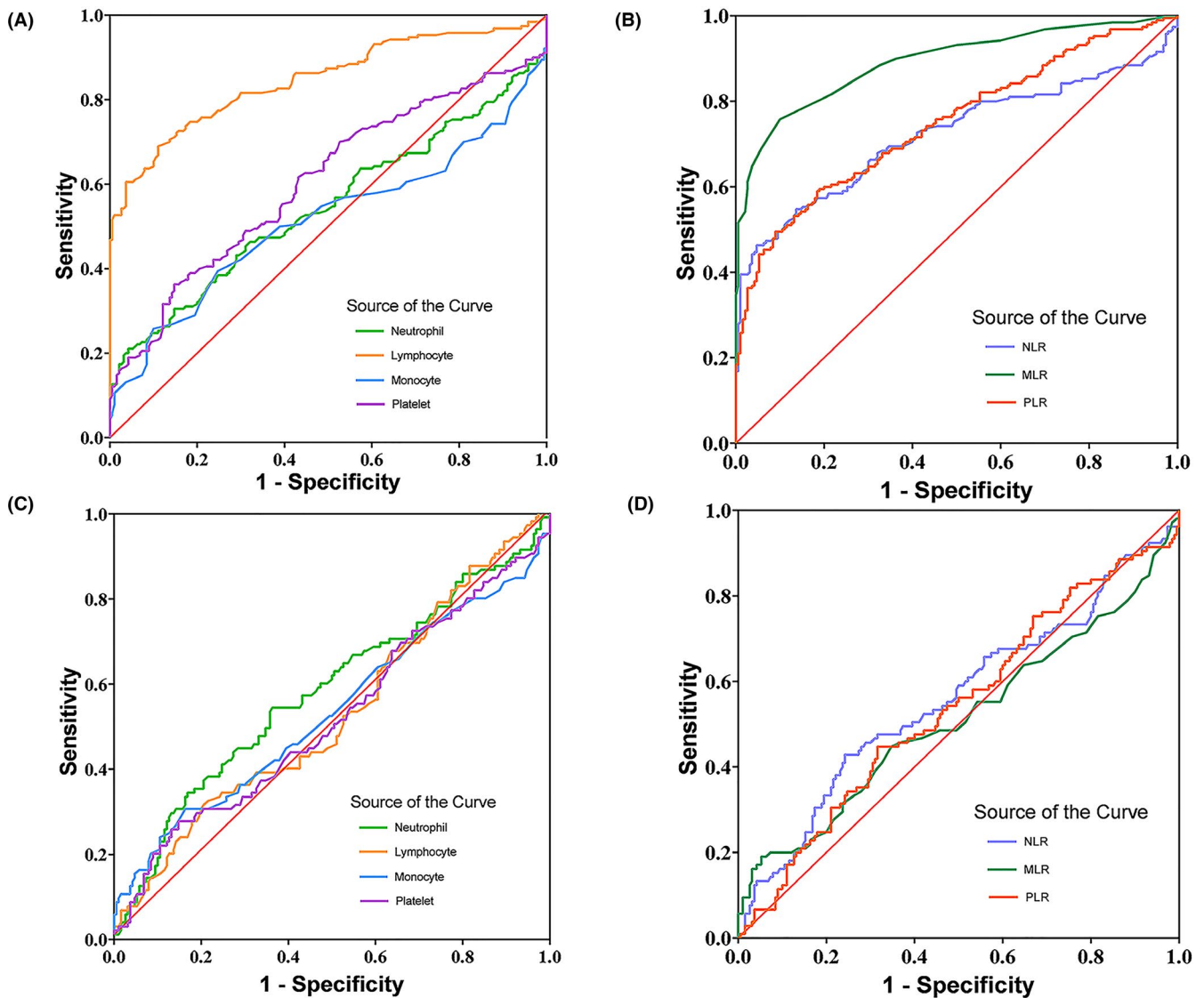


FIGURE 1 Receiver operating characteristic (ROC) curve was carried out to evaluate the diagnostic value of hematologic markers for COVID-19. A, Diagnostic value of neutrophil, lymphocyte, monocyte, and platelet in differentiating COVID-19 patients from healthy subjects; B, diagnostic value of NLR, MLR, and PLR in differentiating COVID-19 patients from healthy subjects; C, diagnostic value of neutrophil, lymphocyte, monocyte, and platelet in differentiating COVID-19 patients from influenza pneumonia patients; D, diagnostic value of NLR, MLR, and PLR in differentiating COVID-19 patients from influenza pneumonia patients

4 | DISCUSSION

Despite extensive implementation of control measures, the global pandemic of COVID-19 is still devastating, with a high rate of complications and mortality. There is an urgent requirement for convenient and cost-effective indicators to simplify the diagnostic process and evaluate the disease severity. In our study, we found that MLR had a high diagnostic value in differentiating COVID-19 patients from healthy subjects, but not from IP patients. The NLR showed positive correlations with PSI, CURB-65, and MuLBSTA, indicating the disease severity of COVID-19. Lymphocyte count had a higher diagnostic value for ARDS in patients with COVID-19 than the other variables.

The complete blood count (CBC) is a quick, easy, and inexpensive measurement in clinical practice, providing rich information

about hematologic contents, including WBCs, neutrophils, lymphocytes, monocytes, platelets, NLR, MLR, and PLR. In recent years, hematologic markers have drawn attention as potential indicators to assist in the diagnosis, early warning, and risk stratification in many infectious diseases, such as sepsis, bacteremia, and urinary tract infection, as well as various non-infectious diseases, including hepatic cirrhosis, coronary artery disease, and solid tumors.^{9,18-20} As reported by Huang et al,²¹ patients with CAP presented with higher NLR and MLR, and NLR was correlated with PSI, suggesting that some hematologic markers may act as potential predictors for CAP and indicate disease severity. However, their study was focused on CAP patients without specific pathogens, and the sample size was relatively small. In our study, 190 COVID-19 patients, 190 healthy subjects, and 105 IP patients

TABLE 2 ROC curve analysis was carried out to evaluate the diagnostic value of hematologic markers for COVID-19

	AUC	95% CI	P	Optimal cutoff value	Specificity (%)	Sensitivity (%)
COVID-19 vs healthy subjects						
Neutrophils	0.546	0.495-0.597	.1236	2.13	95.79	21.05
Lymphocytes	0.847	0.806-0.881	<.0001	1.50	88.90	68.90
Monocytes	0.513	0.462-0.564	.6690	0.50	9.47	74.21
Platelets	0.605	0.554-0.655	.0003	152.00	85.30	36.30
NLR	0.722	0.674-0.766	<.0001	2.72	95.26	46.32
MLR	0.892	0.856-0.921	<.0001	0.23	90.00	75.79
PLR	0.748	0.702-0.791	<.0001	144.39	91.05	49.47
COVID-19 vs IP						
Neutrophils	0.571	0.513-0.629	.0494	3.55	63.68	53.33
Lymphocytes	0.519	0.460-0.577	.6017	0.85	79.47	30.48
Monocytes	0.522	0.463-0.580	.5571	0.53	83.68	29.52
Platelets	0.509	0.450-0.567	.8042	256.00	85.26	26.67
NLR	0.560	0.501-0.617	.1030	3.94	75.79	42.86
MLR	0.513	0.454-0.571	.7383	0.1378	94.74	19.05
PLR	0.540	0.481-0.598	.2645	172.27	68.42	44.76

Abbreviations: AUC, area under the curve; CI, confidence interval; COVID-19, coronavirus disease 2019; IP, influenza pneumonia; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

TABLE 3 Correlation between the variables

	Neutrophils		Lymphocytes		Platelets		Monocytes		NLR		MLR		PLR	
	r	P	r	P	r	P	r	P	r	P	r	P	r	P
ESR	.098	.177	-.050	.023	.023	.752	.036	.624	.127	.082	.099	.175	.086	.240
CRP	.345	<.001	-.027	.709	-.057	.437	.082	.261	.272	<.001	.072	.325	-.007	.919
PCT	.021	.777	-.263	<.001	-.213	.003	-.102	.160	.152	.036	.069	.346	.285	<.001
Body temp	-.068	.349	-.243	.001	-.189	.009	-.019	.792	.114	.118	.193	.008	.052	.476
LHS	.148	.042	-.132	.069	-.034	.643	-.030	.677	.216	.003	.073	.316	.093	.203
ALT	.216	.003	-.098	.181	.034	.640	-.091	.213	.213	.003	-.005	.944	.089	.220
AST	-.028	.702	-.226	.002	-.233	.001	-.275	<.001	.135	.064	-.043	.558	-.002	.983
CREA	.130	.073	-.006	.930	-.111	.129	.147	.042	.120	.098	.117	.109	-.089	.223
CKMB	.019	.799	-.040	.582	-.129	.076	.017	.818	.058	.427	.026	.720	-.022	.764
PSI	.228	.002	-.255	<.001	-.147	.043	-.111	.129	.332	<.001	.107	.144	.090	.218
CURB-65	.059	.419	-.128	.078	-.119	.103	-.037	.613	.144	.047	.105	.833	.015	.833
MuLBSTA	.129	.076	-.175	.016	-.098	.180	-.055	.454	.203	.005	.114	.117	.094	.203

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKMB, creatine kinase isoenzyme; CREA, creatinine; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LHS, length of hospital stay; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PCT, procalcitonin; PLR, platelet-to-lymphocyte ratio; PSI, pneumonia severity index; WBC, white blood cell.

Bold values are significantly $p < .05$.

were enrolled, and our results suggested that the percentages of neutrophils and monocytes, NLR, MLR, and PLR in the COVID-19 group were significantly higher than those of the healthy control group, whereas the numbers of WBCs, lymphocytes, platelets, and hemoglobin were lower. The ROC curve revealed that MLR yielded a higher AUC value than the other variables, and the optimal cutoff value of MLR for COVID-19 was 0.23, with 90.00% specificity and

75.79% sensitivity. MLR showed a significant positive correlation with body temperature. Several studies have suggested that a lymphocyte-to-monocyte ratio value <2 is a surrogate indicator for influenza A.^{12,13} In addition, increased monocyte and decreased lymphocyte counts were found in patients with Middle East respiratory syndrome coronavirus (MERS-CoV), indicating the potential predictive value of MLR for MERS.²² It has been reported

TABLE 4 Comparison of variables between the non-ARDS and ARDS groups

	non-ARDS group (n = 159)	ARDS group (n = 31)	P
Age (years)	45.56 ± 14.89	50.26 ± 15.65	.166
Male (%)	72 (45.28%)	17 (54.84%)	.329
Neutrophils (×10 ⁹ /L)	3.53 ± 1.95	3.53 ± 2.12	.422
Lymphocytes (×10 ⁹ /L)	1.40 ± 0.55	0.83 ± 0.35	<.001
Monocytes (×10 ⁹ /L)	0.40 ± 0.15	0.38 ± 0.15	.637
Platelets (×10 ⁹ /L)	202.77 ± 86.47	147.23 ± 51.96	<.001
NLR	2.95 ± 2.13	5.08 ± 4.48	<.001
MLR	0.32 ± 0.14	0.49 ± 0.22	<.001
PLR	163.37 ± 95.38	201.00 ± 103.79	.013
ESR (mm/h)	31.80 ± 19.90	37.71 ± 22.52	.129
CRP (mg/L)	25.41 ± 29.22	48.14 ± 34.56	<.001
PCT (ng/mL)	0.05 ± 0.05	0.09 ± 0.06	<.001
PSI	56.53 ± 23.32	88.65 ± 29.13	<.001
CURB-65	0.42 ± 0.52	0.97 ± 0.87	.001
MuLBSTA	6.73 ± 2.29	8.94 ± 2.69	<.001

Data are presented as mean ± standard deviation (SD) and n (%).

Abbreviations: ARDS: acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PCT, procalcitonin; PLR, platelet-to-lymphocyte ratio; PSI, pneumonia severity index.

TABLE 5 Diagnostic value of hematological markers, ESR, CRP, PCT, PSI, CURB-65, and MuLBSTA for ARDS

	AUC	95% CI	P	Optimal cutoff value	Specificity (%)	Sensitivity (%)
Neutrophils	0.546	0.472-0.618	.4234	3.20	53.46	67.74
Lymphocytes	0.836	0.776-0.886	<.0001	0.87	88.05	70.97
Monocytes	0.527	0.453-0.599	.6716	0.22	91.82	22.58
Platelets	0.706	0.635-0.769	<.0001	164.00	65.41	70.97
NLR	0.722	0.652-0.784	<.0001	2.23	49.69	87.10
MLR	0.785	0.720-0.841	<.0001	0.30	57.86	87.10
PLR	0.642	0.569-0.710	.0107	138.30	51.57	77.42
ESR	0.586	0.513-0.657	.1078	35.00	67.30	51.61
CRP	0.705	0.634-0.769	.0005	25.87	71.70	70.97
PCT	0.736	0.668-0.797	<.0001	0.04	66.67	70.97
PSI	0.806	0.742-0.860	<.0001	78.62	67.74	78.62
CURB-65	0.674	0.602-0.740	.0017	1.00	98.74	29.03
MuLBSTA	0.730	0.661-0.792	.0001	8.00	88.68	64.52

Abbreviations: ARDS: acute respiratory distress syndrome; AUC, area under the curve; CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PCT, procalcitonin; PLR, platelet-to-lymphocyte ratio; PSI, pneumonia severity index.

that some serum cytokines (IL-6 and IFN- α) and chemokines (IL-8, CXCL-10, and CCL-5) are correlated with increased peripheral blood monocytes in patients with MERS, suggesting a possible effect on increasing the MLR.²³ Notably, the differences in monocyte count between the two groups were not statistically significant in our study, although the COVID-19 group indeed had a higher mean value and wider range than the healthy control group. One possible reason may be that some COVID-19 patients presented with

a decreased WBC count, which may produce a lower monocyte count despite the increased monocyte percentage. Meanwhile, it should also be noticed that these hematologic markers had relatively low diagnostic value in differentiating between COVID-19 and IP. This is consistent with previous studies showing that no single hematologic marker carried sufficient weight to confirm or refute specific respiratory virus.^{24,25} In contrast, Han et al¹⁴ reported that hematologic markers provided an adjunct diagnostic

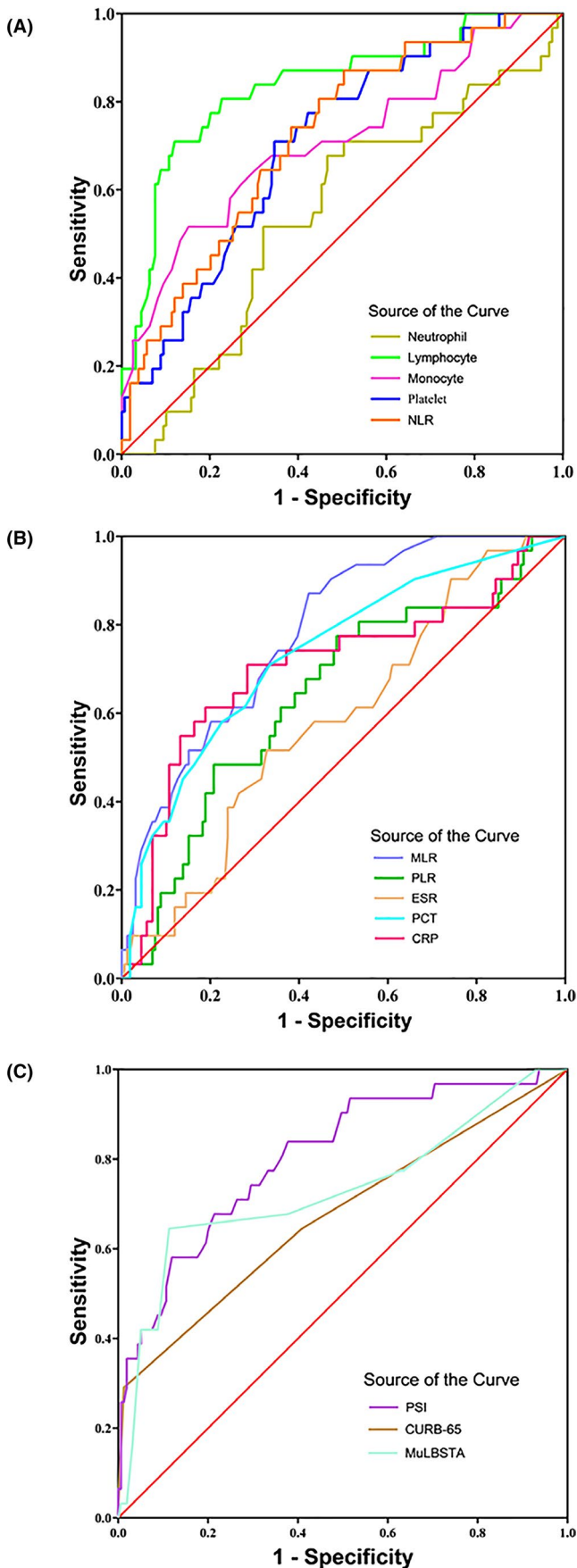


FIGURE 2 Receiver operating characteristic (ROC) curve was carried out to evaluate the diagnostic value of hematologic markers, PSI, CURB-65, and MuLBSTA for the diagnosis of ARDS in the COVID-19 patients. A, Diagnostic value of neutrophil, lymphocyte, monocyte, platelet, NLR; B, diagnostic value of MLR, PLR, ESR level, CRP, and PCT; C, diagnostic value of PSI, CURB-65, and MuLBSTA

approach in the differential diagnosis of respiratory infections due to influenza virus and other respiratory viruses, but their study did not include patients infected with SARS-CoV-2. Thus, the diagnostic value of hematologic markers for different respiratory virus infection deserves more studies.

It has been widely demonstrated that with serious infection or systemic inflammation, NLR increases as a result of the severity of clinical status and outcome.^{10,11} In the present study, we found that NLR was significantly and positively correlated with PSI, CURB-65, and MuLBSTA, indicating the disease severity of COVID-19. Elevated NLR was defined as increased neutrophil and decreased lymphocyte counts. Neutrophil proliferation and lymphocyte apoptosis are physiological responses of the innate immune system to systemic inflammation.²⁶ Although it is well documented that neutrophil levels are elevated during bacterial invasion, accumulating evidence indicates that viral infection stimulates neutrophils and triggers neutrophil-mediated innate immune responses.²⁷ Interaction with other immune cell populations, virus internalization, and inactivation, the release of leukocyte cytokines and antimicrobial components are the major mechanisms by which neutrophils can contribute to the clearance of viruses.²⁷ Qin et al²⁸ found that in patients with COVID-19, severe cases tended to have a higher NLR, and surveillance of NLR is helpful in the early screening of critical illness.

Furthermore, our present study showed that elevated NLR, MLR, PLR, CRP, PCT, PSI, and MuLBSTA but decreased lymphocyte and platelet levels were detected in patients with ARDS compared with those without ARDS. The ROC curve results revealed that the AUC value of lymphocytes was 0.836 (95% CI 0.776-0.886), which was higher than that of other variables. The best cutoff value for lymphocytes was 0.87, with 88.05% specificity and 70.97% sensitivity. The relationship between decreased lymphocyte count in the peripheral blood and the progression of ARDS resulting from SARS-CoV-2 is attracting increased attention, as many COVID-19 patients with ARDS present with a dysregulated immune state.^{24,28,29} Recently, an autopsy report on a 50-year-old COVID-19 patient with ARDS provided further information about this pathological process, showing that although the peripheral blood lymphocyte count was substantially reduced in the patient, there was an inflammatory infiltration of lymphocytes in both lungs and immune hyperactivation, suggesting an exaggerated immunopathological injury.³⁰ Additionally, activated immune cells stimulate further infiltration and induce the production of reactive oxygen species and nitric oxide, which will damage the epithelial-endothelial barrier and cause an imbalance in the ventilation/blood flow ratio, leading to the progression of ARDS.^{23,31}

Previous studies have demonstrated that clinical risk scores and inflammatory biomarkers provide useful diagnostic and prognostic information about infectious diseases. The PSI and CURB-65 scores are the most commonly used tools for the evaluation of disease severity in patients with pneumonia.³² More recently, an early warning model of viral pneumonia, the MuLBSTA score (multilobular infiltrates, lymphopenia, bacterial coinfection, smoking history, hypertension, age \geq 60 years), showed an excellent risk stratification capacity in patients with COVID-19.^{6,16} In addition, some studies have suggested that CRP and PCT are effective indicators to assist in risk stratification of patients with pneumonia.³³ In our study, we found that NLR showed significant positive correlations with PSI, CURB-65, MuLBSTA, CRP, and PCT, indicating its potential value for the evaluation of disease severity in COVID-19. However, MLR had no correlation with these clinical risk scores and inflammatory biomarkers but possessed a higher diagnostic value for COVID-19. In addition, lymphocytes had a higher diagnostic value for ARDS in the COVID-19 patients than CRP, PCT, and ESR. Therefore, it seems that MLR, NLR, and lymphocyte count play different roles in COVID-19, and a combination with clinical risk scores and inflammatory biomarkers may be beneficial for the assessment and management of COVID-19.

This study has several limitations. First, it was of retrospective nature. All included patients were obtained from hospital medical systems after satisfying a series of criteria, which could introduce a selection bias. Second, we only used one measure in time rather than a longitudinal measure because of insufficient data. Third, although some of the conditions were adjusted, we could not have completely removed all the confounding factors that might influence the level of hematologic markers. Fourth, all our patients were Asian descent, and as these hematologic markers have racial differences, the study findings may not be applicable to the white and black populations.^{34,35} Therefore, an additional large-scale multicenter, randomized control study will be required to further confirm our findings.

In conclusion, MLR had a high diagnostic value in differentiating COVID-19 patients from healthy subjects, but failed to rule out IP patients. NLR showed a positive and significant correlation with PSI, CURB-65, and MuLBSTA, indicating the disease severity of COVID-19. Lymphocyte count may be useful to establish the early diagnosis of ARDS in the COVID-19 patients. MLR, NLR, and lymphocyte count may be rapid, cost-effective, and promising potential markers to assist in the diagnosis, early warning, and risk stratification of COVID-19.

AUTHOR CONTRIBUTIONS

Daoxin Wang: Conceptualization, Methodology, Supervision. Junnan Peng: Data curation, Writing-Original draft preparation, Software. Di Qi: Data curation, Writing-Original draft preparation, Validation. Guodan Yuan: Visualization, Investigation. Xinyu Deng: Investigation, Formal analysis. Ying Mei: Resources Data Curation. Longhua Feng: Writing-Reviewing and Editing.

ETHICAL APPROVAL

This study was approved by the institutional ethics board of the Second Affiliated Hospital of Chongqing Medical University (No. 2020-09), Chongqing Public Health Medical Center (No. 2020-015-01-KY), and Qianjiang Central Hospital of Chongqing (No. 2020-07) and was in accordance with the Declaration of Helsinki.

CONSENT FOR PUBLICATION

The manuscript is approved by all authors for publication.

DATA AVAILABILITY STATEMENT

The datasets used during the current study are available from the corresponding author on reasonable request.

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