

ORIGINAL PAPER

Infectious diseases

Role of NLR, PLR, ELR and CLR in differentiating COVID-19 patients with and without pneumonia

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Abstract

Objectives: Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), monocyte/lymphocyte ratio (MLR), eosinophil/lymphocyte ratio (ELR), and C-reactive protein (CRP)/lymphocyte ratio (CLR) are well-established inflammatory indices. This study aimed to examine whether NLR, PLR, MLR, ELR and CLR could differentiate coronavirus disease 2019 (COVID-19) patients with pneumonia from those of without.

Methods: We retrospectively examined the laboratory parameters including CRP, D-dimer, procalcitonin and complete blood count of 306 COVID-19 patients (pneumonic = 152 and non-pneumonic = 154). NLR, PLR, MLR, ELR and CLR values of each patient were calculated. The ability of these indices to distinguish COVID-19 patients with and without pneumonia was determined by receiver operating characteristic (ROC) analysis.

Results: NLR, PLR and CLR values were higher while ELR value was lower in pneumonic COVID-19 patients compared with patients with non-pneumonic COVID-19 infection. MLR value was similar in the two groups. NLR, PLR and CLR were positively correlated with CRP and procalcitonin. ELR was negatively correlated with CRP. The ROC analysis revealed that the optimal cut-off value of CLR for discriminating COVID-19 patients with pneumonia from those without pneumonia was 1.14 and the area under curve (AUC) for CLR was 0.731 (sensitivity = 81.5% and specificity = 55.6%), which was markedly higher than the AUCs of NLR (0.622), PLR (0.585) and ELR (0.613). However, no statistical differences were observed between AUC values of NLR, PLR and ELR ($P > .05$).

Conclusion: Our findings showed that NLR, PLR, ELR and CLR indices can be used in differentiating COVID-19 patients with or without pneumonia. Among them, the CLR index was the best predictor of pneumonia in COVID-19 patients.

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) infection caused by a novel coronavirus, firstly emerged in Hubei Province, China, spread across all continents of the world in a short time. This respiratory tract infection possess a spectrum of symptoms ranging from mild to life-threatening consequences such as acute respiratory distress syndrome (ARDS)

and multiple organ failure.^{1,2} COVID-19 patients are classified according to clinical presentation as mild, moderate, severe and critical. The main criteria for classification of patients are involvement of lung and severity of pneumonia.³ COVID-19 pneumonia is a common cause of hospital admission and death. Computed tomography (CT) images play a key role in determining the presence and severity of pneumonia in COVID-19 patients.⁴ Unfortunately, CT scanning may not be

available in all emergency departments.⁵ Besides, inside the CT suites are high-risk areas for nosocomial COVID-19 transmission.⁶ For this reason, there is need for fast, cheap and widely accessible biomarkers to simplify the diagnostic process and administer timely treatment of COVID-19 pneumonia.

In recent studies, the neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), monocyte/lymphocyte ratio (MLR) and C-reactive protein (CRP)/lymphocyte ratio (CLR), which are novel inflammatory markers, have been considered as useful indicators for diagnosis and prognosis of various infectious diseases, including COVID-19 infection.⁷⁻¹² Eosinophil/lymphocyte ratio (ELR) is another marker of inflammation and can be easily calculated by the ratio of eosinophil count to lymphocyte count.¹³ However, the diagnostic values of these indices for COVID-19 patients with pneumonia have not yet been investigated. Herein, we aimed to investigate the utility of NLR, PLR, MLR, CLR and ELR to distinguish COVID-19 patients with pneumonia from those without pneumonia.

2 | MATERIALS AND METHODS

This retrospective single-center study was performed with 306 adult COVID-19 patients (aged ≥ 18 years) admitted to the Sanliurfa Training and Research Hospital, Turkey between 1 April and 30 July 2020. All COVID-19 cases had positive PCR test results in collected nasopharyngeal swab samples to detect SARS-CoV-2. The COVID-19 patients were divided into two groups: pneumonic group ($n = 152$) and non-pneumonic group ($n = 154$) according to clinical symptoms, CT findings, and laboratory results. All patients were admitted to the general wards of the hospital. Patients with rheumatological disease, malignancy, haematological disorder, thyroid disease, chronic renal failure, chronic liver disease, cerebrovascular disease, allergic disorders, pregnancy, immunosuppressive medication and blood transfusions were excluded from the study. This study was approved by the Harran University Ethics Committee (Protocol number: HRU/20/15/09).

Basic demographic information, comorbidities and laboratory data of the patients on admission were retrieved from the hospital database. Serum urea, creatinine, CRP and procalcitonin levels as well as plasma D-dimer level were measured according to standard methods using Cobas 6000 analyzer (Roche, Germany). Prothrombin time and international normalized ratio were detected with Sysmex CS-2000i analyzer (Sysmex, Japan). Complete blood counts (White blood cell, neutrophil, lymphocyte, monocyte, eosinophil and platelet counts) were measured in EDTA-anticoagulated blood samples using Sysmex XN-1000 analyzer (Sysmex). Afterwards, NLR, PLR, MLR, ELR and CLR values were calculated for each of the patients.

2.1 | Statistical analysis

SPSS version 21.0 (SPSS Inc) and MedCalc version 16.8.4 (MedCalc Software) were used for the statistical analysis. Normality of data

What's known

- COVID-19 can cause life-threatening pneumonia.
- Hyperinflammation plays a crucial role in COVID-19 lung damage.
- NLR, PLR, MLR, ELR and CLR are well-established inflammatory indices.
- Early diagnosis and treatment are crucial to reduce mortality in COVID-19 patients with pneumonia.

What's new

- NLR, PLR and CLR were higher and ELR was lower in pneumonic COVID-19 patients compared with non-pneumonic COVID-19 patients.
- There was a positive correlation between NLR, PLR, CLR values and CRP and procalcitonin levels. ELR value was negatively correlated with CRP.
- CLR was more efficient than NLR, PLR and ELR in differentiating COVID-19 patients with or without pneumonia.

was assessed using Kolmogorov-Smirnov test. Variables were compared using Student's *t* test, Mann-Whitney *U*-test or chi-square test as appropriate. The relationship between inflammatory markers and NLR, PLR, ELR and CLR was determined by Spearman test. The diagnostic potential of derived blood lymphocyte parameters (NLR, PLR, ELR and CLR) for COVID-19 patients with pneumonia was determined by ROC analysis. The area under curve (AUC) values of the NLR, PLR, ELR and CLR were compared using the *z* test. $P < .05$ were considered significant.

3 | RESULTS

Table 1 shows the baseline characteristics of COVID-19 patients classified by pneumonia status. Compared with patients with non-pneumonic COVID-19 infection, pneumonic COVID-19 patients had higher levels of CRP, D-dimer, NLR, PLR and CLR; and lower levels of lymphocyte, monocyte, eosinophil and ELR. Gender ratio, mean age, incidences of comorbidities, procalcitonin and MLR values were similar between the two groups.

In the correlation analysis of NLR, PLR, ELR and CLR indices with inflammatory biomarkers in the COVID-19 patients, a positive correlation was observed between NLR, PLR, CLR values and CRP and procalcitonin. ELR value was negatively correlated with CRP (Table 2).

The AUC, cut-off value, sensitivity and specificity of NLR, PLR, ELR and CLR are presented in Table 3. ROC curve analysis revealed that the cut-off levels of NLR [AUC = 0.622 (0.565-0.677), sensitivity = 62.5%, specificity = 60.4%], PLR [AUC = 0.585 (0.527-0.641), sensitivity = 55.3%, specificity = 60.4%], ELR [AUC = 0.613

TABLE 1 Demographic characteristics and laboratory results of COVID-19 patients on admission

	Non-pneumonic (n = 154)	Pneumonic (n = 152)	P value
Age, years	38.1 ± 13.7	39.4 ± 11.5	.370
Gender, male/female	76/78	71/81	.644
Comorbidities			
Diabetes mellitus, n (%)	13 (8.4)	17 (11.2)	.420
Hypertension, n (%)	24 (15.6)	20 (13.2)	.545
Cardiovascular disease, n (%)	9 (5.8)	6 (3.9)	.442
Hyperlipidemia, n (%)	8 (5.2)	9 (5.9)	.782
Asthma/COPD, n (%)	7 (4.5)	10 (6.6)	.437
Laboratory examinations			
WBC, ×10 ³ /μL	5.64 (2.59-11.56)	5.48 (2.59-13.08)	.530
Neutrophil, ×10 ³ /μL	3.05 (0.88-8.67)	3.25 (1.48-8.85)	.081
Lymphocyte, ×10 ³ /μL	1.99 (0.48-5.05)	1.63 (0.50-3.88)	.005
Monocyte, ×10 ³ /μL	0.59 (0.21-1.50)	0.48 (0.11-1.62)	<.001
Eosinophil, ×10 ³ /μL	0.06 (0.0-1.10)	0.03 (0.0-1.60)	<.001
Platelet, ×10 ³ /μL	242 (95-422)	230 (84-590)	.333
Urea, mg/dL	29.2 ± 9.4	29.2 ± 9.2	.974
Creatinine, mg/dL	0.88 ± 0.19	0.91 ± 0.21	.330
Prothrombin time, sn	11.6 (9.6-16)	11.5 (10.1-14.1)	.306
INR	1.0 (0.84-1.35)	1.0 (0.88-1.17)	.762
D-dimer, μg/mL	0.17 (0.15-3.36)	0.24 (0.11-2.66)	.007
CRP, mg/L	2.03 (0.13-39.71)	6.24 (0.60-202.6)	<.001
Procalcitonin, ng/mL	0.05 (0.02-0.16)	0.05 (0.02-0.24)	.181
NLR	1.56 (0.39-8.79)	2.03 (0.59-13.83)	<.001
PLR	126.9 (36.3-650)	145.2 (47.5-478.2)	.010
MLR	0.28 (0.11-1.73)	0.29 (0.11-1.13)	.830
ELR	0.03 (0.0-0.76)	0.02 (0.0-1.09)	.001
CLR	0.97 (0.05-21.32)	4.14 (0.19-181.18)	<.001

Abbreviations: CLR, C-reactive protein/lymphocyte ratio; CRP, C-reactive protein; ELR, Eosinophil/lymphocyte ratio; INR, International normalised ratio; MLR, Monocyte/lymphocyte ratio; NLR, Neutrophil/lymphocyte ratio; PLR, Platelet/lymphocyte ratio; WBC, White blood cell count.

(0.556-0.668), sensitivity = 48%, specificity = 72.7%] and CLR [AUC = 0.731 (0.677-0.777), sensitivity = 81.5%, specificity = 55.6%] were 1.73, 139, 0.018 and 1.14, respectively. CLR index had significantly higher AUC value than NLR ($z = 3.491$, $P = .001$), PLR ($z = 4.368$, $P = .000$) and ELR ($z = 2.876$, $P = .004$) in distinguishing pneumonic COVID-19 patients from patients with non-pneumonic COVID-19 infection. However, AUC values did not differ significantly among NLR, PLR and ELR ($P > .05$) (Figure 1).

4 | DISCUSSION

As far as we know, this is the first study that investigates the role of NLR, PLR, ELR and CLR indices as inflammatory biomarkers for differentiating COVID-19 patients with and without pneumonia; and their correlation with CRP and procalcitonin. This study

demonstrated that pneumonic COVID-19 patients had significantly higher NLR, PLR and CLR values; and significantly lower ELR compared with the patients with non-pneumonic COVID-19 infection. There was a positive relationship between NLR, PLR, CLR and CRP and procalcitonin levels; and an inverse relationship between ELR and CRP levels. In addition, CLR was found to be more useful than other indices in identifying cases of COVID-19 pneumonia.

An excessive and uncontrolled cytokine production plays an important role in the pathogenesis of COVID-19 pneumonia.¹⁴ The virus enters the alveolar cells via angiotensin converting enzyme 2 receptors¹⁵ and triggers the release of inflammatory factors from the cells resulting in activation of macrophages in the alveolar tissue.¹⁴ The inducing factors and chemokines released from macrophages cause the accumulation of mononuclear cells in the lung tissue. Extreme infiltration of inflammatory cells induces a cytokine storm leading to acute lung injury and ARDS, the severe consequences of COVID-19

pneumonia.^{14,16} Laboratory abnormalities such as decreased platelet, lymphocyte, monocyte and eosinophil counts; and increased neutrophil count and CRP level were reported in COVID-19 patients.¹⁷⁻²⁰ WBC and its differential counts including lymphocytes, neutrophils, eosinophils and monocytes are associated with the inflammation and immune systems.²¹ Platelets, which are anucleate blood cells produced from megakaryocytes in the bone marrow, play an important role in the host inflammatory and immune responses as well as regulation of hemostasis and thrombosis.²² CRP, a positive acute phase protein, is one of the markers reflecting the systemic inflammatory response of body.²³ In the present study, we found that pneumonic COVID-19 patients had lower lymphocyte, monocyte and eosinophil counts and higher neutrophil counts and CRP levels than non-pneumonic group. Moreover, Li et al²⁴ reported that

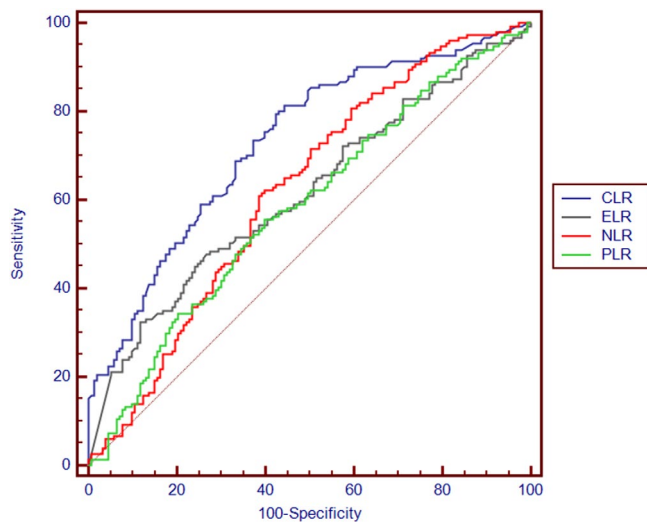


FIGURE 1 ROC curves of the derived blood lymphocyte parameters to predict COVID-19 pneumonia

increased neutrophil percentage and CRP level and decreased lymphocyte and monocyte counts were closely related to the severity of COVID-19 pneumonia. Xie et al²⁵ found that severe COVID-19 patients had remarkably lower eosinophil counts compared with non-severe COVID-19 patients. Another study revealed that the increase in eosinophil count after admission may be a potential indicator of improvement in COVID-19 patients.²⁶

Recently, NLR, PLR, MLR and CLR indices calculated from the abovementioned blood parameters have been extensively investigated for their role in assessing prognosis and severity of COVID-19 infection. Yang et al²⁷ and Sun et al²⁸ examined some haematological indices in COVID-19 patients and found that NLR, PLR and MLR values were significantly higher in severe patients than in non-severe patients. Ding et al²⁹ found that NLR index positively correlated with the length of hospital stay and has a role in predicting the prognosis of disease for COVID-19 patients. Another study reported an elevated NLR in non-survivors than survivors and the magnitude of rising was correlated with severity of illness.³⁰ A recent meta-analysis revealed that high NLR and low LCR (lymphocyte/CRP ratio) may be associated with poor prognosis in COVID-19 patients.¹¹ In the present study, we determined the diagnostic values of NLR, PLR, CLR as well as ELR index for COVID-19 pneumonia. In that regard, NLR, PLR, ELR and CLR indices and inflammatory markers were compared between pneumonic and non-pneumonic COVID-19 patients and ROC analysis of these indices were performed. We found that NLR, PLR and CLR values were higher and ELR values were lower in the pneumonic COVID-19 patients compared with the non-pneumonic patients and that there was a positive correlation between NLR, PLR, CLR indices and CRP and procalcitonin; and a negative correlation between ELR and CRP, suggesting these indices might be potential markers for diagnosis of COVID-19 pneumonia. ROC analysis also showed that the AUC value of CLR (0.731) was higher than the

TABLE 2 Correlation between derived blood lymphocyte parameters and inflammatory biomarkers in COVID-19 patients

	NLR		PLR		ELR		CLR	
	r	P value	r	P value	r	P value	r	P value
CRP	0.385	<.001	0.245	<.001	-0.195	0.001	0.963	<.001
Procalcitonin	0.238	<.001	0.120	.038	-0.101	0.082	0.473	<.001

Abbreviations: CLR, C-reactive protein/lymphocyte ratio; CRP, C-reactive protein; ELR, Eosinophil/lymphocyte ratio; MLR, Monocyte/lymphocyte ratio; NLR, Neutrophil/lymphocyte ratio; PLR, Platelet/lymphocyte ratio.

	AUC (95% CI)	Cut-off level	Sensitivity (%)	Specificity (%)	P value
NLR	0.622 (0.565-0.677)	1.73	62.5	60.4	<.001
PLR	0.585 (0.527-0.641)	139	55.3	60.4	.009
ELR	0.613 (0.556-0.668)	0.018	48.0	72.7	<.001
CLR	0.731 (0.677-0.777)	1.14	81.5	55.6	<.001

Abbreviations: CLR, C-reactive protein/lymphocyte ratio; ELR, Eosinophil/lymphocyte ratio; NLR, Neutrophil/lymphocyte ratio; PLR, Platelet/lymphocyte ratio.

TABLE 3 ROC analysis results of the derived blood lymphocyte parameters

NLR (0.622), PLR (0.585) and ELR (0.613) and there was no significant difference among NLR, PLR, and ELR, thus indicating that CLR was superior to NLR, PLR and ELR in identifying COVID-19 pneumonia cases. Collectively, we speculated that these indices, particularly the CLR, could aid clinicians in early identification of patients with COVID-19 pneumonia.

The major limitation of our study is that being conducted in a single center with retrospective design. Also, the time elapsed since the onset of symptoms, smoking habits and body mass index, which may affect laboratory indexes, could not be evaluated because of missing data.

5 | CONCLUSION

Pneumonic COVID-19 patients had significantly higher NLR, PLR and CLR; and significantly lower ELR compared with the non-pneumonic patients. There was a positive correlation between NLR, PLR, CLR and CRP and procalcitonin levels; and an inverse correlation between ELR and CRP levels. Besides, ROC analysis indicated that the AUC of CLR was significantly greater than the AUCs of NLR, PLR and ELR, and therefore the predictive capacity of CLR for COVID-19 pneumonia was better than the other three. Accordingly, CLR index could help clinicians to identify COVID-19 patients with pneumonia.

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CONFLICT OF INTEREST

The authors have declared no conflicts of interest.

ETHICAL APPROVAL

This study was approved by the Harran University School of Medicine Ethics Committee Commission (Protocol number: HRU/20/15/09).

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