Prognostic Value of Inflammatory Biomarkers in Patients with Severe COVID-19: A Single-Center Retrospective Study

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ABSTRACT

BACKGROUND: The current knowledge about novel coronavirus-2019 (COVID-19) indicates that the immune system and inflammatory response play a crucial role in the severity and prognosis of the disease. In this study, we aimed to investigate prognostic value of systemic inflammatory biomarkers including C-reactive protein/albumin ratio (CAR), prognostic nutritional index (PNI), neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR) in patients with severe COVID-19.

METHODS: This single-center, retrospective study included a total of 223 patients diagnosed with severe COVID-19. Primary outcome measure was mortality during hospitalization. Multivariate logistic regression analyses were performed to identify independent predictors associated with mortality in patients with severe COVID-19. Receiver operating characteristic (ROC) curve was used to determine cut-offs, and area under the curve (AUC) values were used to demonstrate discriminative ability of biomarkers.

RESULTS: Compared to survivors of severe COVID-19, non-survivors had higher CAR, NLR, and PLR, and lower LMR and lower PNI ($P < .05$ for all). The optimal CAR, PNI, NLR, PLR, and LMR cut-off values for detecting prognosis were 3.4, 40.2, 6. 27, 312, and 1.54 respectively. The AUC values of CAR, PNI, NLR, PLR, and LMR for predicting hospital mortality in patients with severe COVID-19 were 0.81, 0.91, 0.85, 0.63, and 0.65, respectively. In ROC analysis, comparative discriminative ability of CAR, PNI, and NLR for hospital mortality were superior to PLR and LMR. Multivariate analysis revealed that CAR ($\geqslant$0.34, $P = .004$), NLR ($\geqslant$6.27, $P = .012$), and PNI ($\leqslant$40.2, $P = .009$) were independent predictors associated with mortality in severe COVID-19 patients.

CONCLUSIONS: The CAR, PNI, and NLR are independent predictors of mortality in hospitalized severe COVID-19 patients and are more closely associated with prognosis than PLR or LMR.

KEYWORDS: Biomarkers, predictive value of tests, coronavirus, mortality

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Introduction

A novel kind of the Coronavirus was first identified with symptoms of respiratory infections in Wuhan, China in late December, and has since spread rapidly worldwide. The new virus is named as Severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) and, the disease it causes as coronavirus disease-2019 (COVID-19) by the World Health Organization (WHO).[1] In most of the cases, COVID-19 presents with mild symptoms, while a considerable number of patients progress to severe pneumonia and even eventually develop acute respiratory distress syndrome (ARDS), multiple organ failure and/or septic shock, and death.[2] Growing evidence suggests that the intense and abnormal response of the host immune system is the main determinant for the severity of COVID-19.[3-5] Intense inflammatory responses cause poor adaptive immune reactions and, eventually, cause an imbalance in the immune system response. Thus, biomarkers which indicate the state of inflammation and immune system can be used to predict the severity of the disease in COVID-19 patients.[5,6]

Inflammation has been shown to be significantly associated with a variety of clinical conditions related to the typical changes in the serum acute phase proteins. C-reactive protein (CRP) and albumin are well-known, acute-phase reactants (APRs). The CRP values increase (positive APR), whereas albumin levels decrease (negative APR) during inflammation. The CRP-to-albumin ratio (CAR), a newly introduced indicator, is believed to be a more reliable predictor of the inflammatory status than CRP or albumin alone. Currently, the CAR

has been used in the evaluation of prognosis and mortality in many diseases as a prognostic score.[7-9]

Several studies have demonstrated that the progression of inflammation causes changes in the levels of many markers such as lymphocytes, monocytes, neutrophils, and platelets.[10] Systemic inflammation markers such as neutrophils, platelets, and lymphocytes and relevant indices such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) have been shown to predict systemic inflammation and can be used as prognostic markers in several diseases.[11,12] Prognostic Nutritional Index (PNI), which is calculated by using plasma albumin levels and lymphocyte count in the peripheral blood is a useful tool to assess nutritional and immunological status of patients and predicting prognosis.[13] Also, a significant correlation between low PNI and poor survival has been reported in various conditions.[13,14] In addition, NLR, PLR, and LMR are indicators of the systematic inflammatory response[10] that have been widely studied for the prognosis of patients with viral pneumonia including COVID-19.[15-22] However, to the best of our knowledge, CAR and PNI have not been addressed in COVID-19, yet. In the present study, therefore, we aimed to investigate the prognostic value of all these inflammatory markers such as CAR, NLR, PLR, LMR, and PNI in COVID-19 patients and to identify possible prognostic factors in this patient population.

Material and Methods

This single-center, retrospective, observational study was approved by the Institutional Ethics Committee (No. 2020/0330). A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

A total of 223 cases of COVID-19 were confirmed at Medeniyet University, Goztepe Training and Research Hospital between March 15th, 2020 and August 15th, 2020. All patients were confirmed positively by SARS-CoV-2 nucleic acid reverse transcriptase-polymerase chain reaction (RT-PCR) (Ct value ⩽38.0; BGI, Shenzhen, China) using specimens derived from oropharyngeal swabs or sputum, prior to or during the hospitalization. Exclusion criteria were as follows: age under 18 years, pregnancy, comorbidities which compromise the immune system such as autoimmune disorders, malignancy and recent chemotherapy, and missing data. Patients with severe disease were categorized based on the seventh edition of the Chinese National Health Commission[23] and should meet any of the following criteria: (1) shortness of breath, a respiratory rate of ⩾30 beats/min; (2) oxygen saturation of ⩽93% at rest; (3) arterial oxygen partial pressure (PaO_2)/oxygen concentration (FiO_2) of ⩽300 mmHg (1 mmHg = 0.133 kPa); and (4) lung images showing obvious progress of a lesion size of >50% within 24 to 48 hours.[24] Demographic and clinical data of the patients including comorbidities, length of hospitalization, and laboratory tests results were collected from the electronic and printed medical records on admission.

Laboratory test results including albumin, CRP, neutrophil count, platelet count, lymphocyte count and monocyte count, and used to calculate CAR, NLR, PLR, and LMR were recorded at admission.

The systemic inflammation biomarkers were calculated as follows: the CAR was calculated by dividing the CRP level by the albumin level; the NLR was defined by dividing the neutrophil count by the lymphocyte count; the PLR was defined by dividing the platelet count by the lymphocyte count; and the LMR was defined by dividing the lymphocyte count by the monocyte count. The PNI was calculated using the following formula: PNI = serum albumin level (g/L) + 5 × total lymphocyte count (/L).[13] The primary outcome measure of the study was mortality during hospitalization. All data were reviewed by 2 physicians.

Statistical analysis

Statistical analysis was performed using the Number Cruncher Statistical System version 2007 (NCSS LLC., Kaysville, UT, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max), or number and frequency. The Shapiro-Wilk test and graphical analysis were used to test the conformity of quantitative data to normal distribution. A Student *t*-test was used to compare normally distributed quantitative variables between 2 groups. The Mann-Whitney *U* test was used to compare quantitative variables that did not show normal distribution between 2 groups. The Pearson's chi-square test and Fisher's exact test were used to compare qualitative data between the groups. The backward stepwise logistic regression analysis was carried out to identify the risk factors of mortality. Significant variables in the univariate analysis were included in the multivariate logistic regression analysis. The receiver operating characteristic (ROC) curve was used to estimate the cut-off values of in-hospital mortality for CAR, NLR, PLR, LMR, and PNI. The area under the curve (AUC) values of the ROCs were analyzed to investigate the discriminative ability of prognostic inflammatory biomarkers. The higher AUC values indicate a better discriminative ability for predicting hospital mortality. A *P* value of $<.05$ was considered statistically significant.

Results

Of a total of 223 cases of severe COVID-19, 47.1% (n = 105) were females and 52.9% (n = 118) were males. The mean age was 59.70 ± 19.01 (range, 21-96) years. Of the patients, 46.2% (n = 103) had hypertension, 27.4% (n = 61) had diabetes, 18.8% (n = 42) had cardiovascular disease, 4.1% (n = 9) had cerebrovascular diseases, and 10.8% (n = 24) had chronic lung disease. The median time from illness onset to hospital admission was 5 days (range 4-7). The median length of hospitalization was 6 (range, 4-10) days, and the in-hospital mortality rate was 16.1% (n = 36). The mean age of non-survivors was 73.97 ± 13.63 years, indicating statistically significantly higher age

than survivors (56.95 ± 17.47 years). The number of comorbid diseases in non-survivors was significantly higher than that in survivors, particularly for hypertension ($P < .01$), cardiovascular disease ($P < .05$). In the laboratory examination, the levels of white blood cell (WBC), neutrophil, and CRP were higher among non-survivors, while the platelet and lymphocyte count, hemoglobin, and albumin levels were lower ($P < .05$ for all). The patients who died were more likely to be admitted to the intensive care unit (ICU) (97.2% vs 9.1%, respectively; $P = .01$) and had a longer length of stay (median 12 vs 6 days, respectively; $P = .001$). There were no significant differences in sex, diabetes, chronic pulmonary disease, cerebrovascular disease, monocyte count, and time from illness onset to hospital admission between the 2 groups ($P > .05$ for all). Compared to survivors of severe COVID-19 patients, non-survivors had higher CAR ($P = .001$), higher NLR ($P = .001$), higher PLR ($P = .019$), lower LMR ($P = .005$), and lower PNI ($P = .001$). Baseline demographic and clinical characteristics of the patients are presented in Table 1.

The results of the univariate analysis and multivariate analysis are shown in Table 2. Multivariate analysis revealed that ICU admission (odds ratio [OR] = 226.30; 95% confidence interval [CI], 20.66-2478; $P < .01$) was the most significantly independently predictors of worse outcome. Among inflammatory biomarkers, CAR ($\geqslant 0.34$) (OR = 10.14; 95% CI, 2.07-49.74; $P = .004$) and PNI ($\leqslant 40.2$) (OR = 10.85; 95% CI, 1.81-65.21; $P = .009$) were the most significantly independent predictors of worse outcome, followed by the NLR ($\geqslant 6.27$) (OR = 6.82; 95% CI, 1.52-30.66; $P = .012$).

Predictive accuracy of systemic inflammation biomarkers

We attempted to establish the optimal thresholds for these biomarkers on our study population through the ROC curve analysis (Figure 1). The optimal cut-off values for the prediction of hospital mortality by ROC analysis were 0.34 for CAR, 40.2 for PNI, 6.27 for NLR, 312 for PLR, and 1.54 for LMR. The AUC values were used to compare the predictive value of the CAR, PNI, NLR, PLR, and LMR. The AUCs for hospital mortality was 0.81 (95% CI, 0.75-0.86) for CAR, 0.91 (95% CI, 0.86-0.94) for PNI, 0.85 (95% CI, 0.80-0.90) for NLR, 0.63 (95% CI, 0.56-0.69) for PLR, and 0.65 (95% CI, 0.59-0.71) for LMR ($P < .05$, for all) (Table 3). The AUCs of CAR, PNI, and NLR were above 0.7, indicating that they were significantly higher from PLR and LMR and good predictors.

To further verify the relationship between these inflammation biomarkers and clinical factors, the patients were categorized into 2 groups with high or low levels, according to the optimal cut-off values of these inflammation biomarkers. The correlations of CAR, NLR, PLR, LMR, and PNI with age, sex, and comorbidity features were analyzed. A total of 174 patients (78%) had a CAR of ⩾0.34, 73 (32%) had a PNI of ⩽40.2, 67 (30%) had a NLR of ⩾6.27, 25 (11.2%) had a PLR of ⩾312, and 26 (11.7%) had a LMR of ⩽1.54. The results showed that elevated CAR was significantly correlated with age ($P = .001$), while elevated NLR was significantly correlated with age ($P = .001$), hypertension ($P = .018$), and cardiovascular disease ($P = .044$). The low PNI was found to be significantly correlated with hypertension ($P = .008$) and age ($P = .001$), whereas the elevated PLR was significantly correlated with age only ($P = .004$). In addition, higher CAR, higher NLR, higher PLR, lower PNI, and lower LMR were associated with prolonged length of hospital stay and an increased need for ICU admission (Table 4).

Discussion

In the present study, we investigated the prognostic value of inflammatory markers such as CAR, PLR, NLR, LMR, and PNI in COVID-19 patients and identified prognostic factors in this patient population. The results of this study showed that CAR, PNI, NLR, PLR, and LMR were significantly associated with the survival of patients with severe COVID-19. In predicting mortality, CAR, PNI, and NLR were found to be superior to the PLR and LMR. Also, elevated CAR, PNI, and NLR were independently associated with an increased in-hospital mortality risk in severe COVID-19 patients. Finally, a cut-off value of CAR of ⩾0.34, NLR of ⩾6.27, and PNI of ⩽40.2 could predict poor clinical results for severe COVID-19 patients.

It has been shown that the severity of the disease caused by the SARS-CoV-2 virus is directly related to the immune system of individuals.[5] While COVID-19 disease remains asymptomatic in some people, serious complications such as interstitial pneumonia and respiratory failure may develop in others, supporting a unique immune dysfunction model. In severe COVID-19, the unique immune dysregulation pattern has been reported to be associated with continuous cytokine production and hyperinflammation.[6,23] Additionally, COVID-19 patients have shown abnormalities in biochemical, hematological, immune, and inflammatory biomarkers.[23,25] In severe cases, lymphocytopenia, decreased monocyte and eosinophil counts, and increased neutrophil counts were reported.[25] Also, the progression of COVID-19 was found to be associated with decreased lymphocyte counts, while an increase in the leukocyte counts was reported in severe COVID-19 patients.[26] Henry et al[27] showed that patients with severe COVID-19 had significantly higher WBC and lower platelet and lymphocyte counts than non-severe cases. Similarly, in our study, non-survivors had decreased lymphocyte, monocyte, platelet, and increased neutrophil counts than the survivors.

Various combinations of hematological parameters (NLR, LMR, PLR, and PNI) have been used to predict the prognosis of disease.[28,29] These simple parameters can be used in predicting mortality of severely ill patients with COVID-19. The NLR, calculated by the ratio of neutrophils count to lymphocytes count, is an inflammatory marker which is used for the prediction of mortality risk in patients with various

Table 1. Demographic, clinical, and laboratory findings of patients with severe COVID-19.

	TOTAL (N = 223)	SURVIVORS (N = 187)	NON-SURVIVORS (N = 36)	*P* VALUE
Age (years)	59.70 ± 19.01	56.95 ± 17.47	73.97 ± 13.63	.00[a],**
Sex (male)	118 (52.9)	103 (87.3)	15 (12.7)	.140[b]
Comorbidity				
Hypertension, n (%)	103 (46.2)	78 (41.7)	25 (69.4)	.002[b],**
Diabetes, n (%)	61 (27.4)	47 (25.1)	14 (38.8)	.090[b]
Cardiovascular disease, n (%)	42 (18.8)	31 (16.5)	11 (30.5)	.049[b],*
Cerebrovascular diseases, n (%)	9 (4.1)	6 (3.2)	3 (8.3)	.164[c]
Chronic pulmonary disease, n (%)	24 (10.8)	18 (9.6)	6 (16.6)	.239[c]
Laboratory findings				
White blood cell count, $\times 10^9$ per L	6.4 (4.8-9.2)	6.1 (4.7-7.8)	12 (7.8-18.3)	.001[d],**
Hemoglobin concentration, mg/dL	13.4 (11.9-14.2)	13.5 (12.3-14.3)	11.2 (9.5-13.55)	.001[d],**
Platelet count, $\times 10^9$ per L	182 (144-234)	183 (150-234)	143 (121-219)	.018[d],*
Monocyte count, $\times 10^9$ per L	0.4 (0.28-0.51)	0.42 (0.28-0.51)	0.33 (0.2-0.53)	.178[d]
Lymphocyte count, $\times 10^9$ per L	1.1 (0.9-1.6)	1.2 (0.9-1.6)	1 (0.6-1.1)	.001[d],**
Neutrophil count, $\times 10^9$ per L	4.49 (3.07-6.7)	4.2 (2.96-5.52)	7.34 (4.85-12.83)	.001[d],**
Albumin, g/L	39 (32-43)	40 (35-43)	26 (23-29)	.001[d],**
C-reactive protein, mg/dL	5.2 (1.3-10)	4.24 (1-8.59)	13 (8.12-15)	.001[d],**
CAR	0.14 (0.03-0.31)	0.12 (0.02-0.22)	0.46 (0.21-0.63)	.001[d],**
PNI	43.36±9.45	45.51±8.23	32.20±7.37	.001[a],**
NLR	3.8 (2.3-6.9)	3.5 (2.2-5.6)	10.4 (6.3-20.3)	.001[d],**
PLR	152.5 (119-220)	150 (118.8-204)	202.7 (122.5-336.4)	.019[d],*
LMR	3.1 (2-4.3)	3.1 (2.1-4.4)	2.5 (1.3-3.6)	.005[d],**
ICU admission, n (%)				
No	171 (76.7)	170 (90.9)	1 (2.8)	.001[b],**
Yes	52 (23.3)	17 (9.1)	35 (97.2)	
Time from illness onset to hospital admission (days)	5 (4-7)	5 (4-7)	5 (3-7)	.157[d]
Length of stay at hospital (days)	6 (4-10)	6 (4-8)	12 (8-15)	.001[d],**

Abbreviations: CAR, C-reactive protein to albumin ratio; COVID-19, coronavirus disease 2019; ICU, intensive care unit; LMR, lymphocyte–monocyte ratio; NLR, neutrophil–lymphocyte ratio; OR, odds ratio; PLR, platelet–lymphocyte ratio.
[a]Student-*t* test.
[b]Pearson Chi-Square test.
[c]Fisher's exact test.
[d]Mann Whitney *U* test, n (%).
*$P < .05$. **$P < .01$.

diseases.[11,12,30] It has also been reported as a predictive marker of sepsis patients.[31] A meta-analysis reported that severe COVID-19 patients had significantly higher NLR values.[19] The NLR was also shown to be an independent risk factor for severe disease[19-21] and an independent factor for poor clinical outcomes with COVID-19 patients.[22] Previous studies demonstrated that the platelet count was significantly lower in non-survivor COVID-19 patients. The association between decreased platelet count and increased severity of COVID-19 has been also reported; therefore, it can be considered as the

Table 2. Univariate and multivariate analyses for predicting mortality in patients with severe COVID-19.

	UNIVARIATE MODEL			MULTIVARIATE MODEL		
	OR	95% CI	*P* VALUE	OR	95% CI	*P* VALUE
Age	1.07	1.04-1.10	.001**			
Sex (male)	0.59	0.29-1.20	.140			
Hypertension	3.18	1.48-6.84	.002**			
Diabetes	1.90	0.90-4.01	.090			
Cardiovascular disease	2.21	0.99-4.96	.049*			
Cerebrovascular diseases	2.72	0.65-11.45	.164			
PNI (⩽*40.2*)	40.43	11.79-138.65	.001**	10.85	1.81-65.21	.009**
CAR (⩾*0.34*)	16.11	7.00-37.04	.001**	10.14	2.07-49.74	.004**
NLR (⩾*6.27*)	16.24	6.61-39.91	.001**	6.82	1.52-30.66	.012*
PLR (⩾*312*)	8.24	3.36-20.21	.001**			
LMR (⩽*1.54*)	7.52	3.11-18.19	.001**			
ICU history	350.00	45.09-2716.96	.001**	226.30	20.66-2478.12	.001**

Abbreviations: CAR, C-reactive protein to albumin ratio; CI, confidence interval; COVID-19, coronavirus disease 2019; ICU, intensive care unit; LMR, lymphocyte–monocyte ratio; NLR, neutrophil–lymphocyte ratio; OR, odds ratio; PLR, platelet–lymphocyte ratio; PNI, prognostic nutritional index.
**$P < .01$.

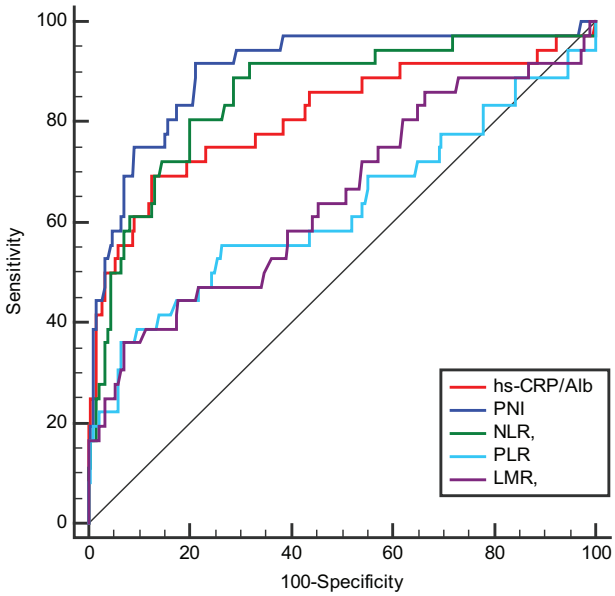

Figure 1. ROC curve analyses for the prognostic role of the inflammation biomarkers in patients with COVID-19.
Abbreviations: CAR, C-reactive protein to albumin ratio; LMR: lymphocyte–monocyte ratio; NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio; PNI, prognostic nutritional index.

indicator of the disease progression throughout hospitalization.[28] Recent studies have suggested PLR as a potential marker for severity of disease[16,17] and as a prognostic marker in patients with COVID-19.[17] Low LMR has been also shown to correlate with disease severity.[18,19] In our study, higher NLR and higher PLR and lower PNI and lower LMR were associated with poor outcomes in COVID-19 patients. The PNI and NLR had higher AUC values than PLR, LMR, and were independently correlated with an increased in-hospital mortality risk in severe COVID-19 patients.

The CRP is an inflammatory marker regulated by proinflammatory cytokines, specifically by interleukin-6 (IL-6). The systemic inflammatory state, reflected by a high CRP level, is accompanied by serum albumin concentration, which is often decreased in this condition.[32] The CRP is elevated in most COVID-19 patients and has been associated with disease severity[6,33] and prognosis.[34] Hypoalbuminemia was found to be independently associated with mortality in COVID-19 patients and the inverse relationship between CRP and albumin levels in COVID-19 patients might indicate the presence of an overactive inflammatory state.[35]

As a novel inflammation-based biomarker, CAR has been shown to be associated with disease severity and mortality risk in the ICU setting.[7-9] Recent studies have suggested that the CAR may reflect infection and inflammatory responses better,[7-9] and it can be utilized as a possible marker for COVID-19 patients. In our study, for predicting mortality in severe COVID-19 patients, the CAR was found to be superior to PLR and LMR and similar to NLR and PNI. We also observed that CAR could be considered an independent predictor of in-hospital mortality in severe COVID-19 patients.

Besides the SARS-CoV-2 infection, chronic diseases, aging, in some cases, may affect these inflammatory biomarkers. However, such superimposed effects may better reflect the characteristics of severe COVID-19 cases. In a study, Yang et al[22] predicted that NLR and age might be associated with

Table 3. Results of receiver operating characteristics analysis for inflammation biomarkers in predicting mortality patients with severe COVID-19.

TEST RESULT VARIABLE (S)	CUT-OFF	AUC	STD. ERROR[a]	ASYMPTOTIC 95% CONFIDENCE INTERVAL		*P* VALUE
				LOWER BOUND	UPPER BOUND	
PNI	⩽40.2	0.91	0.03	0.86	0.94	.001**
CAR	⩾0.34	0.81	0.05	0.75	0.86	.001**
NLR	⩾6.27	0.85	0.03	0.80	0.90	.001**
PLR	⩾312	0.63	0.06	0.56	0.69	.019*
LMR	⩽1.54	0.65	0.06	0.59	0.71	.005**

Abbreviations: AUC, areas under the curve; CAR, C-reactive protein to albumin ratio; COVID-19, coronavirus disease 2019; ICU, intensive care unit; LMR, lymphocyte–monocyte ratio; NLR, neutrophil–lymphocyte ratio; OR, odds ratio; PLR, platelet–lymphocyte ratio; PNI, prognostic nutritional index.
*$P < .05$. **$P < .01$.

the severity and prognosis of COVID-19 and concluded that the NLR was an independent prognostic biomarker for COVID-19 patients. In our study, CAR, NLR, and PLR were positively correlated with age, while the PNI was negatively correlated with age. Additionally, the patients who had ⩾3.4 CAR, ⩾6.27 NLR, ⩾312 PLR, ⩽1.54 LMR, and ⩽ 40.2 PNI were more likely to require ICU support with longer length of hospital stay. These findings indicate that all these inflammatory biomarkers, particularly CAR, PNI, and NLR, can be used to predict the prognosis in severe COVID-19 patients. An increased CAR and NLR, and decreased PNI may induce systemic inflammatory response syndrome in severe COVID-19 patients.

Limitations

Nonetheless, there are some limitations in this study that need to be taken into account when interpreting the results. First, it has a single-center and retrospective design. Second, we evaluated hospitalized severe COVID-19 cases and, therefore, our results cannot be generalized to all patients with COVID-19, particularly those with a less severe form of the disease. Moreover, the heterogeneous population in the present study was a disadvantage. Various confounding conditions may have affected the levels of serum CRP, albumin, and other hematological inflammatory biomarkers, including nutritional status, age, comorbidities, and undocumented drugs that we cannot fully manage. The study was conducted in a single center, the number of patients was small to achieve a subgroup analysis. In addition, the timing of blood draws is another possible confounding factor. In our study, we examined inflammatory biomarkers only at admission; there was no difference between the 2 groups in terms of mean onset of symptoms and duration of hospital admission. But over time it may have provided more information about the prognosis of variation in CAR, NLR, LMR, PLR, and PNI. However, since the outcome estimation is designed to investigate the acceptance potential of CAR, NLR, LMR, PLR, and PNI, it is simply not serially measured of these markers. Moreover, the heterogeneous population was a disadvantage in this study. Various confounding conditions may have affected the levels of serum CRP, albumin, and other hematological inflammatory biomarkers, including nutritional status, age, comorbidities, and undocumented medications. The study was conducted in a single center, the number of patients was small to achieve a subgroup analysis. In addition, the timing of blood draws is another possible confounding factor. In our study, we examined inflammatory biomarkers only at admission; there was no difference between the 2 groups in terms of mean onset of symptoms and duration of hospital admission. The changes in CAR, NLR, LMR, PLR, and PNI over time might have provided more information about disease prognosis. However, no continuous CAR, NLR, LMR, PLR, and PNI values over time were measured in this study, since it was designed to explore the potential of admission CAR, NLR, LMR, PLR, and PNI in outcome prediction. Finally, all patients included in this study met non-strict inclusion criteria, which may have caused a selection bias. Therefore, we believe that further multi-center, large-scale, prospective studies are needed to examine these inflammatory biomarkers accurately and to identify their predictive value for mortality in severe COVID-19 patients.

Conclusions

In conclusion, our study results demonstrated that CAR, PNI, NLR, LMR, and PLR were significantly correlated with prognosis of severe COVID-19 patients. Furthermore, CAR, PNI, and NLR were significant independent prognostic indicators with a better discriminative ability than PLR and LMR. Further studies would provide additional information to this underexamined field of research.

Table 4. Correlations of CAR, PNI, NLR, PLR, and LMR the with the clinical characteristics of patients with severe COVID-19.

CHARACTERISTIC	CAR < 0.34	CAR ⩾ 0.34	*P* VALUE	PNI > 40.2	PNI I ⩽ 40.2	*P* VALUE	NLR < 6.27	NLR ⩾ 6.27	*P* VALUE	PLR < 3.12	PLR ⩾ 3.12	*P* VALUE	LMR > 1.54	LMR ⩽ 1.54	*P* VALUE
	N = 49	N = 174		N = 150	N = 73		N = 156	N = 67		N = 198	N = 25		N = 196	N = 26	
Age			.001[b],**			.001[b],**			.001[b],**			.004[b],*			.337[b]
<60	96 (55.2)	9 (18.8)		86 (57.3)	19 (26)		87 (55.8)	18 (26.9)		100 (50.5)	5 (20)		95 (48.5)	10 (38.5)	
>60	78 (44.8)	39 (81.3)		64 (42.7)	54 (74)		69 (44.2)	49 (73.1)		98 (49.5)	20 (80)		101 (51.5)	16 (61.5)	
Sex			.874[b]			.915[b]			.183[b]			.923[b]			.072[b]
Male	82 (47.1)	22 (45.8)		71 (47.3)	34 (46.6)		78 (50)	27 (40.3)		93 (47)	12 (48)		97 (49.5)	8 (30.8)	
Female	92 (52.9)	26 (54.2)		79 (52.7)	39 (53.4)		78 (50)	40 (59.7)		105 (53)	13 (52)		99 (50.5)	18 (69.2)	
Hypertension			.052[b]			.008[b],**			.018[b],*			.296[b]			.390[b]
No	100 (57.5)	20 (41.7)		90 (60)	30 (41.1)		92 (59)	28 (41.8)		109 (55.1)	11 (44)		108 (55.1)	12 (46.2)	
Yes	74 (42.5)	28 (58.3)		60 (40)	43 (58.9)		64 (41)	39 (58.2)		89 (44.9)	14 (56)		88 (44.9)	14 (53.8)	
Diabetes			.305[b]			.197[b]			.063[b]			.132[b]			.647[b]
No	129 (74.1)	32 (66.7)		113 (75.3)	49 (67.1)		119 (76.3)	43 (64.2)		147 (74.2)	15 (60)		144 (73.5)	18 (69.2)	
Yes	45 (25.9)	16 (33.3)		37 (24.7)	24 (32.9)		37 (23.7)	24 (35.8)		51 (25.8)	10 (40)		52 (26.5)	8 (30.8)	
ICU admission			.001[b],**			.001[b],**			.001[b],**			.001[b],**			.001[b],**
No	150 (86.2)	20 (41.7)		139 (92.7)	32 (43.8)		138 (88.5)	33 (49.3)		162 (81.8)	9 (36)		161 (82.1)	9 (34.6)	
Yes	24 (13.8)	28 (58.3)		11 (7.3)	41 (56.2)		18 (11.5)	34 (50.7)		36 (18.2)	16 (64)		35 (17.9)	17 (65.4)	
Length of stay hospital (days)			.001[d],**			.001[d],**			.001[d],**			.001[d],**			.001[d],**
Median (Q1-Q3)	5 (3-8)	10 (8-15)		5 (3-8)	10 (7-15)		5 (3-8)	8 (6-14)		6 (4-9)	11 (7-15)		6 (4-9)	11 (6-15.3)	

Abbreviations: CAR, C-reactive protein to albumin ratio; LMR, lymphocyte–monocyte ratio; NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio; PNI, prognostic nutritional index.
[a]Student-*t* test.
[b]Pearson Chi-Square test.
[c]Fisher's exact test.
[d]Mann Whitney *U* test.
*$P < .05$. **$P < .01$.

Author Contributions

Conception: Gönül Açıksarı, Mustafa Caliskan, Lütfiye Nilsun Altunal; **Design:** Mehmet Kocak, Yasemin Cag, Adem Atıcı; **Supervision:** Kurtulus Açıksarı, Mustafa Caliskan; **Materials:** Gönül Açıksarı, Fatma Betul Çelik, Furkan Bolen, Kurtulus Açıksarı; **Data collection and processing:** Mehmet Kocak, Yasemin Cag, Lütfiye Nilsun Altunal, Fatma Betul Çelik, Furkan Bolen; **Analysis and interpretation:** Gönül Açıksarı, Mehmet Kocak, Adem Atıcı, Mustafa Caliskan; **Literature review:** Gönül Açıksarı, Mehmet Kocak, Kurtulus Açıksarı, Lütfiye Nilsun Altunal; **Writer:** Gönül Açıksarı, Mehmet Kocak, Furkan Bolen; **Critical review:** Gönül Açıksarı, Mehmet Kocak, Yasemin Cag, Lütfiye Nilsun Altunal, Adem Atıcı, Fatma Betul Çelik Furkan Bolen, Kurtulus Açıksarı, Mustafa Caliskan.

Ethical Approval

This study was approved by the Istanbul Medeniyet University and Goztepe Prof. Dr. Suleyman Yalcin City Hospital Ethics Committee with the Approval No.: 2020/0654.

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