Cerrahpaşa Med J 2022; 46(2): 156-163 ORIGINAL ARTICLE

Assessment of 7 Inflammatory Indexes as an Early Predictor of COVID-19 Severity

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Cite this article as: Çalışkan Z, Bozdağ E, Sönmez S, Dağıstanlı S, Bulut N, Dinçer Y. Assessment of 7 inflammatory indexes as an early predictor of COVID-19 severity. *Cerrahpaşa Med J.* 2022;46(2):156-163.

Abstract

Objective: Early identification of severe patients with coronavirus disease 2019 is important for reducing mortality rates. The current study was conducted to evaluate the predictive value of certain inflammatory indexes, including C-reactive protein to albumin ratio, fibrinogen to albumin ratio, procalcitonin to albumin ratio, procalcitonin to CRP ratio, neutrophil to lymphocyte ratio, monocyte to lymphocyte ratio, and platelet to lymphocyte ratio for the severity of coronavirus disease 2019. We aimed to assess whether these indexes could be efficient early indicators of severe disease.

Methods: Five hundred forty-eight hospitalized coronavirus disease 2019 patients were divided into 2 groups according to their condition: nonsevere group (n = 435) and severe group (n = 113).

Results: Severe coronavirus disease 2019 patients had higher C-reactive protein to albumin ratio, fibrinogen to albumin ratio, procalcitonin to albumin ratio, neutrophil to lymphocyte ratio, monocyte to lymphocyte ratio, and platelet to lymphocyte ratio compared with nonsevere patients ($P < .05$). Logistic regression analysis demonstrated that C-reactive protein to albumin ratio (OR, 1.359; 95% CI, 1.143-1.615) and D-dimer (OR, 1.054; 95% CI, 1.010-1.100) were the independent risk factors for severe coronavirus disease 2019. The area under the curve for C-reactive protein to albumin ratio, fibrinogen to albumin ratio, procalcitonin to albumin ratio, neutrophil to lymphocyte ratio, monocyte to lymphocyte ratio, and platelet to lymphocyte ratio was 0.763, 0.629, 0.681, 0.708, 0.605, and 0.644, respectively.

Conclusion: C-reactive protein to albumin ratio was the best inflammatory predictor compared with other indexes for the early identification of severe coronavirus disease 2019 and it was demonstrated for the first time that procalcitonin to albumin ratio could be used to evaluate disease severity of coronavirus disease 2019 with relatively high sensitivity.

Keywords: Coronavirus disease 2019, severe acute respiratory syndrome coronavirus 2, inflammation, C-reactive protein, procalcitonin, albumin

Introduction

In December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused an outbreak of coronavirus disease 2019 (COVID-19) which probably originated from a seafood wholesale market in Wuhan, China.[1] Due to the rapid spread of COVID-19, it has turned into a pandemic on March 11, 2020. As of December 29, 2021, a total of 280 119 931 confirmed cases included 5 403 662 deaths reported globally*. The major clinical features include persistent fever, dry cough, sputum, fatigue, sore throat, loss of smell and taste, and shortness of breath. Common laboratory findings include low lymphocyte count, high neutrophil count, hypertransaminasemia, elevated lactate dehydrogenase, high C-reactive protein (CRP), and high ferritin levels.[1-5] Increasing age, male gender, and having underlying diseases such as hypertension, cardiovascular disease, diabetes mellitus, chronic respiratory diseases, and cancer were associated with a higher risk of poor prognosis and outcome for COVID-19 patients.[5,6] Although the majority of cases are mild, some patients may rapidly progress to acute respiratory distress syndrome (ARDS), septic shock, coagulation disorders, multi-organ failure, and death.[7,8] Due to the high infectivity rate of COVID-19, the unexpected and rapid influx of large numbers of patients needing intensive care has caused great pressure on the intensive care units (ICUs). Early diagnosis and timely treatment of high-risk patients are very important to improve control of disease and reduce admission to ICU and mortality rates. Therefore, the identification of simple, quick, and reliable laboratory indexes for the prediction of severity of COVID-19 infection can help clinicians to make better treatment decisions.

The inflammatory response plays a crucial role in the clinical presentation, severity, and prognosis of COVID-19. Previous studies have revealed that aggressive inflammatory response with cytokine storm negatively correlates with disease severity and the poor prognosis in patients with COVID-19.[1,9,10] Thus, circulating biomarkers representing the immune status of the body are potential predictors for the disease severity and outcome. Lymphocytes are involved in the human immune response. Their level decreases

World Health Organization Coronavirus disease (COVID-19) outbreak (2019). WHO Coronavirus Disease (COVID-19) Dashboard [online]. Website [accessed December 29, 2021].

Received: January 25, 2022 **Accepted:** April 11, 2022 **Available Online Date:** May 30, 2022
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DOI: 10.5152/cjm.2022.22004

following SARS-CoV-2 infection.[11] Tan et al[12] (2020) suggest that low lymphocyte count is a safe and efficient indicator of the severity and hospitalization in COVID-19 patients. Albumin is a negative acute phase reactant and has antioxidant properties. Researchers reported that low levels of circulating albumin were associated with increased COVID-19-related mortality.[13] It also has been suggested that low albumin levels could be an early sign of severe COVID-19 and can aid clinicians to make appropriate determinations for the treatment of their patients.[14] Based on this knowledge, we speculated that a combination of markers for systemic inflammation which easily obtained from routine laboratory assessments could be used as a predictive marker for disease severity. Recent studies showed that neutrophil to lymphocyte ratio (NLR) is a disease marker in inflammatory conditions including inflammatory bowel disease,[15] thyroiditis,[16] type 2 diabetes mellitus,[17] and SARS-Cov-2 infection.[18] Similarly, platelet to lymphocyte ratio (PLR) has been introduced as a marker in thyroid cancer,[19] diabetes mellitus,[20] irritable bowel disease,[21] and COVID-19 infection.[22] Monocyte to lymphocyte ratio (MLR) is suggested as a disease marker in malignancy,[23] diabetic nephropathy,[24] functional bowel conditions,[21] and COVID-19 infection.[22] Fibrinogen to albumin ratio (FAR) is reported to be a prognostic factor in hepatocellular carcinoma[25] and valuable in reflecting ankylosing spondylitis activity.[26] Finally, the CARE TIME study suggested CRP to albumin ratio (CAR) as a marker of inflammation in patients with diabetic nephropathy.[27] It has also been served as a prognostic marker in various human malignancies.[28] All of these conditions are associated with inflammation just as in COVID-19 infection. The aim of this study is to assess the clinical significance of inflammatory indexes including CAR, FAR, procalcitonin to albumin ratio (PAR), procalcitonin to CRP ratio (PCR), (NLR), MLR, and (PLR) and investigate their value in predicting COVID-19 severity.

Methods

Study Group

This single-center study with a retrospective database of 548 patients aged 18-97 with COVID-19 pneumonia hospitalized at the İstanbul Kanuni Sultan Süleyman Training and Research Hospital from March 21 to April 30, 2020. COVID-19 was diagnosed in line with the Republic of Turkey Ministry of Health's COVID-19 (SARS-CoV-2 infection) guidance. Nasal and pharyngeal swab specimens of each patient were analyzed by real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay and the lung was examined using a computed tomography scan (CT) to confirm each diagnosis. All included subjects were laboratory-confirmed positive for COVID-19 virus. Patients were categorized into 2 groups based on disease severity as nonsevere group (n = 435) and severe group (n = 113) group. The patients in nonsevere group have fever and at least one other respiratory symptoms (severe cough, shortness of breath or difficulty breathing, sputum, etc.) with radiological findings of pneumonia. Those who met any of the criteria as follows were defined as severe cases: respiratory distress (respiratory rate ≥30/min), hypoxemia (blood oxygen saturation ≤93%), and lung infiltrates progression >50% within 24-48 hours on pulmonary imaging. All of the patients received standard therapy according to the Republic of Turkey Ministry of Health's COVID-19 (SARS-CoV-2 infection) guidance.

The study protocol complied with the standards of the Declaration of Helsinki and the current ethical guidelines and was approved by the Institutional Review Board of Istanbul Yeni Yuzyil University (date: May 11, 2020; no. 2020/04-05). Written informed consent for the use of clinicopathological data for study purposes was obtained from each participant on admission.

Data Collection

The general condition of the patients, baseline demographic data, and laboratory examinations of patients was collected from medical records. The demographic data were included age, gender, and presence of underlying diseases (hypertension, diabetes mellitus, respiratory diseases, cardiovascular diseases, cancer, others, and having more than 2 kinds of diseases). The laboratory examinations consisted of white blood cell count (WBC), absolute basophil count (BASO), absolute eosinophil count (EO), absolute lymphocyte count (LYM), absolute monocyte count (MON), absolute neutrophil count (NEU), platelet count (PLT), red blood cell count (RBC), hemoglobin (HGB), hematocrit (Hct), mean platelet volume (MPV), procalcitonin (PCT), CRP, D-dimer, fibrinogen, albumin, and CT scans were performed within 24 hours after hospitalization (before treatment). The CAR was calculated by dividing the CRP level by the albumin level; the FAR was calculated by dividing the fibrinogen content by the albumin level; PAR was calculated by dividing the procalcitonin level by the albumin level; the PCR was calculated by dividing the procalcitonin level to the CRP level; NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count; the MLR was calculated by dividing the absolute monocyte count by the absolute lymphocyte count; and the PLR was calculated by dividing the platelet count by the absolute lymphocyte count.

Statistical Analysis

Statistical significance was analyzed by using IBM Statistical Package for the Social Sciences 22 (IBM SPSS Corp., Armonk, NY, USA). The Kolmogorov–Smirnov test was applied to test for the distribution of continuous variables and none of these variables had a normal distribution. Categorical variables were presented as frequency and percentage, and continuous variables were presented as median and interquartile range (IQR). Pearson's chi-square test was applied to compare categorical variables, while Mann–Whitney U-test was used in the analysis of continuous variables. Multifactorial analysis of the risk factors that were identified after univariate analysis, OR values, and 95% CIs were determined by logistic regression analysis. The optimal cutoff values for significant inflammatory indexes to predict the severity of the COVID-19 infection were estimated by receiver operating characteristic (ROC) curve analysis and the areas under the curve (AUC) were calculated. Cutoff values showing the highest accuracy were identified using a sensitivity/specificity versus criterion value plot. The *P* values of <.05 were accepted as significant. In addition, we have to clarify that, because these inflammatory indexes have internal correlations, all combinations were incorporated into logistic regression analysis one by one.

Results

A total of 548 patients with laboratory- and radiologically confirmed COVID-19 were included in the study. The baseline demographic data and clinical laboratory examinations of nonsevere and severe groups are given in Table 1. Age was significantly higher in severe group 64 [21] than in nonsevere group 56 [26] (*P* = .001). Gender distribution was also found to be different for severe group compared to nonsevere group (*P* = .011), and we suggested that males were more susceptible to severe COVID-19. Patients in the nonsevere group are more likely to have hypertension and at least 2 comorbidities in comparison to the patients in the severe group (*P* = .005 and *P* = .014, respectively). No

Table 1. Comparison of Baseline Data and Laboratory Findings Between Nonsevere Group and Severe Group[†]

Variables	Nonsevere Group (n = 435)	Severe Group (n = 113)	*P*
Age (year)	56 [26] (435)	64 [21] (113)	**.001[a]**
Gender			**.011[b]**
Male	215 (49.4)	71 (62.8)	
Female	220 (50.6)	42 (37.2)	
Comorbidities			
Hypertension	233 (61.5)	52 (46.4)	**.005[b]**
Diabetes mellitus	138 (36.4)	43 (38.4)	.703[b]
Cardiovascular disease	123 (32.5)	26 (23.2)	.062[b]
Chronic lung disease	99 (26.1)	26 (23.2)	.535[b]
Cancer	9 (2.4)	5 (4.5)	.243[b]
Others	234 (61.7)	62 (55.4)	.225[b]
At least 2 comorbidities	291 (76.8)	73 (65.2)	**.014[b]**
Survivor	434 (99.8)	47 (41.6)	**.001[c]**
ICU admission	5 (1.1)	68 (60.2)	**.001[c]**
WBC count ($\times 10^9$/L)	6.26 [3.40]	7.61 [4.62]	**.001[a]**
BASO ($\times 10^9$/L)	0.02 [0.02]	0.02 [0.02]	.092[a]
EO ($\times 10^9$/L)	0.01 [0.06]	0.01 [0.03]	**.022[a]**
LYM ($\times 10^9$/L)	1.40 [0.9]	1.1 [0.775]	**.001[a]**
MON ($\times 10^9$/L)	0.52 [0.35]	0.5 [0.397]	.229[a]
NEU ($\times 10^9$/L)	4.04 [2,72]	5.77 [5,15]	**.001[a]**
PLT ($\times 10^9$/L)	215 [94.75]	222 [116.75]	.373[a]
RBC ($\times 10^{12}$/L)	4.6 [0.76]	4.49 [0.89]	**.027[a]**
HGB (g/dL)	13 [2.27]	12.45 [3.27]	**.018[a]**
Htc (%)	38.75 [6.47]	37.2 [8.62]	**.008[a]**
MPV (fL)	10.5 [1.4]	10.3 [1.17]	.157[a]
PCT (ng/mL)	0.06 [0.07]	0.16 [0.3]	**.001[a]**
CRP (mg/L)	28.5 [60.68]	96.76 [153.62]	**.001[a]**
D-dimer (mg/L)	0.88 [1.43]	2.73 [5.8]	**.001[a]**
Fibrinogen (mg/dL)	426 [151]	482 [264]	**.012[a]**
Albumin (g/L)	38.7 [6.6]	33.7 [5]	**.001[a]**
CAR (%)	0.73 [1.69]	3 [4.71]	**.001[a]**
FAR (%)	11.7 [4.39]	13.65 [7.88]	**.002[a]**
PAR (%)	0.0017 [0.001]	0.0052 [0.01]	**.001[a]**
PCR (%)	0.0024 [0.01]	0.0021 [0.003]	.154[a]
NLR (%)	2.87 [2.79]	5.57 [7.11]	**.001[a]**
MLR (%)	0.36 [0.25]	0.5 [0.4]	**.001[a]**
PLR (%)	151.98 [112.37]	213.01[183.69]	**.001[a]**

[†]Data are presented as n (%), medians, and inter-quartile ranges. [a]Mann–Whitney U-test. [b]Pearson chi-square test. [c]Fisher's exact test.
WBC, white blood cell; BASO, absolute basophil count; EO, absolute eosinophil count; LYM, absolute value of lymphocyte; MON, absolute value of monocyte; NEU, absolute value of neutrophil; PLT, platelet count; RBC, red blood cell count; HGB, hemoglobin; Hct, hemotocrit; MPV, mean platelet volume; PCT, procalcitonin, CRP, C-reactive protein; CAR, CRP to albumin ratio; FAR, fibrinogen to albumin ratio, PAR, procalcitonin to albumin ratio; PCR, procalcitonin to CRP ratio; NLR, neutrophil to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; ICU, intensive care unit.
P-values set in boldface indicate statistical significance. Significance level was determined as $P < .05$.

significant difference was found between the 2 groups for underlying diseases including diabetes mellitus, cardiovascular disease, respiratory diseases, cancer, and other diseases ($P > .05$). The laboratory findings including WBC, NEU, PCT, CRP, D-dimer, and fibrinogen were significantly higher and EO, LYM, RBC, HGB, Htc, and albumin were significantly lower in the severe group than those of the nonsevere group. However, there was no significant difference identified between the nonsevere and the severe group with regard to BASO, MON, PLT, and MPV. It was determined that CAR, FAR, PAR, NLR, MLR, and PLR were significantly higher in the severe group compared to the nonsevere group, while PCR was not revealed significant difference between the groups. When comparing nonsevere and severe patients, we found a significant difference in ICU requirement ($P = .001$) and mortality rates (-.

The parameters with $P < .05$ in Table 1 were analyzed by logistic regression analysis to assess the risk factors of the baseline data and laboratory findings on the severity of COVID-19 patients (Table 2). The included parameters were age, gender, hypertension, having at least 2 comorbidities, WBC, EO, LYM, NEU, RBC, HGB, Hct, PCT, D-dimer, fibrinogen, and CAR. All inflammatory indexes including CAR, FAR, PAR, NLR, MLR, and PLR were incorporated in the logistic regression analysis one by one and among them, only the CAR was statistically significant. We found that D-dimer and CAR were independent risk factors for severe disease (Table 2).

Receiver operating characteristic curve analysis was used to define the optimal cutoff values of CAR, FAR, PAR, NLR, MLR, and PLR to predict disease severity. The ROC curves were generated (Figure 1 and Figure 2) and the AUC values were estimated and compared (Table 3). When the occurrence of severe illness was used as an endpoint, all calculated AUC values and optimal cutoff values were found to be statistically significant. Regarding AUC values, the CAR proved to have a much better predictive power to distinguish severe patients from nonsevere patients compared with FAR, PAR, NLR, MLR, and PLR.

Discussion

The current pandemic of COVID-19 is a serious condition that affects various human systems such as respiratory, cardiovascular, nervous, gastrointestinal, circulatory, and immune systems.[29-31] In the treatment of patients, it is crucial to determine which patient is more likely to develop severe disease, and so is at greatest risk for need ICU admission and death. Viral load alone does not sufficiently determine the development of severe disease and patient outcomes in COVID-19, which may be due to differences in patients' genetic background, immune response, and underlying conditions. It is generally accepted that the inflammatory response plays a major role in the COVID-19 prognosis.[32] Various types of circulating blood cells such as lymphocytes, neutrophils, platelets, and circulating proteins including albumin, C-reactive protein, and procalcitonin are involved in body's immune response to the virus. Their abnormal levels could assist with valuable information for clinicians to treat patients in the most appropriate way. Numerous studies provide that the ratios obtained from circulating blood cells such as NLR, PLR, CAR, and FAR seem to be superior in predicting disease severity, compared to evaluating each parameter individually.[2,9,33] Identification of new indexes with high sensitivity and specificity for the earlier diagnosis and treatment for high-risk COVID-19 patients could help clinicians to decide on the best therapeutic approach. In this retrospective study, we investigated the prognostic significance of 7 combinations, CAR, FAR, PAR, PCR, NLR, MLR, and PLR, as an inflammatory index for predicting severe infection in COVID-19 patients. We hypothesize

Table 2. Logistic Regression Analysis of Variables Associated with the Severity of COVID-19

Variables	OR	95% CI		*P*
Age	1.007	0.984	1.030	.562
Gender	1.879	0.831	4.250	.130
Hypertension	0.731	0.330	1.616	.438
At least 2 comorbidities	0.778	0.349	1.732	.538
WBC count ($\times 10^9$/L)	1.000	0.999	1.000	.458
EO ($\times 10^9$/L)	2.752	0.040	1.880	.639
LYM ($\times 10^9$/L)	1.013	0.657	1.561	.954
NEU ($\times 10^9$/L)	1.255	0.801	1.966	.321
RBC ($\times 10^{12}$/L)	1.416	0.369	5.437	.613
HGB (g/dL)	1.362	0.672	2.761	.392
Htc (%)	0.870	0.661	1.147	.323
PCT (ng/mL)	1.034	0.960	1.113	.380
D-dimer (mg/L)	1.054	1.010	1.100	**.017**
Fibrinogen (mg/dL)	1.000	0.998	1.002	.984
CAR **(%)**	1.359	1.143	1.615	**.001**

WBC, white blood cell; EO, absolute eosinophil count; LYM, absolute value of lymphocyte; NEU, absolute value of neutrophil; RBC, red blood cell count; HGB, hemoglobin; Hct, hemotocrit; PCT, procalcitonin, CAR, CRP to albumin ratio.
P-values set in boldface indicate statistical significance. Significance level was determined as $P < .05$.

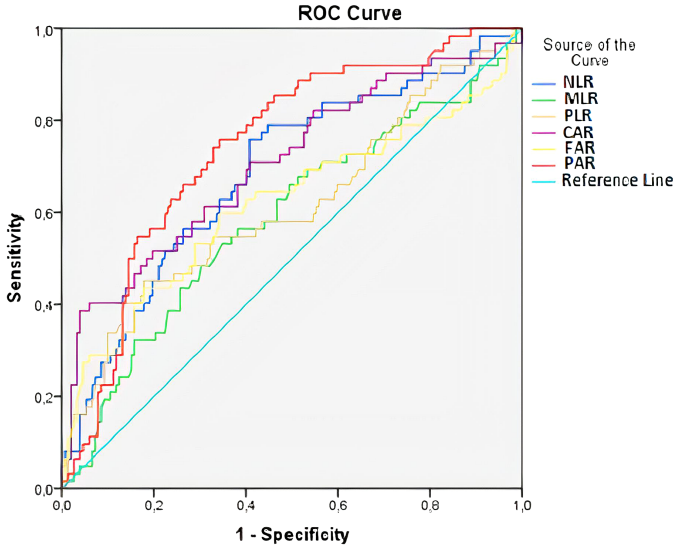

Figure 1. ROC curves of CAR, FAR, PAR, NLR, MLR, and PLR in patients with severe COVID-19.
CAR, CRP to albumin ratio; COVID-19, coronavirus disease 2019; FAR, fibrinogen to albumin ratio; PAR, procalcitonin to albumin ratio; NLR, neutrophil to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; ROC, receiver operating characteristic.

that these combinations may be more effective than all the individual parameters in predicting disease progression. The predictive value of these 7 combinations previously has not been sufficiently analyzed and evaluated in any study on COVID-19.

Similar to previous studies, we showed that age[2-4,34-36] and male gender[5,37] were confirmed as significant risk factors related to hospitalization and the development of severe illness. Hypertension and diabetes mellitus are the most frequently reported diseases in COVID-19 patients.[2] The current study does not support previous findings regarding underlying diseases. Hypertension and having at least 2 comorbidities were reported significantly higher in the nonsevere group in comparison to the severe group in our study.[1,2,9] A reasonable explanation for that would be that the large difference between groups regarding the number of patients may result in certain biases. Consistent with other studies,[38,39] we found that LYM, EOS, RBC, HGB, Htc%, and albumin levels in the severe group were lower than in the nonsevere group ($P < .05$). We found higher WBC, NEU, PCT, CRP, D-dimer, and fibrinogen levels in the severe group which confirms previous findings in the literature.[1,2,18,34] While MON and PLT levels were generally equal between nonsevere and severe groups, MLR and PLR were notably higher in the severe group. This shows that the ratio of inflammatory markers is a more predictive measure as suggested by others.[2,9,33]

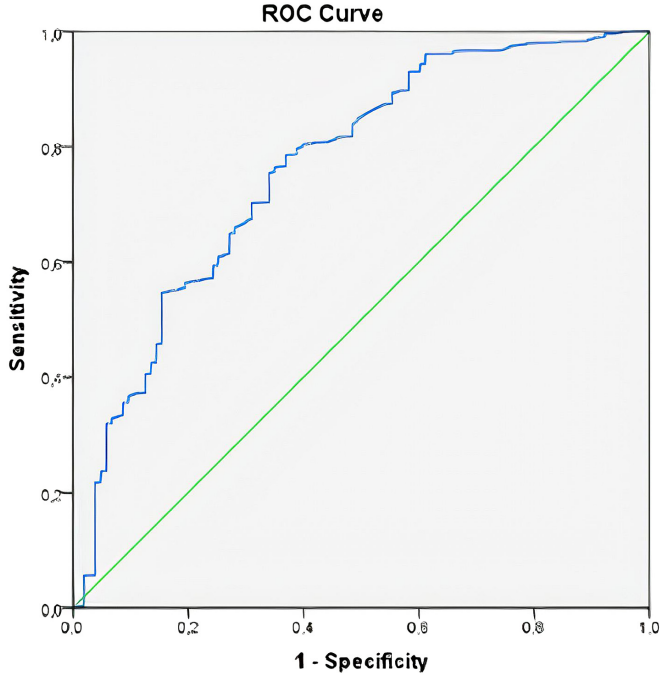

Figure 2. ROC curve of CAR in patients with severe COVID-19.
CAR, CRP to albumin ratio; COVID-19, coronavirus disease 2019; ROC, receiver operating characteristic.

Table 3. The AUC and Optimal Thresholds of Each Combinations for Disease Severity

Combi-nations	AUC	*P*	Optimal Threshold	Sensitivity	Specificity	95% CI
CAR (%)	0.763	**.0001**	≤2.19	78.55	63.11	0.719-0.804
FAR (%)	0.629	**.005**	≤14.79	83.23	45.31	0.563-0.692
PAR (%)	0.681	**.0001**	≤0.00	84.74	52.08	0.628-0.729
NLR (%)	0.708	**.0001**	≤3.67	65.66	72.32	0.667-0.746
MLR (%)	0.605	**.0014**	≤0.49	73.15	50.89	0.562-0.646
PLR (%)	0.644	**.0001**	≤197.89	70.14	57.14	0.602-0.684

AUC, area under curve; CI, confidence interval; CAR, CRP to albumin ratio; FAR, fibrinogen to albumin ratio, PAR, procalcitonin to albumin ratio; PCR, procalcitonin to CRP ratio; NLR, neutrophil to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

The need for ICU support and mortality rate was elevated in the severe group. Patients in the severe group had higher CAR, FAR, PAR, NLR, MLR, and PLR compared to patients in nonsevere group. The present study shows that levels of CAR, FAR, PAR, NLR, MLR, and PLR correlate with COVID-19 disease severity.

C-reactive protein is an acute-phase protein produced in response to inflammation, therefore it is regarded as one of the most commonly used nonspecific inflammatory markers. Numbers of studies have indicated that CRP could be correlated with the high risk of development of severe disease.[8,34,36] Albumin is an acute-phase protein and its levels decrease following an acute infection. It has been shown that the clinical prognosis is worse in COVID-19 when albumin is low.[14] Wang et al.[39] first reported that CAR was an independent risk factor and can signal as an early warning sign of severe illness in combination with the NLR and age. Our results have a number of similarities with Wang's et al[39] findings that CAR and also D-dimer were independent risk factors to predict the occurrence of severe COVID-19. Logistic regression analysis revealed that an increase of 1 for the CAR was linked to a 13% increase in the risk of severe disease. In other words, an elevated CAR within 24 hours of hospitalization was independently related to an increased risk for the development of the severe illness. Our results demonstrate that CAR is higher in patients in the severe group compared with patients in the nonsevere group and a cutoff value of 2.19 can be used to identify patients with severe disease. CRP to albumin ratio yielded the best AUC value compared to other combinations for disease severity. Fibrinolysis, the enzymatic degradation of fibrin in blood clots, results in the formation of a minuscule protein fragment called D-dimer which is a sensitive marker of coagulopathy. Previous studies have shown that COVID-19 patients with increased D-dimer levels have higher risk for severe illness due to an increased risk of thrombosis. Similar to the results of Tang et al.[40] we found D-dimer values nearly 3.5-fold higher in severe group (median: 2.73 mg/L; IQR: 5.8 mg/L) than in nonsevere group (median: 0.88 mg/L; IQR: 1.43 mg/L). A few studies reported that increased D-dimer levels are associated with disease severity.[1,2] We believe that no other authors have found that D-dimer is an independent risk factor for severe disease. Besides, elevated D-dimer has been related to negative outcomes including the development of ARDS and death.[3] Therefore, the scrutiny of D-dimer levels in COVID-19 patients is of grave importance in predicting disease prognosis.

A study by Bi et al[33] reported that FAR and PLT count together could be used to predict severe disease development and were considered as independent risk factors. Our results demonstrate that FAR could identify severe patients with 83.23% sensitivity and 45.31% specificity and relatively low AUC values (0.629).

As a novel finding, this investigation showed that PAR was elevated in patients with severe COVID-19. So far, no studies have explored the links between PAR in COVID-19. Here, we demonstrated for the first time that PAR can be used to identify severe patients with relatively high sensitivity. A calcitonin precursor, PCT, is synthesized and released by parafollicular C cells of the thyroid gland. During bacterial infection, it can also be produced by extrathyroidal tissues due to increased concentration of cytokines. A recent meta-analysis showed that increased levels of PCT strongly correlated with COVID-19 severity,[41] they suggested further iresearch to determine the possible bacterial origin of PCT elevation in patients with severe COVID-19.

In agreement with recent studies,[2,9,18,22,37,42,43] NLR was especially higher in the severe group compared to the nonsevere group and suggesting that it could be a reliable indicator for predicting COVID-19 severity. It has been reported that the presence of systemic inflammation indicated by elevated NLR could be associated with poor clinical outcomes.[18,22,42] An important finding of our study is that the PLR and MLR were found higher ($P = .001$) in the severe group, while levels of monocytes and platelets alone did not be statistically significant. While Khalid et al[18] have found any significant difference regarding PLR between severe and nonsevere COVID-19 cases, Qu et al[44] showed that among 30 hospitalized patients with COVID-19, high PLR may indicate a more pronounced cytokine storm and associated with worse outcomes. To sum up, these indexes have been considered as prognostic markers of disease severity in COVID-19 patients.[22]

Study Limitations

A number of limitations need to be considered. First, this was a retrospective, single-center study and there was no external or internal validation cohort. Second, a large difference in sample size between groups limited the power of the tests. Third, not all data points were available for all patients. Finally, a single measurement of all biochemical parameters may not reflect the relation over time. These results require further evaluation with large-scale prospective validation studies.

As far as we are aware, this is the first time that the prognostic value of various inflammatory indexes in COVID-19 patients has been extensively discussed. These parameters are routinely measured in most hospital laboratories with no need for additional effort in all COVID-19 patients. They are simple, inexpensive, and reproducible parameters of the inflammatory response as well as a predictor of disease severity. Both CAR, FAR, PAR, NLR, MLR,

and PLR are useful tools in the prediction of the disease severity. On the other hand, only the CAR was found to be an independent risk factor for severe disease in logistic regression analysis. The CAR was found to be superior to FAR, PAR, PCR, NLR, MLR, and PLR for predicting disease severity. Our work has led us to the conclusion that these indexes especially CAR can be used as a reliable predictor of COVID-19 progression. They are valuable for clinicians in decision-making and could be used in identifying severe cases at early stages, estimating prognosis, and evaluating complications and response to therapy. Inexpensive and easy-to-assess nature of these tests may also contribute to their utility in clinical practice.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of İstanbul Yeni Yüzyıl University (Date: May 11, 2020; No. 2020/04-05).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Z.Ç., E.B., Y.D.; Design – Z.Ç., E.B., Y.D.; Supervision – Y.D. Funding – E.B., S.S., S.D.; Materials – E.B., S.S., S.D.; Data Collection and/or Processing – Z.Ç., E.B., S.S., S.D., N.B.; Analysis and/or Interpretation – Z.Ç., E.B., S.S., S.D., N.B.; Literature Review – Z.Ç., Y.D.; Writing – Z.Ç.; Critical Review – Z.Ç, E.B., Y.D.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declared that this study received no financial support.

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