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The value of C-reactive protein/albumin, fibrinogen/albumin, and neutrophil/lymphocyte ratios in predicting the severity of COVID-19

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SUMMARY

OBJECTIVE: This retrospective study aimed to determine the predictive values of the C-reactive protein (CRP)/albumin ratio (CAR), fibrinogen/albumin ratio (FAR), and neutrophil/lymphocyte ratio (NLR) parameters, which reflect the systemic inflammatory status, for the severity of COVID-19.

METHODS: A total of 188 patients diagnosed with COVID-19 were enrolled in this study. Among them, 118 were in the severe group, and 70 were in the non-severe group. Levels of albumin, CRP, D-dimer, procalcitonin, fibrinogen, and hemoglobin; leukocyte, neutrophil, lymphocyte, and monocyte counts; and the FAR, CAR, and NLR were compared between the two groups.

RESULTS: The CAR, FAR, and NLR values were significantly higher in the severe group compared to the non-severe group. CAR, FAR, and NLR were positively correlated with leukocyte and neutrophil counts and CRP, procalcitonin, and fibrinogen levels. On the other hand, they were inversely correlated with monocyte (except for NLR) and lymphocyte counts. Receiver operator characteristic analysis showed that the area under the curve (AUC) for CAR, FAR, and NLR was 0.841, 0.737, and 0.802, respectively.

CONCLUSIONS: Our investigation revealed that the CAR, FAR, and NLR indices can be used to predict the severity of COVID-19, among which CAR was the best predictor of severe COVID-19.

KEYWORDS: COVID-19. C-reactive protein. Fibrinogen. Neutrophils.

INTRODUCTION

The COVID-19 pandemic started in China in December 2019 and is still ongoing worldwide. This highly contagious disease, which is a priority public health problem in countries affected by the pandemic, is transmitted among humans via close contact and respiratory droplets. The patients present with a wide clinical spectrum ranging from asymptomatic infection to mild or severe viral pneumonia, or respiratory failure leading to death[1,2]. The course of the disease was reported to be more severe in frail patients, that is, elderly persons and patients with preexisting chronic illnesses[3,4]. Early diagnosis and discriminating the critical cases to administer timely therapy is very important to slow down or prevent the progression of the disease. Thus, for rapid clinical decision-making, easy-to-access, quick, and low-cost markers are needed. Among several laboratory parameters assessed in many studies, lymphocyte,

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platelet, albumin, C-reactive protein (CRP), fibrinogen, procalcitonin, D-dimer, interleukin-6, and their derived neutrophil/lymphocyte ratio (NLR) and fibrinogen/albumin ratio (FAR) have been proposed as predictive markers for the severity of COVID-19[5-9]. The CRP/albumin ratio (CAR) is a novel index calculated by dividing the CRP to albumin level, and many studies have shown that CAR can be used to predict the activity, severity, and prognosis of various conditions[10-13]. However, whether CAR is an efficient indicator in determining the severity of COVID-19 has not been investigated so far. Therefore, in this retrospective study, we aimed to determine the predictive values of the CAR, FAR, and NLR indices for the severity of COVID-19.

METHODS

A total of 188 patients diagnosed with COVID-19 at the Sanliurfa Training and Research Hospital from April to July 2020 were included in this retrospective study. The COVID-19 diagnosis was confirmed by a positive PCR result from nasopharyngeal swab specimens. The patients were categorized into two groups, including the non-severe (mild/moderate cases) and severe (severe/critical cases) groups, according to the disease severity[14]. Non-severe cases had either mild clinical symptoms without signs of pneumonia on imaging (mild type) or fever and respiratory symptoms, with signs of pneumonia on imaging (moderate type). Cases in the severe group met at least one of the following criteria:

1. Respiratory rate ≥30/min;
2. Oxygen saturation ≤93%;
3. The ratio of arterial partial oxygen pressure to inspiratory oxygen fraction (PaO_2/FiO_2) ≤300 mmHg;
4. Respiratory failure and requiring mechanical ventilation;
5. Shock;
6. Other organ failure requiring intensive care support.

Among the 188 included patients, 118 were in the severe group and 70 were in the non-severe group. Patients with connective tissue disorders, hematologic diseases, kidney or liver dysfunction, thyroid diseases, cancers, age less than 18 years, who were pregnant, and those receiving albumin transfusion before treatment were not included in the study. This retrospective study was approved by the Harran University Ethics Committee.

The age, gender, comorbidities, and laboratory results of the participants on admission were obtained from the database of the hospital information system. Complete blood count parameters (leukocyte, neutrophil, lymphocyte, monocyte, and hemoglobin) were determined using a Sysmex XN-1000 analyzer (Sysmex, Japan). Albumin, CRP, D-dimer, and procalcitonin levels were analyzed using the classical methods in a Cobas 8000 analyzer (Roche Diagnostics, Germany); the fibrinogen level was measured using a Sysmex CS-2000i analyzer (Sysmex, Japan). The FAR, CAR, and NLR values were calculated as follows: FAR=(fibrinogen/albumin ratio), CAR=(CRP/albumin ratio), and NLR=(neutrophil/lymphocyte ratio).

Statistical analysis

Data analysis was done using SPSS version 20 (IBM Corp, Armonk, NY) and a $p<0.05$ was considered significant. Demographic and laboratory data were compared between the severe and non-severe groups using the independent sample t-test, Mann-Whitney U-test, or χ^2. Correlations between CAR, FAR, and NLR and inflammatory markers in the COVID-19 patients were determined using the Spearman test. The predictive value of FAR, CAR and NLR in distinguishing severe from non-severe COVID-19 patients was determined by receiver operator characteristic (ROC) analysis.

RESULTS

A total of 188 patients with COVID-19 were included in this study. Of these patients, 112 were in the non-severe group while 70 were in the severe group. As shown in Table 1, the severe group had higher leukocyte and neutrophil counts; CRP, D-dimer, procalcitonin, and fibrinogen levels; and CAR, FAR, and NLR; and lower lymphocyte and monocyte counts and albumin levels than those in the non-severe group ($p<0.05$). The two groups did not differ in terms of age, male/female ratio, incidences of comorbidities, and hemoglobin level ($p>0.05$).

Correlations between CAR, FAR, and NLR and the inflammatory markers studied in COVID-19 patients are shown in Table 2. CAR and FAR were positively associated with leukocyte, neutrophil, CRP, procalcitonin, and fibrinogen levels and negatively associated with monocyte and lymphocyte counts. NLR was positively associated with leukocyte, neutrophil, CRP, procalcitonin, and fibrinogen levels and negatively associated with lymphocyte count.

ROC analysis results of the CAR, FAR, and NLR are shown in Table 3. The area under the ROC curve (AUC) was 0.841 (95%CI 0.784–0.899, $p<0.001$) for CAR, 0.737 (95%CI 0.663–0.811, $p<0.001$) for FAR, and 0.802 (95%CI 0.735–0.869, $p<0.001$) for NLR (Figure 1).

DISCUSSION

In this study, we found that the severe COVID-19 group had higher CAR, FAR, and NLR compared to the non-severe

Table 1. Demographics and laboratory characteristics of patients with COVID-19 on admission.

	Non-severe group (n=118)	Severe group (n=70)	p-value
Age, years	59.6±12.2	62.3±12.7	0.146
Gender, male/female	55/63	38/32	0.309
Comorbidities, n (%)			
Diabetes	43 (36.4)	21 (30.0)	0.368
Hypertension	65 (55.1)	37 (52.9)	0.767
Cardiovascular disease	33 (28.0)	20 (28.6)	0.929
Dyslipidemia	31 (26.3)	21 (30.0)	0.581
Pulmonary disease	18 (15.3)	8 (11.4)	0.463
Laboratory Parameter			
Leukocyte, x10^3/µL	6.28 (2.15–15.28)	9.33 (2.10–25.92)	<0.001
Neutrophil, x10^3/µL	3.98 (1.18–14.22)	8.11 (1.42–23.25)	<0.001
Lymphocyte, x10^3/µL	1.58 (0.49–5.05)	1.10 (0.27–6.35)	<0.001
Monocyte, x10^3/µL	0.60 (0.12–1.79)	0.45 (0.11–11.06)	0.017
Hemoglobin, g/dL	13.52±1.52	13.73±1.69	0.381
Albumin, g/dL	4.18±0.43	3.65±0.42	<0.001
D-dimer, ug/mL	0.28 (0.11–3.92)	0.58 (0.15–26.87)	<0.001
CRP, mg/L	13.2 (0.7–267.5)	91.9 (4.63–408.1)	<0.001
Procalcitonin, ng/mL	0.07 (0.02–0.39)	0.15 (0.03–87.63)	<0.001
Fibrinogen, mg/dL	374.9 (102.8–888.9)	516.6 (101.6–900)	<0.001
CAR	3.18 (0.16–84.12)	25.62 (1.08–126.35)	<0.001
FAR	94.8 (25.1–279.6)	138.5 (23.6–262)	<0.001
NLR	2.56 (0.51–26.33)	6.25 (1.19–52.44)	<0.001

CRP: C-reactive protein; CAR: C-reactive protein (CRP)/albumin ratio; FAR: Fibrinogen/albumin ratio; NLR: Neutrophil/lymphocyte ratio.

Table 2. Correlations of C-reactive protein/albumin ratio, fibrinogen/albumin ratio and neutrophil/lymphocyte ratio with the inflammatory markers in COVID-19 patients.

	CAR		FAR		NLR	
	r	p	r	p	r	p
Leukocyte	0.336	<0.001	0.289	<0.001	0.606	<0.001
Neutrophil	0.504	<0.001	0.414	<0.001	0.818	<0.001
Lymphocyte	-0.532	<0.001	-0.348	<0.001	-0.722	<0.001
Monocyte	-0.229	0.002	-0.175	0.018	-0.089	0.224
CRP	0.998	<0.001	0.713	<0.001	0.635	<0.001
Fibrinogen	0.611	<0.001	0.970	<0.001	0.391	<0.001
Procalcitonin	0.671	<0.001	0.438	<0.001	0.560	<0.001

CRP: C-reactive protein; CAR: C-reactive protein (CRP)/albumin ratio; FAR: Fibrinogen/albumin ratio; NLR: Neutrophil/lymphocyte ratio.

COVID-19 group. In addition, the values of these 3 parameters were positively correlated with the leukocyte and neutrophil counts and CRP, procalcitonin, and fibrinogen levels and negatively correlated with monocyte (except for NLR) and lymphocyte counts. ROC analysis illustrated that CAR had the highest AUC value, thus demonstrating that it was more efficient than FAR and NLR in predicting the severity of COVID 19. To our knowledge, this is the first study

Table 3. Receiver operator characteristic analysis results of C-reactive protein/albumin ratio, fibrinogen/albumin ratio and neutrophil/lymphocyte ratio.

	AUC (95%CI)	Cut-off level	Sensitivity (%)	Specificity (%)	p-value
CAR	0.841 (0.784–0.899)	7.54	82.6	66.7	<0.001
FAR	0.737 (0.663–0.811)	113.5	69.6	65.8	<0.001
NLR	0.802 (0.735–0.869)	3.16	78.3	68.4	<0.001

AUC: area under the curve; CAR: C-reactive protein/albumin ratio; FAR: Fibrinogen/albumin ratio; NLR: Neutrophil/lymphocyte ratio.

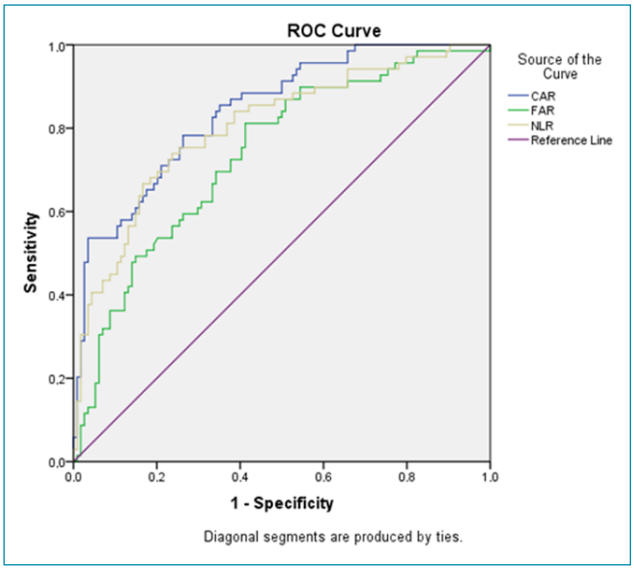

Figure 1. Receiver operator characteristic curves of C-reactive protein/albumin ratio, fibrinogen/albumin ratio and neutrophil/lymphocyte ratio in predicting severe COVID-19 on admission.

that explores the predictive values of CAR for the COVID-19 severity.

COVID-19 infection has a wide clinical spectrum ranging from asymptomatic infection to severe/critical disease. Patients with severe COVID-19 can progress rapidly to develop worse clinical outcomes such as acute respiratory distress syndrome, multiple organ failure, and eventually death, while non-severe patients have a good prognosis[15]. Therefore, efficient indicators are needed to distinguish between severe and non-severe patients for timely treatment. In this context, the researchers focused on the predictive value of various laboratory parameters like lymphocyte count, NLR, CRP, albumin, and fibrinogen in severe COVID-19 disease[5-9].

Lymphopenia and neutrophilia are commonly observed hematological abnormalities in COVID-19 patients and have been proposed as effective indicators of disease severity and poor prognosis in COVID-19[16-18]. Recently, Nalbant et al.[19] found that the NLR index, which can be easily calculated by dividing the neutrophil count by the lymphocyte count, is an independent predictor for COVID-19 diagnosis. Moreover, some studies have reported that the NLR index is closely related to the progression of COVID-19[20,21]. Concordant with these studies, we observed that the NLR was higher in the severe than the non-severe COVID-19 patients and that it was positively associated with the inflammatory markers (leukocyte count, CRP, procalcitonin, and fibrinogen), suggesting that the NLR might be a potential predictor of severe COVID-19.

Albumin is a negative acute-phase reactant that tends to decrease in response to acute conditions such as inflammation, trauma, surgery, and burns[22]. The albumin level was found to be lower in COVID-19 patients, and the hypoalbuminemia was more severe in critically ill patients[9,23]. On the other hand, fibrinogen is one of the positive acute phase response proteins that increase during inflammation[24]. Recent studies have shown that fibrinogen levels are significantly increased in severe COVID-19 patients compared to non-severe patients[5,6]. In addition, Bi et al.[7] reported that FAR, simply calculated by the ratio of fibrinogen to albumin, could be a new marker for estimating the severity of COVID-19, which is consistent with our results.

CRP, another positive acute phase reactant, increases in response to infections, inflammation, and tissue damage[25]. It has been shown that in COVID-19 patients, CRP reaches high levels and the magnitude of the increase correlates with the severity of the illness[8]. On the other hand, the role of the CAR index, the ratio of CRP to albumin, in predicting the severity of COVID-19 is unknown. Therefore, this study investigated the ability of CAR, as well as NLR and FAR, to differentiate between patients with and without severe COVID-19. We found that the CAR value was higher in severe patients compared to non-severe patients and that it was positively correlated with leukocyte, neutrophil, CRP, procalcitonin, and fibrinogen and negatively correlated with monocyte and lymphocyte counts. In addition, in our ROC curve analysis, the AUC value of CAR was greater than that of FAR and NLR. These results showed that CAR was more efficient than FAR and NLR in predicting the severity of COVID 19.

The main limitation of our study is its retrospective design and it was conducted at a single center. Another limitation was the lack of data on smoking, alcohol use, and body mass index affecting laboratory results.

CONCLUSIONS

In conclusion, we found that the CAR, FAR, and NLR indices could be used as new potential parameters to distinguish severe COVID-19 patients from non-severe patients. Of these, CAR was the best predictor of severe COVID-19.

AUTHORS' CONTRIBUTIONS

AT: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. **TDÇ:** Conceptualization, Data curation, Formal analysis, Investigation, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. **GÇ:** Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Writing – original draft, Writing – review & editing. **RDP:** Investigation, Methodology, Resources, Supervision, Visualization, Writing – review & editing.

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