The Value of the C-Reactive Protein/Albumin and Fibrinogen/Albumin Ratios in Predicting Disease Severity and Mortality in Elderly COVID-19 Patients

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ABSTRACT

Objective: Due to the high mortality levels associated with the novel coronavirus, reliable predictors for determining disease mortality and severity are needed to permit the careful allocation of health services and for earlier clinical intervention and follow-up. The purpose of this study was to determine the predictive value of the C-reactive protein (CRP)/albumin ratio (CAR) and the fibrinogen/albumin ratio (FAR) in determining mortality and evaluate correlations between these values and thoracic computed tomography (CT) findings.

Material and Methods: COVID-19 patients aged over 65 presenting to the emergency department of a tertiary training and research hospital between Oct 15, 2021, and Jan 15, 2022, were examined in this single-center, retrospective study. The study population was established based on inclusion and exclusion criteria. The patients' mortality status and pulmonary involvement percentages were compared with their laboratory parameters.

Results: The relationships between patients' CAR and FAR values and mortality and disease severity were investigated. Cut-off points of 3.0 for CAR (AUC 0.767, sensitivity 76.5% and specificity 70.1%) and 14.4 for FAR (AUC 0.731, sensitivity 75.0% and specificity 69.0%) were determined for the prediction of mortality. In terms of prediction of disease severity, cut-off points were 4.2 for CAR (AUC 0.786, sensitivity 73.7%, and specificity 75.2%) and 15.2 for FAR (AUC 0.789, sensitivity 84.2%, and specificity 69.6%).

Conclusion: Based on our study findings, CAR and FAR values may be useful in the early differentiation of mortality and pulmonary parenchymal involvement in elderly COVID-19 patients.

Key words: COVID-19, C-reactive protein/albumin ratio, Fibrinogen/albumin ratio

INTRODUCTION

With the rapid global spread of the COVID-19 pandemic declared by the World Health Organization (WHO) on Mar 11, 2020, countries began adopting strict precautionary measures in their health systems (1,2). COVID-19 exhibits a wide clinical manifestation, from asymptomatic infection to mild or severe viral pneumonia or fatal respiratory failure (3). It is assumed that the course of the disease may be more severe in elderly patients or those with previously known chronic diseases (4). Due to its high mortality rates, early diagnosis and prompt treatment are essential in terms of preventing the progression of the disease. It is, therefore, necessary to identify rapid, easily accessible, low-cost, and reliable parameters for predicting disease mortality. Several studies have recommended various laboratory parameters as predictive markers of the severity of COVID-19 (3-6). Also, chest CT imaging is a valuable instrument for diagnosing COVID-19 infection (7).

Studies have suggested that high levels of such inflammatory markers as C-reactive protein (CRP) are associated with disease severity in patients with COVID-19. Albumin, a negative acute phase reactant, has long been used as a marker of nutritional status. However, recent studies have shown that low albumin levels are associated with severe COVID-19 disease (6,8). The CRP/albumin ratio (CAR) has the potential to reflect the patient's inflammatory status. It has recently been described as a prognostic biomarker in several inflammatory conditions and disorders (6,9). Fibrinogen is a positive acute-phase reactant released from the liver that plays an active role in coagulation cascade and inflammation. Recent studies have shown that the fibrinogen-albumin ratio (FAR) is associated with poor clinical outcomes in diseases characterized by inflammation and thrombosis. Moreover, studies have also touched on the importance of FAR in predicting the severity of disease in COVID-19 (10,11).

We think that CAR and FAR calculated from albumin, CRP, and fibrinogen levels measured among routine laboratory parameters may constitute predictive markers of disease severity in patients with COVID-19. Based on that hypothesis, this study aimed to determine the prognostic value of CAR and FAR in assessing mortality in elderly COVID-19 patients and evaluate the correlations between these values and thoracic computed tomography (CT) findings.

MATERIAL and METHODS

Study Design: COVID-19 patients aged over 65 presenting to the emergency department of a tertiary training and research hospital between Oct 15, 2021, and Jan 15, 2022, were examined in this single-center, retrospective study. Approval was obtained before commencement from the local ethical committee (decision no. 2022/79).

Diagnosis of COVID-19 was confirmed with a positive PCR result from nasopharyngeal swab specimens. All patients aged over 65 with established COVID-19 disease and not meeting the exclusion criteria were enrolled in the study. Patients transferred to another institution, rejecting diagnosis and treatment, with deficient laboratory and tomographic images at the time of presentation to the emergency department, trauma patients, patients with known connective tissue disease, hematological disease, liver function disorder, or thyroid disease, terminal stage cancer patients, and patients who had received albumin transfusion prior to treatment were excluded.

Study Protocol: The demographic characteristics of the patients included in the study and laboratory data (CRP [mg/ll], fibrinogen [mg/dl], and albumin [g/dl]) at the time of presentation to the emergency department and in the subsequent first 24 hours were retrieved from the hospital's digital archive. Thoracic CT findings recorded at the initial presentation were evaluated. Thoracic CT examinations were based on involvement percentages, with cases with pulmonary parenchymal involvement of 0-50% being regarded as mild-moderate and those with involvement exceeding 50% as severe. Patients' lengths of hospital stay, transfer to the intensive care unit requirements, mortality, and discharges were also subjected to analysis.

Whether CAR and FAR obtained within 24 hours after presentation to the emergency department can determine mortality and the severity of lung parenchymal involvement in elderly patients diagnosed with COVID-19 were adopted as the study endpoints.

Statistical Analysis: All analyses were performed on Jamovi v.1.6 statistical software (The Jamovi Project (2021) Computer Software, version 1.6. Sydney, Australia). Categorical data were expressed in frequency (n) and percentage. Normally distributed continuous variable data were described as mean plus standard deviation (SD), and non-normally distributed data as median and interquartile range (IQR). Normality of distribution was evaluated using the Shapiro-Wilk test. Two-group comparisons were performed using Student's t-test or the Mann-Whitney U test, depending on whether or not the data were normally distributed. P values <0.05 were regarded as statistically significant. A receiver operating characteristic (ROC) curve

was drawn to determine cut-off points for mortality for CAR and FAR. Finally, sensitivity, specificity, likelihood ratios (+LR and -LR), positive predictive values, and negative predictive values were also calculated for CAR and FAR.

RESULTS

Two hundred fifty-two patients were included in the study, of whom 107 (42.5%) were men and 145 (57.5%) were women. The patients' median age was 77 (IQR 70-83). The mortality rate was 27.0% (n=68). Investigation of thoracic CT findings revealed severe pulmonary involvement in 15.1% of patients (n=38). Patients' demographic data and lengths of hospital stay under the study protocol is shown in **Table 1**.

Patients' laboratory values were calculated using the values at the time of initial presentation (**Table 2**). Examination of the laboratory parameters revealed that neutrophil (p=0.014), lymphocyte (p=0.001), and platelet (p=0.003) counts, CRP (p=0.001), Troponin T (p=0.001), D-dimer (p=0.002), fibrinogen (p=0.001), ferritin (p=0.001), CAR (p=0.001) and FAR (p=0.001) were statistically significant in differentiating patients with and without mortality. Comparison of laboratory findings and thoracic CT involvement identified WBC (p=0.005), neutrophil count (p=0.001), CRP (p=0.001), Troponin T (p=0.001), D-dimer (p=0.001), fibrinogen (p=0.001), ferritin (0.001), CAR (P=0.001), and FAR (P=0.001) values as significant in differentiating patients with severe involvement from those with mild-moderate involvement.

The relationship between CAR and FAR values and patients with and without mortality was also investigated. The relationship between CAR and FAR and patients with and without severe tomographic involvement was also assessed. The prognostic value of CAR and FAR is shown in Table 2. ROC analysis was performed, and the results are shown in **Figures 1A, 1B, 2A, and 2B**

CAR and FAR values were higher in the group with mortality than in the non-fatal group. CAR values in the groups with and without mortality were 4.6 (IQR 3.1-6.2) and 1.8 (IQR 0.5-3.7), respectively (p =0.001). FAR values in the groups with and without mortality were 16.6 (IQR 14.4-21.7) and 12.8 (IQR 10.3-15.4), respectively (p=0.001). Area under the curve (AUC) analysis for the prediction of mortality revealed a value of 0.767 for CAR (95% confidence interval: 0.705-0.829, p =0.001). The cut-off value for mortality of CAR was 3.0, exhibiting 76.5% sensitivity and 70.1% specificity. The AUC value for FAR was 0.731 (95% confidence interval; 0.659-0.802, p=0.001) and the cut-off value for FAR was 14.4, exhibiting 75.0% sensitivity and 69.0% specificity.

Patients' CAR and FAR values were also higher in the group with severe tomographic involvement than in the group without (p=0.001 for both). AUC analysis for predicting severe tomographic involvement revealed an AUC value for CAR of 0.786 (95% confidence interval; 0.714-0.859, p=0.001), and of 0.789 for FAR (95% confidence interval; 0.716-0.862, p=0.001). The detection of patients with severe tomographic involvement with cut-off values of 4.2 for CAR (73.7% sensitivity and 75.2% specificity) and 15.2 for FAR (84.2% sensitivity and 69.6% specificity) confirms these as a powerful predictive factor (**Table 3**).

Table 1 - The Patients' Demographic Data and Lengths of Hospital Stay

	According to Mortality		According to Tomographic Involvement	
	No Mortality (n=184)	Mortality (n=68)	Mild-Moderate Involvement (n=214)	Severe Involvement (n=38)
Gender				
Male	69 (27.4%)	38 (15.1%)	89 (35.4%)	18 (7.1%)
Female	115 (45.6%)	30 (11.9%)	125 (49.6%)	20 (7.9%)
Age (Year)	76 (IQR 69.8-82.3)	78.5 (IQR 71.0-83.3)	76 (IQR 70-83)	79 (IQR 73.5-82.8)
Length of Hospitalization (Days)	6 (IQR 0-11)	8 (IQR 3-14)	6 (IQR 0-11)	8.5 (IQR 3-18.8)

*IQR: Interquartile Range, **Note:** Normally distributed data are expressed as Mean ± SD (Min.-Max.), Abnormally distributed data as Median (IQR 25-75)*

Table 2 - Patients' Laboratory Indices

	According to Mortality			According to Tomographic Involvement		
	No Mortality (n=184)	Mortality (n=68)	P Value	Mild-Moderate Involvement (n=214)	Severe Involvement (n=38)	P Value
WBC (10^3/ul)	7.0 (IQR 5.4-9.0)	7.8 (IQR 4.6-11.3)	0.103	6.9 (IQR 5.3-8.7)	8.6 (IQR 6.6-11.0)	**0.005**
Neutrophil (10^3/ul)	5 (IQR 3.6-6.4)	5.9 (IQR 3.6-9.6)	**0.014**	4.9 (IQR 3.4-6.4)	6.6 (IQR 5.0-9.2)	**0.001**
Lymphocyte (10^3/ul)	1.1 (IQR 0.8-1.7)	0.8 (IQR 0.6-1.3)	**0.001**	1.1 (IQR 0.8-1.7)	0.9 (IQR 0.5-1.3)	0.094
Platelet (10^3/ul)	186 (IQR 142-245)	165 (IQR 118-212)	**0.003**	187 (IQR 143-247)	184 (138-227)	0.388
CRP (mg/l)	93.0 (IQR 24.8-157)	151 (IQR 96.9-195)	**0.001**	74 (IQR 20.9-129)	167 (IQR 117-210)	**0.001**
Troponin T (ng/l)	14.0 (IQR 5.9-35.7)	35.3 (IQR 17.9-111)	**0.001**	12.9 (IQR 5.2-29.5)	34.5 (IQR 19.0-95.3)	**0.001**
D-Dimer (µg/ml)	0.6 (IQR 0.3-1.1)	0.9 (IQR 0.5-2.0)	**0.002**	0.5 (IQR 0.3-0.9)	1.1 (IQR 0.5-3.2)	**0.001**
Fibrinogen (mg/dl)	490 (IQR 398-596)	560 (IQR 453-660)	**0.001**	478 (IQR 388-569)	577 (IQR 503-692)	**0.001**
Ferritin (ng/ml)	481 (IQR 270-1088)	928 (IQR 394-1570)	**0.001**	437 (IQR 256-927)	1026 (IQR 458-1560)	**0.001**
CAR	2.5 (IQR 0.7-4.7)	4.6 (IQR 3.1-6.2)	**0.001**	2.0 (IQR 0.5-4.1)	5.1 (IQR 3.7-7.1)	**0.001**
FAR	13.5 (IQR 11-17.6)	16.6 (IQR 14.4-21.7)	**0.001**	12.9 (IQR 10.5-16.3)	18.3 (IQR 15.6-22.1)	**0.001**

*WBC: White Blood Cell, **CRP:** C-reactive protein, **IQR:** Interquartile Range, **CAR:** C-reactive Protein Albumin Ratio, **FAR:** Fibrinogen Albumin Ratio*
***Note:** Normally distributed data are expressed as Mean ± SD (Min.-Max.), Abnormally distributed data as Median (IQR 25-75)*
***Note 2:** Student t-test was used for normally distributed data, Mann Whitney U Testi was used for abnormally distributed data.*

Table 3 - The Cutoff Value of CAR and FAR for Mortality and Severe Tomography Involvement

	CAR for Mortality	CAR for Severe Tomography Involvement	FAR for Mortality	FAR for Severe Tomography Involvement
AUC ± SD	0.767 ± 0.03	0.786 ± 0.04	0.731 ± 0.04	0.789 ±0.04
95% CI	0.705-0.829	0.714-0.859	0.659-0.802	0.716-0.862
Cut-off	3.0	4.2	14.4	15.2
Sensitivity (%)	76.5 (64.6-85.9)	73.7 (56.8-86.6)	75.0 (63.0-84.7)	84.2 (68.8-94.0)
Specificity (%)	70.1 (62.9-76.6)	75.2 (68.9-80.9)	69.0 (61.8-75.6)	69.6 (63.0-75.7)
+ LR	2.56	2.98	2.42	2.77
- LR	0.34	0.35	0.36	0.23
PPV (%)	48.6 (42.2-55.0)	34.6 (28.1-41.7)	47.2 (40.9-53.6)	33.0 (27.8-38.6)
NPV (%)	89.0 (83.9-92.6)	94.2 (90.4-96.5)	88.2 (83.0-91.9)	96.1 (92.2-98.1)
Accuracy (%)	71.83 (83.9-92.6)	75.0 (69.2-80.2)	70.6 (64.6-76.2)	71.8 (65.8-77.3)
P Value	0.001	0.001	0.001	0.001

*CAR: C-reactive Protein Albumin Ratio, **FAR:** Fibrinogen Albumin Ratio, **AUC:** Area Under the Curve, **SD:** Standard Deviation, **LR:** Likelihood Ratio,*
***PPV:** Positive Predictive Value, **NPV:** Negative Predictive Value, **CI:** Confidence Interval*

Figure 1A, 1B, 2A, 2B - ROC Curve and Cutoff Value of CAR and FAR at Mortality and Severe Tomography Involvement

1A- CRP Albumin Ratio for Mortality
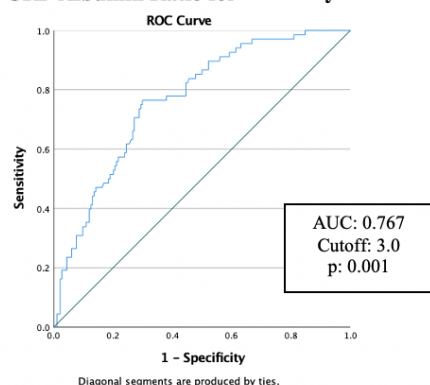
AUC: 0.767
Cutoff: 3.0
p: 0.001

1B- Fibrinogen Albumin Ratio for Mortality
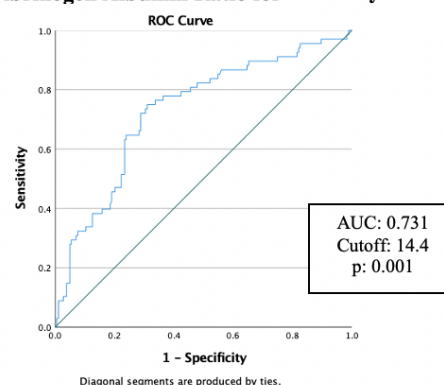
AUC: 0.731
Cutoff: 14.4
p: 0.001

2A- CRP Albumin Ratio for Severe Tomography Involvement

AUC: 0.786
Cutoff: 4.2
p: 0.001

2B- Fibrinogen Albumin Ratio for Severe Tomography Involvement

AUC: 0.789
Cutoff: 15.2
p: 0.001
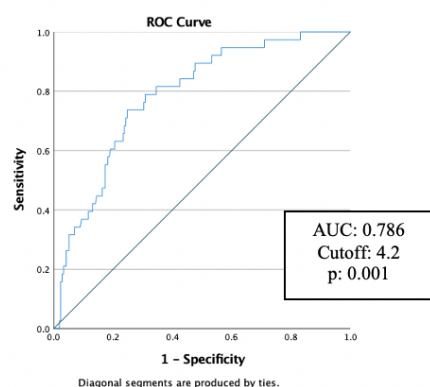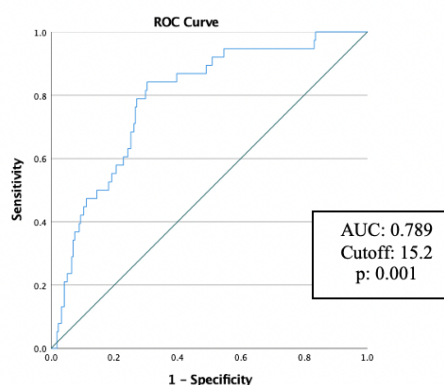
DISCUSSION

COVID-19 disease remains a significant public health problem with high in-hospital mortality (4). High levels of resources are set aside for combatting this disease in the provision of inpatient health services. Prudent use of healthcare resources, early intervention, and reliable markers for predicting disease severity and mortality and determining clinical outcomes are therefore needed (5).

The present study investigated the relationship between CAR and FAR and severe tomographic pulmonary involvement and mortality in patients with COVID-19. The results showed that CAR and FAR at laboratory examinations in the first 24 hours after presentation to the emergency department could be used as markers of disease severity (CAR p=0.001, FAR p=0.001). ROC analysis was applied to evaluate CAR and FAR in the prediction of disease severity. We determined AUC values of 0.786 for CAR and 0.789 for FAR. Our cut-off point for CAR at 73.7% sensitivity and 75.2% specificity was 4.2, and the cut-off point for FAR at 84.2% sensitivity and 69.6% specificity was 15.2. ROC analysis was also applied to determine the prognostic value of CAR and FAR in terms of mortality in COVID-19 infection. We decided on AUC values of 0.767 for CAR and 0.731 for FAR.

Our cut-off point for CAR, with 76.5% sensitivity and 70.1% specificity, was 3.0, and the cut-off point for FAR, with 75.0% sensitivity and 69.0% specificity, was 14.4. Kalyon et al. investigated the association between the neutrophil-lymphocyte ratio (NLR) and CAR and length of hospital stay in mortality in elderly patients with COVID-19. They reported that NLR and CAR calculated at the initial presentation were helpful in predicting the length of hospital stay and the risk of mortality in those patients (12). Li et al. investigated whether or not CAR values are helpful in terms of risk classification in COVID-19 patients and found that CAR may represent an excellent prognostic biomarker for risk classification in severe COVID-19 cases (13).

Several studies have mentioned the prognostic importance of CAR and FAR in terms of mortality and disease severity in patients with COVID-19. Kalabin et al. investigated the prognostic value of CAR in terms of disease severity in COVID-19 and found that it can be employed as a prognostic factor for disease severity (6). Torun et al. investigated the prognostic value of CAR, FAR, and NLR in determining the severity of disease in COVID-19 and found that these were capable of use for predicting severity. They calculated AUC values of 0.841 for CAR, 0.737 for FAR, and 0.802 for NLR at ROC analysis (14).

Ayrancı et al. investigated the potential for the use of NLR and CAR as markers of mortality in elderly COVID-19 patients and found that both were capable if used as prognostic factors for mortality (15). In another study, Küçükceran et al. investigated whether the D-Dimer-albumin ratio (DAR) and FAR constituted a mortality marker in COVID-19 and found that both were capable of use as a prognostic marker of mortality in COVID-19. Those authors calculated AUC values of 0.773 for DAR and 0.703 for FAR at ROC analysis (3). Various positive and negative biomarkers change with the resulting inflammatory response in infectious diseases. Markers that exhibit a positive change in the inflammatory response are known as positive acute-phase proteins and those that show a negative change as negative acute-phase proteins (16). Examples of positive acute-phase proteins include CRP and fibrinogen, while albumin is a negative acute-phase protein (17,18). Since, apart from the acute phase response, these markers may also increase and decrease due to secondary causes, we hypothesized that their combined use would yield more accurate results than using them alone.

Limitations: There are a number of limitations to this study. In particular, the research was small in scope and single-center, and retrospective in nature. Further studies with more significant numbers of patients and more centers are therefore needed. In addition, similarly to other retrospective studies, there was concern over the possibility of selection bias. However, in order to eliminate that concern, we included all elderly patients presenting to our emergency department during the study period and diagnosed with COVID-19. Further prospective studies are needed to confirm our findings.

CONCLUSION

Based on our findings, we think that CAR and FAR values may be helpful in the early differentiation of mortality and severity of pulmonary parenchymal involvement in elderly COVID-19 patients. We, therefore, think that high values for CAR and FAR, rapid, inexpensive, reproducible inflammatory biomarkers, will attract greater attention in early treatment plans.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

REFERENCES

1. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475-481.

2. World Health Organization (WHO). Coronavirus disease 2019 Situation Report 51 [Internet] 2020 Mar 11. Available from: https://www.who.int/docs/defaultsource/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf.

3. Küçükceran K, Ayranci MK, Girişgin AS, Koçak S. Predictive value of D-dimer/albumin ratio and fibrinogen/albumin ratio for in-hospital mortality in patients with COVID-19. Int J Clin Pract. 2021;75(7):e14263.

4. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 28;395(10229):1054-1062.

5. Henry BM, Aggarwal G, Wong J, Benoit S, Vikse J, Plebani M, et al. Lactate dehydrogenase levels predict coronavirus disease 2019 (COVID-19) severity and mortality: A pooled analysis. Am J Emerg Med. 2020;38(9):1722-1726.

6. Kalabin A, Mani VR, Valdivieso SC, Donaldson B. Does C reactive protein/Albumin ratio have prognostic value in patients with COVID-19. J Infect Dev Ctries. 2021;15(8):1086-1093.

7. Kant A, Kostakoğlu U, Atalar S, Erensoy Ş, Sevimli T, Ertunç B, at al. The relationship between diagnostic value of chest computed tomography imaging and symptom duration in COVID infection. Ann Thorac Med. 2020;15(3):151-154.

8. Aziz M, Fatima R, Lee-Smith W, Assaly R. The association of low serum albumin level with severe COVID-19: a systematic review and meta-analysis. Crit Care. 2020;24(1):255.

9. Oh TK, Song IA, Lee JH. Clinical usefulness of C-reactive protein to albumin ratio in predicting 30-day mortality in critically ill patients: A retrospective analysis. Sci Rep. 2018;8(1):14977.

10. Zhang Yi, Xiao G. Prognostic significance of the ratio of fibrinogen and albumin in human malignancies: a meta-analysis. Cancer Manag Res. 2019;11: 3381–3393.

11. Afşin A, Tibilli H, Hoşoğlu Y, Asoğlu R, Süsenbük A, Markirt S, et al. Fibrinogen-to-albumin ratio predicts mortality in COVID-19 patients admitted to the intensive care unit. Adv Respir Med. 2021 Dec 9.

12. Kalyon S, Gültop F, Şimşek F, Adaş M. Relationships of the neutrophil-lymphocyte and CRP-albumin ratios with the duration of hospitalization and fatality in geriatric patients with COVID-19. J Int Med Res. 2021;49(9):3000605211046112.

13. Li Y, Li H, Song C, Lu R, Zhao Y, Lin F, et al. Early Prediction of Disease Progression in Patients with Severe COVID-19 Using C-Reactive Protein to Albumin Ratio. Dis Markers. 2021;2021:6304189.

14. Torun A, Çakırca TD, Çakırca G, Portakal RD. The value of C-reactive protein/albumin, fibrinogen/albumin, and neutrophil/lymphocyte ratios in predicting the severity of CoVID-19. Rev Assoc Med Bras (1992). 2021;67(3):431-436.

15. Ayrancı MK, Küçükceran K, Dundar ZD. NLR and CRP to albumin ratio as a predictor of in-hospital mortality in the geriatric ED patients. Am J Emerg Med. 2021;44:50-55.

16. Gulhar R, Ashraf MA, Jialal I. Physiology, Acute Phase Reactants. 2021 Apr 30.

17. Fairclough E, Cairns E,Hamilton J,Kelly C. Evaluation of amodified early warning system for acute medical admissions and comparison with C-reactive protein/albümin ratio as a predictor of patient outcome. ClinMed (Lond). 2009;9:30–3.

18. Bi X, Su Z, Yan H, et al. Prediction of severe illness due to COVID-19 based on an analysis of initial Fibrinogen to Albumin Ratio and Platelet count. Platelets. 2020;31:674-679

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