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Coronavirus Pandemic

Ferritin / albumin ratio could be a new indicator of COVID-19 disease mortality

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Abstract

Introductions: Despite significant advances in the management of patients with COVID-19, there is a need for markers to guide treatment and predict disease severity. In this study, we aimed to evaluate the relationship of the ferritin/albumin (FAR) ratio with disease mortality.
Methodology: Acute Physiology and Chronic Health Assessment II scores and laboratory results of patients diagnosed with severe COVID-19 pneumonia were retrospectively analyzed. The patients were divided into two groups: survivors and non-survivors. Data for ferritin, albumin, and ferritin/albumin ratio among COVID-19 patients were analyzed and compared.
Results: The mean age was higher in non-survivors ($p = 0.778$, $p < 0.001$, respectively). The ferritin/albumin ratio was significantly higher in the non-survival group ($p < 0.05$). Taking the cut-off value of the ferritin/albumin ratio of 128.71 in the ROC analysis, it predicted the critical clinical status of COVID-19 with 88.4% sensitivity and 88.4% specificity.
Conclusions: ferritin/albumin ratio is a practical, inexpensive, and easily accessible test that can be used routinely. In our study, the ferritin/albumin ratio has been identified as a potential parameter in determining the mortality of critically ill COVID-19 patients treated in intensive care.

Key words: Albumin; COVID-19; ferritin/albumin ratio; ferritin; mortality; predictive.

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Introduction

SARS-CoV-2, which has caused millions of deaths worldwide and is called the new coronavirus, emerged in the city of Wuhan, China in December 2019. A pandemic was declared by WHO in 2020 [1]. Coronavirus disease 19 (COVID 19) caused by virus is an infectious disease with a clinical course ranging from asymptomatic to life-threatening acute respiratory distress syndrome (ARDS) [2]. Approximately 80% of the patients have a mild-moderate disease, 15% have a severe form requiring admission to the intensive care unit, and 5% have a form that can result in death [3].

Early detection of cases is very important in terms of mortality and morbidity because the virus spreads rapidly in a concise time and can create clinical severe conditions. Although many theories have been proposed to explain the physiopathology of COVID-19 disease, the most accepted one is the cytokine storm caused by the host immune system against the viruses [4]. Cytokine storm is a reaction that results in the uncontrolled overproduction of cytokines. As a result of this excessive uncontrolled production, ARDS may develop in patients [5].

Since it is known that hyperinflammation is the cause of the poor prognosis in COVID-19 disease, biochemical markers indicating the inflammation status and their combinations may be good alternatives for predictive and prognostic indicators [6]. Many studies evaluated laboratory parameters are lymphocyte, thrombocyte, albumin, C-reactive protein (CRP), fibrinogen, procalcitonin, D-dimer, interleukin-6, and inflammatory indices derived from them [7]. Studies show that the CRP/albumin ratio (CAR) may be a prognostic marker in predicting morbidity and mortality in critically ill patients [8]. However, there are also studies stating the opposite [9].

In this study, we aimed to investigate the role of the ferritin/albumin (FAR) ratio in predicting 28-day mortality in patients treated for severe COVID-19 pneumonia in an intensive care unit in a tertiary hospital.

Methodology

This study was designed retrospectively in a tertiary hospital. The ethics committee of Kastamonu Training and Research Hospital approved this study, which was

written according to the principles of the Declaration of Helsinki (1964) (ethical consent: 12.01.2022, 2020-KAEK-143-147).

Medical records of patients with severe COVID-19 pneumonia admitted to the intensive care unit between January 2020 and December 2021 were retrospectively reviewed. The patients had positive polymerase chain reaction tests (PCR), which the hospital laboratory confirmed. Patients with known collagen tissue disease, malignancy, inflammatory bowel disease history, and/or those receiving medical treatment, for this reason, hemoglobin value < 10 g/dL, chronic renal failure, cirrhosis, malnutrition, and pregnancy, or who did not have a laboratory evaluation at the time of admission to the hospital were excluded from the study. Patients whose laboratory data were evaluated before starting treatment (such as steroids, antiviral, and antibiotics) were included in the study.

After exclusion criteria were met, 611 patients were divided into two groups according to 28-day mortality. The laboratory values and Acute Physiology and Chronic Health Evaluation II scores of the groups during the intensive care hospitalization were compared. Serum ferritin and albumin values and ferritin/albumin ratio were calculated in the intensive care unit admission of the groups, and the ferritin/albumin ratio was compared between the two groups.

Statistical Analysis

All statistical analyzes were performed using SPSS 26 (SPSS Inc, Chicago, USA). The assumption of normality of all continuous variables was checked by Q-Q plots, histograms, and Kolmogorov-Smirnov tests. Data were described as median (1st quartile-3rd quartile) for non-normal continuous variables and frequency (percentage) for categorical variables. Mann-Whitney U tests were performed for non-normal distributed continuous variables. Pearson's chi-square test was used to determine the relationship in proportions of categorical variables between two groups. The optimal cut-off values of continuous ferritin, albumin, and ferritin/albumin ratio (FAR) were calculated by applying the Receiver Operating Curve

Table 1. Baseline characteristics and laboratory measurements of patients regarding mortality.

Variables	Total n = 611, Median (Q1-Q3)	Non-survival Group, n = 447 (73.2%), Median (Q1-Q3)	Survival Group, n = 164 (26.8%), Median (Q1-Q3)	*p*
Age (years)	72 (63.0 – 81.0)	73.0 (66.0-82.0)	68.5 (59.0-76.0)	**< 0.001**
Gender				
Female	231 (37.8%)	171 (38.3%)	60 (36.6%)	0.706*
Male	380 (62.2%)	276 (61.7%)	90 (63.4%)	
Comorbid	448 (73.3%)	327 (73.2%)	121 (73.8%)	0.877*
≥ 2 Comorbid	215 (35.2%)	154 (34.5%)	61 (37.2%)	0.529*
Diabetes mellitus	138 (22.6%)	103 (23.0%)	35 (21.5%)	0.682*
Hypertension	243 (39.8%)	174 (38.9%)	69 (57.9%)	0.481*
Renal diseases	70 (11.5%)	54 (12.1%)	16 (9.8%)	0.424*
Cardiovascular diseases	186 (30.4%)	138 (30.9%)	48 (29.3%)	0.703*
Respiratory diseases	87 (14.2)	65 (14.5%)	22 (13.4%)	0.724*
Ferritin (ng/mL)	611.0 (346.0-1162.0)	905.0 (551.0-1267.0)	174.0 (103.0-374.0)	**< 0.001**
Albumin (g/dL)	3.17 (2.84-3.44)	3.1 (2.8-3.36)	3.4 (3.1-3.8)	**< 0.001**
Procalcitonin ng/mL	0.43 (0.12-1.51)	4.5 (0.14-1.5)	0.4 (0.1-1.9)	0.313
LDH (U/L)	447.0 (325.0-606.25)	485.0 (354.75-677.5)	357.5 (243.5-461.75)	**< 0.001**
CRP (mg/L)	125.1 (74.0-189.0)	141.8 (87.0-199.0)	80.8 (45.05-132.02)	**< 0.001**
CRP/Albumin	38.75 (22.75-62.25)	45.41 (28.8-66.31)	23.38 (12.57-38.40)	**< 0.001**
Ferritin/Albumin	195.88 (102.63-380.0)	295.3 (177.63-429.08)	50.57 (31.72-103.21)	**< 0.001**
Hemoglobin (g/dL)	12.90 (11.7-14.1)	12.8 (11.7-14.1)	13.2 (11.8-14.2)	0.169
Leucocyte (10^3/μL)	9.86 (7.58-12.42)	10.2 (7.6-12.8)	9.33 (7.41-11.77)	**0.041**
Platelet (10^3/μL)	207.0 (154.0-263.0)	201.0 (152.0-255.0)	216.5 (167.25-280.0)	**0.015**
Neutrophil (10^3/μL)	7.8 (5.7-10.77)	8.37 (5.9-11.01)	7.1 (5.51-9.8)	**0.001**
Lymphocyte (10^3/μL)	0.7 (0.05-1.10)	0.7 (0.49-1.05)	0.74 (0.54-1.2)	0.075
Monocyte (10^3/μL)	0.47 (0.28-0.77)	0.42 (0.26-0.7)	0.6 (0.32-0.9)	**< 0.001**
NLR	10.93 (6.14-19.13)	11.73 (0.65-20.16)	8.69 (5.17-16.01)	**0.002**
PLR	289.23 (171.33-431.34)	290.9 (174.73-431.34)	286.88 (159.29-430.89)	0.777
MLR	0.62 (0.36-1.07)	0.6 (0.35-1.03)	0.71 (0.39-1.13)	**0.049**
D-Dimer (mg/L)	1.7 (0.09-3.5)	1.87 (0.01-3.8)	1.29 (0.7-3.0)	**< 0.001**
APACHE II	22.0 (18.0-26.0)	23.0 (20.0-27.0)	18.5 (15.0-22.0)	**< 0.001**

*Pearson Chi-Square test; CRP: c-reactive protein; NLR: Neutrophil-lymphocyte Ratio; PLR: Platelet-lymphocyte Ratio; MLR: Monocyte-lymphocyte Ratio; APACHE: Acute Physiology and Chronic Health Evaluation; LDH: Lactate Dehydrogenase.

(ROC) analysis. The association of independent parameters with survival was determined by binary logistic regression analysis. Binary logistic regression with a stepwise method was used to determine the effects of age, LDH, neutrophil, monocyte, APACHE II, and FAR $p < 0.05$ was considered as statistically significant.

Results

A total of 611 patients (447, 73.2% non-survival and 164, 26.8% survival) were included in this study (median age, 72 years [interquartile range, 63-81; range, 23-97 years]; 37.8% females). A statistical difference was found between the groups in terms of age, ferritin, albumin, LDH, CRP, CRP/albumin, ferritin/albumin ratio ($p < 0.001$), leucocyte ($p = 0.041$), platelet ($p = 0.015$), neutrophil, monocyte ($p < 0.001$), NLR ($p = 0.002$), MLR ($p = 0.049$), D-dimer, APACHE II ($p < 0.001$) (Table 1).

Binary logistic regression analysis with a stepwise method was performed to ascertain the prognostic factors of mortality in patients. The binary logistic regression model was statistically significant χ^2 (6) = 528.571, $p < 0.001$. The model explained 84.3% (Nagelkerke R^2) of the variance in mortality and correctly classified 73.1% of cases. According to the regression analysis, mortality was associated with LDH (OR 1.002, CI 1.001-1.004, $p = 0.006$), neutrophil (OR 1.101, CI 1.021-1.186, $p = 0.012$), monocyte (OR 0.124, CI 0.42-0.364, $p < 0.001$), APACHE II (OR 1.276, CI 1.173-1.388, $p < 0.001$), FAR (OR 1.043, CI 1.033-1.054, $p < 0.001$) and age (OR 1.049, CI 1.018-1.082, $p = 0.002$) (Table 2). Increasing FAR and APACHE II was associated with an increased likelihood of mortality. However, increasing monocyte was related to decreasing the likelihood of mortality.

ROC analysis was used to determine optimal cut-off values of ferritin, albumin, and FAR. In Table 3, the areas under the curve (AUC) of ferritin, albumin, and FAR were 0.951, 0.295, and 0.958, respectively. Diagnostic accuracy was excellent for ferritin and FAR. The variables were potential predictive biomarkers of mortality. The optimal cut-off values of ferritin, albumin, and FAR were 423.9, 3.225, and 128.71, respectively. Sensitivity and specificity were 86.6% and 86.6% for ferritin, 35.1% and 35.4% for albumin, and 88.4% and 88.4% for FAR (Table 4). Any value of Youden's index above 50% indicated good diagnostic accuracy. Youden's index was 0.732 for ferritin and 0.768 for FAR. Youden's index of albumin was -0.295, so it had poor diagnostic accuracy. Figure 1 indicates ROC curves of ferritin, albumin, and FAR.

Table 2. Logistic regression for prognostic factors.

Variables	B	SE	p	Exp(β)	95% CI for Exp(β)	
					Lower	Upper
Constant	-13.680	1.832	< 0.001	< 0.001		
LDH (U/L)	0.002	0.001	0.006	1.002	1.001	1.004
Neutrophil (10^3/μL)	0.096	0.038	0.012	1.101	1.021	1.186
Monocyte (10^3/μL)	-2.086	0.549	< 0.001	0.124	0.042	0.364
APACHE II	0.244	0.043	< 0.001	1.276	1.173	1.388
FAR	0.043	0.005	< 0.001	1.043	1.033	1.054
Age (years)	0.048	0.016	0.002	1.049	1.018	1.082

Nagelkerke R Square 0.843; LDH: Lactate Dehydrogenase; FAR: Ferritin albümin ratio.

Table 3. Areas under the curve (AUC) of ferritin, albumin, and ferritin/albumin variables.

Variables	Area	SE	Asymptotic Sig.	Asymptotic 95% CI	
				Lower	Upper
Ferritin (ng/mL)	0.951	0.008	< 0.001	0.936	0.966
Albumin (g/dL)	0.295	0.024	< 0.001	0.248	0.342
Ferritin/Albumin	0.958	0.007	< 0.001	0.945	0.972

Table 4. Cut-off, sensitivity, specificity, and Youden index of ferritin, albumin, and ferritin/albumin variables.

Variables	Cut-off	Sensitivity (%)	Specificity (%)	Youden's Index
Ferritin (ng/mL)	423.9	86.6	**86.6**	0.732
Albumin (g/dL)	3.225	35.1	**35.4**	-0.295
Ferritin/Albumin	128.71	88.4	**88.4**	0.768

Discussion

According to our study, the ferritin/albumin ratio can be considered a predictive index in patients with COVID-19 pneumonia in intensive care.

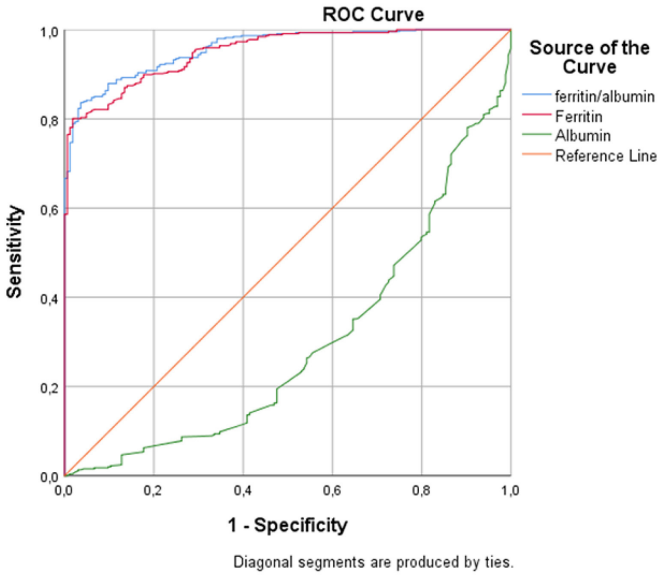
Although Covid 19 disease targets the lung, it is a multisystemic infection involving hematological and immunological systems [10,11]. The role of the systemic inflammatory response is gaining more and more importance in the pathophysiology of COVID-19 infection. In this context, many studies have focused on the predictive value of various inflammatory parameters such as Interleukin-6, D-dimer, neutrophil/lymphocyte ratio, fibrinogen, and procalcitonin in determining the severity of COVID-19 disease [12-14].

Since the hematologic system response affects the prognosis of the disease, it is natural to have changes in routine blood tests. Therefore, some blood tests can determine the severity of the disease [11]. Regarding ferritin, Wu *et al.* showed that higher serum ferritin was associated with the development of ARDS [15]. Zhou *et al.* supported the association between higher serum ferritin levels and death [16]. Regarding albumin, Zeng *et al.* reported a decreased value of albumin in patients with COVID-19 [17]. In a meta-analysis, it was reported that hypoalbuminemia is associated with prognosis [18]. However, we could not find any study evaluating the ferritin/albumin ratio in COVID-19 patients in the literature. Our study showed that FAR can predict disease severity and is superior to CAR, NLR, MLR, D-Dimer, ferritin, and albumin in this regard. The reason for this was thought to be that the ferritin/albumin ratio has the potential to represent both the inflammatory response and the nutritional status of the host at the same time. This can be beneficial both in terms of early application of treatments that can improve prognosis and reduce hospital costs.

The literature shows that changes in iron metabolism can be used to predict mortality in patients admitted to intensive care units. ferritin is an acute phase reactant that rises with inflammation [19]. Many publications show that high ferritin levels along with proinflammatory markers (such as CRP and IL-6) are associated with worse outcomes in COVID-19 disease and may even help predict these outcomes [20-23]. Similarly, in our study, we found that ferritin was significantly associated with mortality.

Albumin is a negative acute-phase reactant, and it reflects the nutritional status of the patient and decreases in cases such as burns, surgery, and inflammation [24]. Studies have reported that hypoalbuminemia is a common condition in patients

Figure 1. ROC curve of ferritin, albumin, and ferritin/albumin variables.



with COVID-19 and is an independent predictive factor for mortality [25]. In our study, hypoalbuminemia was similarly associated with mortality, regardless of other known indicators such as lymphocyte count or comorbidities.

Although there are studies regarding the relationship between ferritin and albumin, both for covid patients and for many non-covid diseases, we could not find a study evaluating the ferritin/albumin ratio. However, studies have emphasized that high ferritin and low albumin levels can be important indicators of severity and mortality in COVID-19 patients as well as in inflammatory diseases. Therefore, we expect an increase in ferritin value with inflammation and a decrease in albumin value with inflammation. In light of this information, we think that the FAR ratio may be more significant than the ferritin and albumin values alone in inflammation. In our study, we saw that albumin, ferritin, and FAR were able to distinguish patients with severe COVID-19 pneumonia, but we found that FAR was superior to both ferritin and albumin. Therefore, we think that ferritin/albumin ratio can be a predictive index in determining disease severity and mortality in patients with severe COVID-19 pneumonia to prevent unnecessary or inappropriate use of health resources.

The main limitation of our study is its retrospective design and that it was conducted in a single center. Further prospective studies are needed to confirm our findings.

Conclusions

In conclusion, ferritin/albumin ratios are practical, inexpensive, and easily accessible tests that can be used routinely. and our study showed that; the ferritin/albumin ratio could be a predictor for the severity and mortality of critically ill COVID-19 patients.

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Authors' contributions

Study concept and design: Öztürk Taşkın; Acquisition of data: Öztürk Taşkın, Ayşe Yılmaz; Analysis and interpretation of data: Öztürk Taşkın, Funda Çatan İnan; Drafting of the manuscript: Öztürk Taşkın, Ufuk Demir; Critical revision of the manuscript for important intellectual content: Öztürk Taşkın, Veysel Garani Soylu; Statistical analysis: Funda Çatan İnan; Study supervision: Öztürk Taşkın.

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