Research Article / Araştırma Makalesi
doi: 10.18678/dtfd.1108086

Duzce Med J, 2022;24(2):176-181
Düzce Tıp Fak Derg, 2022;24(2):176-181

The Value of Fibrinogen/Albumin Ratio on Prognosis of COVID-19 Patients

Fibrinojen/Albümin Oranının COVID-19 Hastalarının Prognozundaki Değeri

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Received / Geliş Tarihi : 23.04.2022
Accepted / Kabul Tarihi : 06.08.2022
Available Online / Çevrimiçi Yayın Tarihi : 15.08.2022

ABSTRACT

Aim: Fibrinogen and albumin are proteins that play a role in inflammation. In this study, it was aimed to investigate the role of fibrinogen, albumin, and fibrinogen/albumin ratio (FAR) levels as markers of disease severity and prognosis in coronavirus disease 2019 (COVID-19) patients.

Material and Methods: Seventy-one patients aged between 19 and 84 years diagnosed with COVID-19 who were hospitalized in Sakarya University Training and Research Hospital, Neurology Department between March and May 2020 were analyzed retrospectively. Fibrinogen, albumin, FAR, D-dimer, platelet, and C-reactive protein (CRP) levels of the patients were compared according to the length of hospitalization duration, survival, and clinical severity of COVID-19.

Results: Twenty-eight (%39.4) of the patients were male and 43 (%60.6) were female, and the mean age was 55.7±20.7 years. There was a significant difference between the groups of COVID-19 clinical severity in terms of age, fibrinogen, albumin, FAR, D-dimer, and CRP values (all p values were <0.001). Also, significantly higher fibrinogen, FAR, D-dimer, and CRP values were found in patients hospitalized longer, while the albumin level was lower in these patients (all p values were <0.001). FAR values were higher and albumin values were lower in non-surviving patients compared to surviving patients (p=0.025 and p<0.001, respectively).

Conclusion: FAR levels may be useful in predicting mortality risk in COVID-19 patients. In addition, it may be helpful and useful in determining the prognosis since it has higher levels as the severity of the disease and the length of hospital stay increase.

Keywords: Fibrinogen; albumin; fibrinogen/albumin ratio; COVID-19.

ÖZ

Amaç: Fibrinojen ve albümin inflamasyonda rol oynayabilen proteinlerdendir. Bu çalışmada, koronavirüs hastalığı 2019 (coronavirus disease 2019, COVID-19) hastalarında fibrinojen, albümin ve fibrinojen/albümin oranı (FAR) düzeylerinin hastalık şiddeti ve prognoz belirteçleri olarak rolünün araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Çalışmada Mart ve Mayıs 2020 tarihleri arasında COVID-19 tanısı ile Sakarya Eğitim ve Araştırma Hastanesi Nöroloji Kliniği'ne yatırılan 19 ve 84 yaş arasındaki 71 hasta geriye dönük olarak analiz edildi. Hastaların fibrinojen, albümin, FAR, D-dimer, trombosit ve C-reaktif protein (CRP) düzeyleri, hastanede kalış süresinin uzunluğu, hayatta kalma ve COVID-19 klinik şiddetine göre karşılaştırıldı.

Bulgular: Hastaların 28'i (%39,4) erkek ve 43'ü (%60,6) kadın olup yaş ortalaması 55,7±20,7 yıl idi. COVID-19 klinik şiddetine göre ayrılmış olan gruplar arasında yaş, fibrinojen, albümin, FAR, D-dimer ve CRP değerleri açısından anlamlı bir farklılık vardı (tüm p değerleri <0,001). Ayrıca, hastanede daha uzun süre yatan hastalarda fibrinojen, FAR, D-dimer ve CRP değerleri anlamlı olarak daha yüksek bulunurken, bu hastalarda albümin düzeyleri daha düşüktü (tüm p değerleri <0,001). Hayatta kalamayan hastalarda yaşayan hastalara göre FAR değerleri daha yüksek ve albümin değerleri daha düşüktü (sırasıyla, p=0.025 ve p<0.001).

Sonuç: FAR seviyeleri, COVID-19 hastalarında ölüm riskini tahmin etmede faydalı olabilir. Ayrıca hastalığın şiddeti ve hastanede kalış süresi arttıkça daha yüksek seviyelere sahip olduğu için prognozu belirlemede de yardımcı ve faydalı olabilir.

Anahtar kelimeler: Fibrinojen; albümin; fibrinojen/albümin oranı; COVID-19.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) outbreak was categorized as a pandemic by the World Health Organization (WHO) on March 11, 2020. Since then, COVID-19 has caused ~6.4 M deaths worldwide. Among the clinical conditions caused by COVID-19, respiratory disorders and sepsis are the main ones responsible for the severity of COVID-19 (1,2).

COVID-19 patients may progress to the pro-inflammatory process. This pro-inflammatory condition has been related to coagulopathy (3). The causes of organ failures in patients with severe COVID-19 have been investigated before, where previous studies focused on systemic vasculitis and cytokine-mediated coagulation disorders (4). COVID-19 patients show elevated fibrinogen and D-dimer levels as a result of hypercoagulation. This coagulation disorder is usually detected in COVID-19 patients who require hospitalization. Therefore, disease severity is highly related to hypercoagulation (5).

D-dimer, a soluble degradation product of fibrin, results from the systematic degradation of vascular thrombus through the fibrinolytic mechanism. Mortality of COVID-19 highly correlates with the increase in the D-dimer value (3,5,6). On the other hand, fibrinogen, the substrate of thrombin in the coagulation cascade, is an acute phase reactant that increases in the inflammatory process (7). Albumin is a negative acute-phase reactant, and its levels decrease in acute infection. Decreased albumin levels have been related to high mortality in hospitalized COVID-19 patients (8). In addition, the fibrinogen to albumin ratio (FAR) was found to be more sensitive and specific as a predictor of progression of hypercoagulation compared to fibrinogen levels alone (9). COVID-19 patients are difficult to manage due to their rapid deterioration and high mortality rate. Furthermore, prolonged symptoms after COVID-19 infection negatively affect patients' quality of life. Thus, there is a critical need for useful test parameters that can predict clinical prognosis in these patients. Having early information about the prognosis of patients can be a guide for patient management and the selection of adjunctive treatments.

In this study, we aimed to investigate the role of FAR as a predictive mediator on the prognosis of COVID-19 patients. In addition, we examined the D-dimer, platelet, and C-reactive protein (CRP) values of COVID-19 patients.

MATERIAL AND METHODS

A hundred and twenty COVID-19 patients hospitalized for isolation in Sakarya University Training and Research Hospital, Neurology Department between March and May 2020 were evaluated in the study. 71 patients aged between 19 and 84 years who met the criteria were included. The information of the patients recorded in the electronic system of our hospital was reviewed retrospectively.

Forty-nine patients who were transferred to another center, or who did not have serum fibrinogen and albumin levels in the file were excluded from the study. Other exclusion criteria were cancer, severe kidney or renal failure, hematological diseases, and use of drugs such as antiaggregant, oral contraceptives, steroids before admission, and human albumin therapy treatments that may cause hematological side effects.

Gender, age, symptoms of COVID-19, examination findings, serum fibrinogen, albumin, D-dimer, platelet, and CRP levels were measured at the time of their first hospitalization, and imaging findings were recorded in the patients' forms. Blood tests were taken within the first 24 hours after the patients were admitted to the hospital.

Patients were divided into four subgroups according to Chinese management guidelines for COVID-19 (version 6.0): 1-Mild: Patients with mild symptoms and have no pneumonia; 2-Typical: Fever or respiratory symptoms and patients have pneumonia on imaging; 3-Severe: Having one of the three conditions: respiratory distress, respiratory rate ≥30 beats/min; oxygen saturation ≤%93 at rest; arterial blood oxygen partial pressure/oxygen concentration ≤300 mm Hg; 4-Critical: Having one of the three conditions: respiratory failure, shock incidence and requiring mechanical ventilation; admission to intensive care unit (ICU) with other organ function failure (5,10).

Each group was compared in terms of fibrinogen, albumin, FAR, D-dimer, platelet, CRP values, and clinical severity of COVID-19.

Statistical Analysis

IBM SPSS v.23 statistical software program was used for statistical analysis. Compliance of the data with normality and variance homogeneity was examined with the Kolmogorov-Smirnov and Levene tests. The student's t and One-Way ANOVA (post hoc LSD) tests were used for data that meet the criteria of normality and homogeneity, while Mann-Whitney U and Kruskal-Wallis (post hoc Dunn) tests were used for the data which not meet. The mean and standard deviation values or median, interquartile range, and minimum-maximum values were used for numerical data, as appropriate. Chi-square or Fisher's exact test was used to compare categorical data. All reported statistical tests were two-sided, and the level of statistical significance was considered as $p<0.05$.

RESULTS

A total of 71 patients, 28 (%39.4) male, and 43 (%60.6) female were included in the study. The mean age of the patients was 55.7±20.7 years. The mean ages of males and females were 56.1±21.2 years and 55.4±20.7 years, respectively. There was no significant difference between the genders (p=0.883). 38 (%53.5) of the patients had at least one chronic disease. Hypertension (HT) was the most common chronic disease in the patient group (Table 1).

The median hospitalization duration of all patients was 6 (range, 1-28) days. 36 (%50.7) patients' hospitalization duration was less than a week (15 male, 21 female), while 35 (%49.3) patients' hospitalization duration was more than a week (13 male, 22 female). There was no significant difference between the genders in terms of hospitalization for less or more than one week (p=0.697).

Fibrinogen, FAR, D-dimer, and CRP values were significantly higher in patients with hospitalization duration >1 week than in those hospitalized for a short period (less than a week), and albumin values were significantly lower (all p values were <0.001, Table 2).

We found that patients with chronic disease had higher fibrinogen, FAR, D-dimer, and CRP values, and significantly lower albumin values than patients without the chronic disease (all p values were <0.001, Table 3).

Of the 71 patients, 66 (93%) were surviving, and 5 (7%) died. FAR (p=0.025) and D-dimer (p<0.001) values were higher while albumin (p<0.001) and platelet (p=0.035) values were lower in non-surviving patients compared to surviving patients (Table 4).

Patients were divided into 4 groups according to the clinical severity of the COVID-19. Groups were compared in terms of age, fibrinogen, albumin, FAR, D-dimer, platelet, and CRP values (Table 5). There was a significant difference between the groups in terms of age (p<0.001). According to the post hoc test results severe and critical patients were significantly older than mild (both p values were <0.001) and typical (p=0.013 and p=0.006, respectively) patients. Also, the typical group was older than the mild group (p<0.001), while there was no significant difference between the severe and critical groups (p=0.392).

Fibrinogen values were significantly different between the groups (p<0.001). Post hoc test results revealed that fibrinogen values were higher in severe and critical groups than in mild (p<0.001 and p=0.004, respectively) and typical (p=0.002 and p=0.038, respectively) groups. There was no significant difference between the mild and typical (p=0.111), and also severe and critical (p=0.734) groups.

Albumin values were significantly different between the groups (p<0.001). According to the post hoc test results albumin values were significantly lower in critical patients than in all other severe (p=0.024), typical (p=0.002), and mild (p<0.001) groups. While no statistically significant difference was found between the severe and typical groups (p=0.154), albumin values in both of these groups were found as statistically significantly lower than in the mild group (p<0.001 and p=0.001, respectively).

Table 1. Chronic diseases of patients by gender, n (%)

Chronic diseases	Male (n=28)	Female (n=43)	p	Total (n=71)
Hypertension	10 (35.7)	17 (39.5)	0.746	27 (38.0)
Diabetes mellitus	6 (21.4)	4 (9.3)	0.177	10 (14.1)
Coroner artery disease	1 (3.6)	1 (2.3)	0.999	2 (2.8)
Asthma	0 (0.0)	3 (7.0)	0.273	3 (4.2)
Cerebrovascular diseases	1 (3.6)	3 (7.0)	0.649	4 (5.6)

Table 2. Comparison of the patients with hospitalization duration <1 and >1 week

	<1 week (n=36)	>1 week (n=35)	p
Fibrinogen (mg/dL)	316 (78) [180-647]	368 (80) [109-819]	**<0.001**
Albumin (g/L)	41.2 (4.7) [30.0-47.0]	32.3 (12.6) [19.9-46.7]	**<0.001**
FAR	7.42 (2.81) [3.83-20.47]	11.20 (4.04) [4.88-29.15]	**<0.001**
D-dimer (µg FEU/L)	352 (479) [34-6300]	1790 (2909) [124-29400]	**<0.001**
Platelet (K/uL)	218 (76) [124-389]	206 (104) [53-471]	0.084
CRP (mg/L)	3 (2) [3-176]	15.7 (71.7) [1.4-459]	**<0.001**

FAR: fibrinogen/albumin ratio, CRP: C-reactive protein

Table 3. Comparison of the patients with and without chronic disease

	Chronic Disease (+) (n=38)	Chronic disease (-) (n=33)	p
Fibrinogen (mg/dL)	364 (93) [109-819]	308 (89) [180-483]	**<0.001**
Albumin (g/L)	31.8 (11.4) [19.9-43.8]	42.5 (3.7) [25.4-47.0]	**<0.001**
FAR	10.88 (4.33) [5.45-29.15]	7.33 (2.55) [3.83-19.02]	**<0.001**
D-dimer (µg FEU/L)	1515 (1927) [73-29400]	340 (529) [34-12200]	**<0.001**
Platelet (K/uL)	223 (104) [53-471]	206 (87) [124-335]	0.699
CRP (mg/L)	11.3 (42.1) [1.4-459]	3 (2) [3-196]	**<0.001**

FAR: fibrinogen/albumin ratio, CRP: C-reactive protein

Table 4. Comparison of the surviving and non-surviving patients

	Surviving (n=66)	Non-surviving (n=5)	p
Fibrinogen (mg/dL)	329 (74) [180-647]	483 (477) [109-819]	0.086
Albumin (g/L)	40.6 (10.4) [19.9-47.0]	25.4 (6.5) [20.0-28.3]	**<0.001**
FAR	8.75 (3.92) [3.83-20.47]	19.02 (18.40) [5.45-29.15]	**0.025**
D-dimer (µg FEU/L)	573 (1384) [34-29400]	5670 (8420) [2020-12200]	**<0.001**
Platelet (K/uL)	217 (87) [107-471]	159 (154) [53-279]	**0.035**
CRP (mg/L)	3.5 (12.8) [3-288]	74.7 (269.9) [1.4-459]	0.082

FAR: fibrinogen/albumin ratio, CRP: C-reactive protein

Table 5. Comparison of the patients in terms of COVID-19 clinical severity

	Mild (n=11)	Typical (n=32)	Severe (n=23)	Critical (n=5)	p
Age (years)	27.0±5.5[a]	53.9±18.9[b]	66.9±13.3[c]	78.8±3.9[c]	**<0.001**
Fibrinogen (mg/dL)	289 (83) [180-348][a]	318 (69) [207-647][a]	373 (80) [185-472][b]	483 (477) [109-819][b]	**<0.001**
Albumin (g/L)	43.8 (2.1) [41.0-47.0][a]	40.4 (7.7) [19.9-46.1][b]	35.8 (10.0) [23.3-46.7][b]	25.4 (6.5) [20.0-28.3][c]	**<0.001**
FAR	6.39 (2.01) [3.83-7.98][a]	8.27 (2.69) [4.88-20.47][b]	11.20 (3.69) [4.63-17.59][c]	19.02 (18.40) [5.45-29.15][c]	**<0.001**
D-dimer (μg FEU/L)	93 (43) [34-6300][a]	537 (866) [73-4140][b]	1530 (1583) [92-29400][c]	5670 (8420) [2020-12200][c]	**<0.001**
Platelet (K/uL)	214 (64) [156-302]	207 (90) [107-389]	230 (96) [125-471]	159 (154) [53-279]	0.098
CRP (mg/L)	3 (0) [3-29.7][a]	3.1 (4.9) [3-231][b]	13.7 (48.4) [3-288][c]	74.7 (269.9) [1.4-459][c]	**0.001**

FAR: fibrinogen/albumin ratio, CRP: C-reactive protein, [a,b,c]: different superscript letters denote significant differences between groups

There was a significant difference between the groups in terms of FAR (p<0.001). According to the post hoc test results FAR in severe and critical patients were higher than in mild (both p values were <0.001) and typical (p=0.005 and p=0.017, respectively) patients. Also, the typical group had higher values than the mild group (p=0.015), while there was no significant difference between the severe and critical groups (p=0.445).

D-dimer values were statistically significantly different between the groups (p<0.001). Post hoc test results revealed that D-dimer values in severe and critical patients were significantly higher than in mild (both p values were <0.001) and typical (p=0.018 and p=0.001, respectively) patients. Also, the D-dimer values in the typical group were significantly higher than in the mild group (p=0.012), while there was no statistically significant difference between the severe and critical groups (p=0.065) although the critical group had a very high level of D-dimer.

No significant difference was found between the groups according to the clinical severity of the COVID-19 in terms of platelet values (p=0.098).

CRP values were significantly different between the groups (p=0.001). According to the post hoc test results severe and critical groups had significantly higher CRP values than mild (p<0.001 and p=0.002, respectively) and typical (p=0.017 and p=0.049, respectively) patients. Also, CRP values in the typical group were higher than in the mild group (p=0.048). While CRP values in the critical group were higher than in the severe group, there was no significant difference between the groups (p=0.547).

DISCUSSION

When the four groups formed according to the clinical severity of the COVID-19 infection were compared significant differences were found in terms of age, fibrinogen, albumin, FAR, D-dimer, and CRP values. Disease severity and fibrinogen, FAR, D-dimer, and CRP values were positively correlated, while albumin values were negatively correlated. Inflammatory markers checked at the first presentation of the patient were valuable in terms of providing early information about the severity and prognosis of the disease.

Fibrinogen, FAR, D-dimer, and CRP values were higher and album values were lower in patients with a hospital stay longer than 1 week and in patients with chronic disease. These results may be because patients with chronic diseases have a more severe COVID-19 infection clinic and are hospitalized for longer periods.

Several studies have examined the relationship between D-dimer levels and the clinical severity of COVID-19. Many studies have shown the relationship between the disease severity and D-dimer, and it has been stated that D-dimer monitoring will be a very important approach in the clinical practice of COVID-19 infection (11-13). Most studies have shown that high CRP levels are associated with disease severity and mortality in COVID-19, and our results are consistent with this (14,15). In previous studies, when the patients who experienced long-term symptoms after COVID-19 infection were examined, it was reported that these patients had high pro-inflammatory markers such as CRP and D-dimer. Based on this, we can say that patients with high D-dimer and CRP should be followed more closely in terms of prolonged symptoms after COVID-19 infection (16). Reduced protein synthesis, including albumin, is strongly associated with the poor prognoses of these patients (17). It could be useful to control albumin values and replace them when necessary, during hospitalization in COVID-19 patients.

In some previous studies on COVID-19, thrombocytopenia was associated with poor prognosis and mortality (14,18,19). Although, some studies did not find a significant relationship between prognosis and platelet levels (20-23). In this study, when the platelet values were examined according to the hospitalization period of the patients, the clinical severity of the COVID-19 disease, whether they had a chronic disease, and whether they survived/non-survived, no significant relationship was found in terms of these parameters and platelet values.

In this study, FAR values were higher and albumin values were lower in non-surviving patients compared to the surviving patients. This difference was statistically significant. Previous studies have also shown that low albumin levels are associated with mortality (8,24-26).

Although Kucukceran et al. (1) found that D-dimer, fibrinogen, albumin, D-dimer/albumin ratio (DAR), and FAR parameters were significant as predictors of hospital mortality in COVID-19 patients; they said that FAR is a more valuable predictor compared to fibrinogen. In this study, fibrinogen values were not significantly different between surviving and non-surviving groups. FAR value was found more significant than fibrinogen in terms of mortality. FAR may be a more valuable parameter than fibrinogen to predict mortality risk in patients hospitalized for COVID-19. However, low albumin was found to be more significant in non-surviving patients compared to high FAR. There is a need for studies with larger patient series on this subject.

This is a single-center study that included a small number of patients. Patients transferred to the ICU after clinical worsening was not included in the study. Also, various COVID-19 treatment protocols were not included. These can be pointed out as the limitations of the study.

CONCLUSION

In conclusion, FAR levels were found significantly better predicted the mortality risk in COVID-19 patients than fibrinogen levels alone. In addition, looking at the FAR levels could help determine the prognosis as they increase with the severity of the disease and the length of hospital stay.

Ethics Committee Approval: The study was approved by the Ethics Committee of Sakarya University Faculty of Medicine (01.08.2021, 404).

Conflict of Interest: None declared by the authors.

Financial Disclosure: None declared by the authors.

Acknowledgments: None declared by the authors.

Author Contributions: Idea/Concept: EÇ, DK; Design: EÇ, DK; Data Collection/Processing: SS, ESD; Analysis/Interpretation: EÇ, SS; Literature Review: EÇ, ESD; Drafting/Writing: EÇ; Critical Review: EÇ, DK.

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