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Fibrinogen to albumin and C-reactive protein to albumin ratio can play an important role in catheterization decisions in COVID-19 pneumonia patients: A retrospective cohort study

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Ethics Committee Approval
The study was approved by the Harran University Clinical Research Ethics Committee (HRÜ/22.19.05-03.10.2022).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Elevated troponin T (Tp) is an important indicator in the decision to catheterize. However, since COVID-19 infection may cause elevated Tp, different biomarkers are needed to make the decision for catheterization. We aimed to investigate the importance of fibrinogen-to-albumin ratio (FAR) and CRP-to-albumin ratio (CAR) values in predicting obstructive coronary artery disease (CAD) in patients hospitalized with COVID-19 pneumonia and catheterized with the suspicion of acute coronary syndrome (ACS).

Methods: In this retrospective cohort study, clinical, laboratory, catheterization, and electrocardiography data of all patients were analyzed. Patients with obstructive CAD were defined as the MI group, and patients with normal coronary arteries were defined as the normal group.

Results: The MI group consisted of 49 patients (66.2%), and the normal group consisted of 25 patients (33.8%). Both FAR and CAR were significantly higher in the MI group (P=0.007; P=0.009, respectively). FAR and CAR were found to be independent predictors of obstructive CAD (95% CI 0.06 [0.000-34.052], P=0.024; 95% CI 1.35 [0.803-2.255], P=0.025, retrospectively). A cut-off value of 0.64 for FAR has an 80% sensitivity and a 40% specificity, and a cut-off value of 0.65 for CAR has an 83% sensitivity and a 41% specificity in predicting obstructive CAD.

Conclusion: A decision for ACS and catheterization in patients hospitalized with COVID-19 pneumonia in the ICU should not be based only on elevated Tp, as it is useful to evaluate FAR and CAR values in addition to Tp.

Keywords: COVID-19 pneumonia, catheterization, fibrinogen, albumin, C-reactive protein, hospitalization

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Introduction

Coronavirus-19 (COVID-19) was first identified in 2019 in Wuhan, China, and the first case was seen in Turkey in March 2020 [1]. The number of cases increased rapidly in Turkey and in the whole world, and isolation measures and quarantine processes were put in place. The quarantine brought a significant decrease in emergency department admissions; however, it has been observed that the number of emergency service admissions due to acute coronary syndrome (ACS) has also decreased [2].

Patients with moderate-to-severe pneumonia developing secondary to COVID-19 were hospitalized in pandemic wards and intensive care units (ICU). These patients may develop myocardial damage due to either the direct effect of the virus or the systemic inflammation caused by the infection. The presence of myocardial damage as assessed by troponin (Tp) elevation is common in patients with COVID-19 and is associated with poor prognosis [3]. COVID-19 can cause cardiac diseases such as myocardial infarction, pericarditis, myocarditis, and arrhythmia other than pneumonia [4]. Tp elevation in COVID patients may also be caused by other factors (such as pulmonary embolism, right ventricular dysfunction due to lung disease, etc.) [5]. For the reasons mentioned above, it is very difficult to diagnose ACS in COVID-19 patients by evaluating only Tp values. Due to the intensity of the health system during the pandemic and to prevent individuals from being infected by COVID-19, especially healthcare professionals, and ensure that personal protective gear can be used more effectively, it has become more important to recognize genuine ACS patients and to use additional laboratory parameters to support the diagnosis of ACS in COVID-19 patients with elevated Tp.

Fibrinogen is a plasma protein synthesized in the liver. It is a substrate of thrombin in the coagulation cascade and an acute phase reactant (APR), and its plasma level increases in inflammatory conditions. It plays a role in the development of vascular inflammation and atherosclerosis [6]. Many studies show that a high serum fibrinogen level is associated with disease severity in coronary artery disease (CAD), which is an inflammatory process [7, 8]. Albumin is the main protein in the extracellular matrix and is a negative APR. Albumin accelerates fibrinolysis, reduces platelet and red blood cell aggregation, and neutralizes fibrinogen binding sites in the endothelium [9]. Studies have shown that high fibrinogen and low albumin levels are associated with CAD [10–12]. CRP is a positive APR protein; its plasma level is increased in inflammatory conditions such as ischemia and infection [13]. Many studies in the literature show a relationship between CRP-to-albumin ratio (CAR) and ACS, which is an ischemic and inflammatory process [14, 15].

In clinical routine practice, the decision for cardiac catheterization is based on cardiac biomarkers, electrocardiography (ECG) changes, and the presence of typical angina. However, there is no study investigating other biomarkers, such as FAR and CAR, in determining whether to catheterize patients hospitalized in the ICU due to COVID-19 pneumonia. In our study, we investigated the fibrinogen-to-albumin (FAR) and CAR parameters to predict obstructive CAD and use that information in making the decision to catheterize COVID-19 pneumonia patients hospitalized in the ICU and suspected of ACS due to elevated Tp.

Materials and methods

Source of data and study population

Our study is a retrospective cohort study. Patients over 18 years of age who were hospitalized in the ICU due to COVID-19 pneumonia, had elevated Tp, and underwent coronary angiography (CAG) between April 2020 and September 2022 with the suspicion of myocardial infarction without ST-segment elevation (NSTEMI) were included the study. CAG was performed on patients who were hospitalized in the ICU with positive COVID-19 polymerase chain reaction (PCR) test results, with moderate or advanced lung involvement, receiving high-dose reservoir oxygen therapy, receiving continuous positive airway pressure (CPAP) therapy, under high-flow nasal oxygen device therapy, or intubated; they were included in the study. Those with negative PCR test results were not included. The mean hospitalization time in the ICU was 23 (2.2) in the MI group and 20 (3.1) in the normal group. The patients had undergone CAG within 24 to 36 hours.

In the diagnosis of NSTEMI, increases in the control Tp values as well as the basal Tp elevation were also taken into consideration. The diagnosis of NSTEMI was accepted according to the current cardiovascular guidelines. Nine patients were excluded from the study because CAG was performed due to ST-segment elevation on ECG, and five patients were excluded because their CAG results were reported as stable angina pectoris. In addition, those who developed additional diseases such as myocarditis, pulmonary thromboembolisms, and cerebrovascular events that cause Tp elevation were not included in the study. According to CAG results, patients with obstructive epicardial coronary stenosis were labeled the “MI group,” and those without such stenosis were labeled the “normal group.”

Clinical, laboratory, and ECG data of all patients were scanned and analyzed retrospectively. Our study was approved by the local ethics committee (Harran University, Ethics Committee, date: 03.10.2022, number: HRÜ/22.19.05). Our study complies with the Declaration of Helsinki Principles.

Statistical analysis

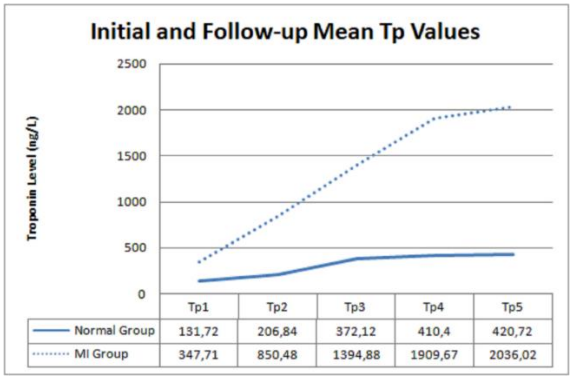
Statistical analysis was performed using the 20.0 SPSS for Windows (SPSS Inc., Chicago, Illinois, USA). Categorical variables were presented as counts and percentages. Continuous variables were evaluated for normal distribution using the Kolmogorov-Smirnov test and presented as mean (standard deviation) or median with interquartile range. The Students’ t-test was used for normally distributed variables, the Mann-Whitney U test for non-normally distributed variables, and the chi-square test for categorical variables to assess the differentiation between the groups. The Spearmen correlation test was used for correlation analysis between FAR, CAR, and other variables. Receiver operating characteristics (ROC) were generated to determine cut-off values of FAR and CAR for the obstructive CAD. In addition, univariate and multivariate binary regression analyses were used to define independent predictors of obstructive CAD. Variables resulting in a *P*-value less than 0.10 in univariate analysis were included in the multivariate

analysis. A *P*-value less than 0.5 was accepted as statistically significant.

Results

Seventy-four COVID-19 pneumonia patients who underwent CAG with the suspicion of NSTEMI were included. Obstructive epicardial coronary stenosis was detected in 49 patients (66.2%), while normal coronary artery was detected in 25 patients (33.8%). The rates of diabetes mellitus (DM), hypertension (HT), and chronic renal disease (CRD), which are classical risk factors for CAD, were found to be significantly higher in the MI group (*P*=0.006, *P*=0.001, *P*=0.006, respectively). Laboratory parameters ferritin, D-dimer, and procalcitonin levels were found to be significantly higher in the MI group, while albumin levels were lower (*P*=0.006, *P*=0.008, *P*=0.021, *P*=0.001, respectively). Tp levels (Tp1) measured at admission were found to be above the upper reference limit (14 ng/L) in both groups and were significantly higher in the MI group than in the normal group. There was an increase in follow-up Tp levels in both groups compared to the initial value, but these increases were higher in the MI group (Figure 1).

Figure 1: Initial and follow-up mean troponin values in the MI group and normal group.



In addition, both FAR and CAR values were significantly higher in the MI group (*P*=0.007, *P*=0.009, respectively). Baseline characteristics, laboratory parameters, angiographic data, and clinical features of the patients are shown in Table 1.

The perioperative mortality rate was found to be significantly higher in the MI group. The proportion of patients requiring intubation and patients who were intubated at the time of angiography and then extubated during follow-up was similar in the two groups. In the MI group, three vessel disease was the most common. LAD was the vessel most frequently revascularized, and RCA was the second most frequently revascularized vessel (Table 1).

The Spearmen correlation analysis revealed that procalcitonin, creatinine, and ferritin were positively correlated with both FAR and CAR. Hemoglobin was negatively correlated with FAR. D-dimer and NLR were positively correlated with CAR, while lymphocyte was negatively correlated with CAR. All correlated parameters are presented in Table 2.

Univariate and multivariate analyses were performed to predict the presence of obstructive CAD. Creatinine, FAR, and CAR were found to be independent predictors of obstructive CAD (95% CI: 0.06 [0.000-34.052], *P*=0.024; 95% CI: 1.35 [0.803-2.255], *P*=0.025, respectively) (Table 3). No significant *P*-value (*P*<0.10) was obtained with age, gender, and other cardiovascular risk factors in univariate analysis.

Table 1: Baseline clinical, catheterization, and laboratory characteristics of COVID-19 positive patients who underwent catheterization.

Variables	MI group (n=49)	Normal group (n=25)	*P*-value
Age (year)	66.6 (10.8)	64.4 (12.5)	0.452
Gender (male), n (%)	27 (36.5)	13 (17.6)	0.811
BMI (kg/m^2)	28.2 (5.6)	27.5 (5.2)	0.468
DM, n (%)	24 (49.0)	4 (16.0)	**0.006**
HT, n (%)	30 (61.0)	5 (20.0)	**0.001**
HPL, n (%)	7 (14.3)	3 (12.0)	0.546
Smoking, n (%)	7 (14.3)	1 (4.0)	0.172
CKD, n (%)	4 (8.2)	2 (8)	0.676
CVD, n (%)	1 (2.0)	0 (0.0)	0.662
Creatinine (mg/dL)	1.33 (1.00-1.69)	0.91 (0.88-1.09)	**0.006**
Hgb (g/dL)	12.5 (2.6)	12.9 (2.5)	0.480
Platelet (10^3/uL)	265.33 (116.11)	298.24 (93.29)	0.193
Neutrophil (10^3/uL)	11.52 (5.40)	10.27 (4.85)	0.317
Lymphocyte (10^3/uL)	1.75 (1.50)	1.51 (1.05)	0.452
MPV (fL)	10.7 (0.9)	10.3 (1.2)	0.158
CRP (mg/L)	56.0 (14.5-109.5)	21.0 (10.0-79.0)	0.073
Ferritin (ng/mL)	386.0 (143.0-828.5)	168.0 (82.5-389.5)	**0.004**
Fibrinogen (mg/dL)	5.0 (1.7)	4.2 (1.4)	0.067
Albumin (g/L)	3.3 (0.6)	3.7 (0.3)	**0.001**
Procalcitonin (ng/mL)	0.55 (0.15-1.20)	0.14 (0.05-0.55)	**0.021**
D-dimer (ug/mL)	2.10 (0.79-5.50)	0.97 (0.58-1.82)	**0.008**
Trop 1 (ng/L)	100.0 (37.5-312.0)	44.0 (16.5-185.5)	**0.025**
Mass CK-MB 1 (ng/mL)	6.0 (2.8-17.0)	7.0 (2.0-11.0)	0.109
NLR	7.9 (4.5-14.5)	7.3 (3.9-17.0)	0.787
PLR	185.0 (120.3-315.4)	270.4 (140.5-383.5)	0.077
FAR	1.59 (0.82)	1.16 (0.48)	**0.007**
CAR	24.90 (13.34)	12.5 (8.20)	**0.009**
LVEF (%)	43.4 (7.4)	42.5 (5.9)	0.578
Discharge status, n (%)			
Discharged	30 (40.5)	23 (25.7)	**0.006**
Deceased	19 (31.1)	2 (2.7)	
Intubation status, n (%)			
Extubated	31 (41.9)	21 (28.4)	0.105
Intubated	18 (24.3)	4 (5.4)	
Culprit lesion, n (%)			
LAD	8 (10.8)		
LCx	2 (2.7)		
RCA	6 (8.1)		
LAD-LCx	7 (9.5)		
LAD-RCA	4 (5.4)		
LCx-RCA	3 (4.1)		
LAD-LCx-RCA	19 (25.7)		
Revascularized vessel, n (%)			
LAD	21 (28.4)		
LCx	9 (12.2)		
RCA	12 (16.2)		
LAD-LCx	1 (1.4)		
LAD-RCA	1 (1.4)		
LCx-RCA	1 (1.4)		
CABG	4 (5.4)		

MI: myocardial infarction; BMI: body mass index; DM: diabetes mellitus; HT: hypertension; HPL: hyperlipidemia; CKD: chronic kidney disease; CVD: cerebrovascular disease; Hgb: hemoglobin; MVP: mean platelet volume; CRP: C-reactive protein; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet to lymphocyte ratio; FAR: fibrinogen to albumin ratio; CAR: CRP to albumin ratio; LVEF: left ventricular ejection fraction; LAD: left anterior descending artery; LCx: left circumflex artery; RCA: right coronary artery; CABG: coronary artery bypass grafting. Bold fonts indicate a *P*-value lesser than 0.05

Table 2: The Spearmen correlation analysis of FAR and CAR with other parameters.

FAR			CAR		
Variables	**Rho**	***P*-value**	**Variables**	**Rho**	***P*-value**
CAR	0.684	<0.001	FAR	0.684	**<0.001**
Procalcitonin	0.274	0.018	Procalcitonin	0.430	**<0.001**
CRP	0.655	<0.001	Creatinine	0.266	**0.022**
Creatinine	0.283	0.015	Ferritin	0.591	**<0.001**
Ferritin	0.391	0.001	Fibrinogen	0.568	**<0.001**
Hgb	-0.244	0.036	D-dimer	0.315	**0.006**
			Lymphocyte	-0.240	**0.040**
			NLR	0.295	**0.011**

FAR: fibrinogen-to-albumin ratio; CAR: CRP-to-albumin ratio; CRP: C-reactive protein; Hgb: hemoglobin; NLR: neutrophil-to-lymphocyte ratio. Bold fonts indicate a *P*-value lesser than 0.05

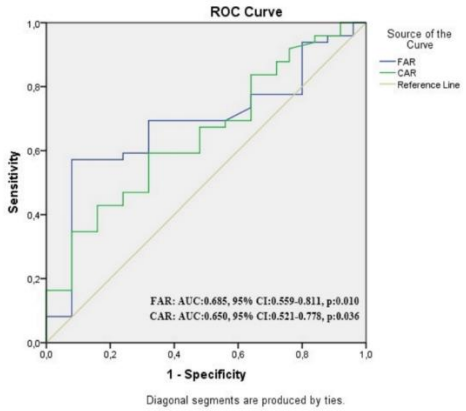
Table 3: The predictors of obstructive CAD in binary logistic regression analysis.

Variables	Unadjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
CRP	1.01 (0.999-1.019)	0.076	0.92 (0.793-1.065)	0.260
Creatinine	29.25 (3.534-242.211)	0.002	34.48 (2.562-464.161)	**0.008**
Ferritin	1.001 (1.000-1.003)	0.092	1.00 (0.999-1.002)	0.547
Fibrinogen	1.34 (0.974-1.854)	0.072	5.04 (0.378-67.398)	0.221
Albumin	0.18 (0.055-0.620)	0.006	0.27 (0.020-3.848)	0.339
FAR	3.48 (1.213-9.992)	0.020	0.06 (0.000-34.052)	**0.024**
CAR	1.035 (1.002-1.068)	0.036	1.35 (0.803-2.255)	**0.025**

CAD: coronary artery disease; CRP: C-reactive protein; FAR: fibrinogen-to-albumin ratio; CAR: CRP-to-albumin ratio; OR: odds ratio; CI: confident interval. Bold fonts indicate a *P*-value lesser than 0.05

The ROC analysis indicated that a cut-off value of 0.64 for FAR has an 80% sensitivity and a 40% specificity in predicting obstructive epicardial coronary stenosis (AUC: 0.685, 95% CI: 0.559-0.811, *P*=0.010). A cut-off value of 0.65 for CAR has an 83% sensitivity and a 41% specificity (AUC: 0.650, 95% CI: 0.521-0.778, *P*=0.036) (Figure 2).

Figure 2: ROC analysis of FAR and CAR values.



Discussion

The main purpose of the present study is to investigate the predictive value of FAR and CAR in patients with COVID-19 pneumonia who underwent coronary catheterization due to elevated Tp levels. We found that FAR and CAR levels were higher in patients with obstructive CAD than in patients with normal coronary function. Additionally, FAR and CAR had a significant correlation with other laboratory parameters in CAD patients. In the ROC analysis, FAR and CAR had a good sensitivity in predicting obstructive CAD and were independent predictors of obstructive CAD in multivariate regression analysis.

CAD and ACS are the leading causes of mortality and morbidity worldwide. The main symptom in ACS is acute chest discomfort. Acute myocardial infarction (AMI) defines cardiomyocyte necrosis in a clinical setting consistent with acute myocardial ischemia. It is diagnosed by the presence of myocardial ischemia symptoms, ECG changes, detection of wall motion abnormalities by echocardiography, and presence of Tp elevation [16]. According to the fourth universal definition of AMI published in 2018, Type-1 MI is myocardial necrosis that occurs as a result of disruption of flow in the epicardial coronary arteries caused by intramural thrombus developing due to atherosclerotic plaque erosion or rupture. Type-2 MI is myocardial necrosis caused by an imbalance between oxygen supply and demand without plaque instability [17]. The diagnosis of STEMI is easily made by ECG, but the ECG may be completely normal in patients without ST elevation. In this case, the parameter supporting the diagnosis is Tp. However, it should be kept in mind that Tp levels increase in various clinical conditions (such as kidney diseases, tachycardia, and bradycardia) [16,18]. Tp elevation is also common in patients hospitalized with COVID-19 pneumonia for various reasons [19]. It is difficult to diagnose ACS in these patients who were hospitalized in the ICU as intubated due to moderate-to-severe pneumonia, had no findings of myocardial ischemia in the ECG, could not communicate verbally due to respiratory support, and had increased Tp in follow-up blood tests. For this reason, it is important to use laboratory parameters other than Tp to support the diagnosis of obstructive CAD.

In our study, no obstructive epicardial coronary stenosis was found in 25 (33.8%) of 74 patients who were hospitalized for COVID-19 pneumonia and underwent CAG with the suspicion of NSTEMI. The most striking point was that both the MI group and the normal group had Tp values above the normal reference range at the time of admission, along with an increase in follow-up Tp values. Although the Tp value was found to be higher than the reference value in both groups at the time of admission, it was significantly higher in the MI group than in the normal group. Considering other laboratory parameters, ferritin, D-dimer, and procalcitonin levels, which are positive APRs, were found to be significantly higher in the MI group, while albumin, which is a negative APR, was found to be lower. In the literature, it has been shown that the frequency of CAD is higher in people with high serum ferritin levels [20,21]. Zakai et al. [22] showed in their study that D-dimer elevation increased the risk of CAD independently of other cardiovascular risk factors. Similarly, high procalcitonin level has been shown to be associated with the severity of CAD in ACS patients [23]. Duan et al. [24] observed that the severity of CAD was higher in ACS patients with low serum albumin levels. The fact that the results of our study are similar to the literature data supports the reliability of our data and results.

Previous studies have shown that both FAR and CAR levels are high in patients with CAD and/or ACS [11–15,25]. In a study evaluating the relationship between CAD burden and FAR in NSTEMI patients, it was found that FAR was higher in patients with medium-high (22 and above) SYNTAX scores [25]. Similarly, it has been shown that there is a correlation between the severity of CAD and CAR in patients with NSTEMI [26]. In our study, both FAR and CAR rates were higher in the MI group than the normal group. The risk of mortality is higher in COVID-19 patients with high FAR [27]. Similarly, there are studies showing that the risk of COVID-19 mortality increases with high CAR [28]. In our study, the in-hospital mortality rate was higher in the group with higher FAR and CAR values.

In the correlation analyses, we found that the parameters of procalcitonin, CRP, creatinine, ferritin, fibrinogen, and albumin were associated with both FAR and CAR. We also found that hemoglobin was associated with FAR, and D-dimer, NLR, and lymphocyte were associated with CAR. In the regression analysis, the independent predictors of the presence of obstructive CAD were serum creatinine level, FAR, and CAR.

In ROC analyses, we found that the cut-off value of 0.64 for FAR had an 80% sensitivity and a 40% specificity, and the cut-off value of 0.65 for CAR had an 83% sensitivity and a 41% specificity in predicting obstructive CAD. Duan et al. [24] found that a FAR value of 0.706 predicted a high Gensini score in ACS patients. Previous studies have shown that FAR value has higher specificity and sensitivity than albumin alone or fibrinogen alone in predicting cardiac events [29, 30]. In the study of Karabağ et al. [15], the sensitivity of CAR value over 0.63 in predicting >22 SYNTAX score was 86.8% and the specificity was 43.4% [15].

Limitations

The main limitations of our study were its retrospective nature, its single-center scope, and its relatively small number of patients. The lack of serial follow-up of FAR and CAR was another limitation. The value of our study would have increased if patients had undergone intracoronary imaging. However, considering the general condition of the patients and the risk of spreading COVID-19, the shortest possible procedure time was pursued, and therefore intracoronary imaging was not performed.

Conclusions

Since COVID-19 pneumonia is an infective and inflammatory disease, a significant increase in Tp is observed in these patients. FAR and CAR values have a predictive value for obstructive CAD and can be evaluated in order to understand whether Tp elevation is associated with obstructive CAD or COVID-19 pneumonia. FAR and CAR can help medical staff decide on whether catheterization is necessary for a given patient. In this way, the number of unnecessary CAGs and the risk of infecting personnel will be minimized. Further studies are needed on biomarkers other than Tp in catheterization decisions in infectious diseases such as COVID-19 pneumonia.

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