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ARAŞTIRMA / RESEARCH

Diagnostic precision of C-reactive protein to albumin ratio for coagulopathy in patients with COVID-19

COVID-19 hastalarında koagülopati için C-reaktif protein/albumin oranının tanısal doğruluğu

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Abstract

Purpose: This study aims to assess the diagnostic utility of C-reactive protein (CRP) to albumin ratio (CAR) for predicting elevated D-dimer levels in COVID-19.

Materials and Methods: This retrospective cohort study collected data from 145 hospitalized patients with confirmed COVID-19 in a university hospital. Patients were divided into two groups based on their D-dimer levels, as elevated D-dimer levels and normal D-dimer levels. Demographic data, comorbidities, clinical symptoms, CAR, and laboratory results were obtained from the patients' medical records and compared between the groups.

Results: The mean age of patients was 52.9±17.9 years, and 76 of them were male. The median of CAR was significantly higher in those with higher D-dimer (134.1 vs. 20.7). CRP, procalcitonin, leukocyte, neutrophil, lactate dehydrogenase, ferritin, and fibrinogen were higher in patients with elevated D-dimer levels. There was a highly significant positive correlation between CAR and D-Dimer. Logistic regression analysis revealed that CAR was a significant determinant for elevated D-dimer levels . The area under the ROC curve (AUC) was 0.741 for CAR. The verified cut-off value of CAR for predicting elevated D-dimer levels in patients with COVID-19 was 81.8, with a sensitivity of 58% and a specificity of 70%.

Conclusion: Our study revealed that CAR was significantly correlated with D-dimer and can be used to predict elevated D-dimer levels in patients with COVID-19.

Keywords:. Albumin, C-reactive protein, coagulopathy, D-Dimer

Öz

Amaç: Bu çalışma, COVİD-19'da D-dimer yüksekliğini öngörmede C-reaktif proteinin (CRP) albümine oranının (CAR) tanısal faydasını değerlendirmek amaçlamıştır.

Gereç ve Yöntem: Bu retrospektif kohort çalışmasında, bir üniversite hastanesinde COVID-19 olduğu doğrulanmış 145 yatan hastadan veri topladık. Hastalar D-dimer düzeylerine göre D-dimer düzeyi yüksek olanlar ve D-dimer düzeyi normal olanlar olarak iki gruba ayrıldı. Hastaların tıbbi kayıtlarından demografik veriler, komorbiditeler, klinik semptomlar, CAR ve laboratuvar sonuçları elde edildi ve gruplar arasında kıyaslamalar yapıldı.

Bulgular: Hastaların yaş ortalaması 52,9±17,9 yıl olup, 76'sı erkek idi. CAR medyanı, D-dimer değeri yüksek olanlarda anlamlı olarak daha yüksekti (134,1'e karşı 20,7,). D-dimeri yüksek hastalarda CRP, prokalsitonin, lökosit, nötrofil, laktat dehidrojenaz, ferritin ve fibrinojen daha yüksekti. CAR ve D-Dimer arasında oldukça anlamlı pozitif korelasyon vardı. Lojistik regresyon analizi, CAR'ın D-dimer yüksekliği için önemli bir belirleyici olduğunu ortaya koydu. ROC eğrisi altında kalan alan (AUC) CAR için 0,741 idi. COVİD-19 hastalarında D-dimer yüksekliğini öngörmek için CAR'ın doğrulanmış eşik değeri, %58 duyarlılık ve %70 özgüllük ile 81,8 idi.

Sonuç: Çalışmamız, CAR'ın D-dimer ile önemli ölçüde korele olduğunu ve COVİD-19'u olan hastalarda D-dimer yüksekliğini öngörmek için kullanılabileceğini göstermiştir.

Anahtar kelimeler: Albumin, C-reaktif protein, koagülopati, D-Dimer

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INTRODUCTION

The new coronavirus disease (COVID-19), first reported in November 2019 and defined as a pandemic by the World Health Organization (WHO) three months later, continues as a pandemic infection in the world in 2021[1]. As a result of studies and observations, it has been shown that coagulopathy frequently occurs and can cause severe comorbidity and mortality in patients with COVID-19[2,3].

Many studies on COVID-19 have shown that D-Dimer elevation is associated with the risk of first venous thromboembolism (VTE) occurrence, VTE recurrence, and mortality[4]. Naymagon et al. reported that admission D-dimer level was a predictor for death, intubation, and VTE[5]. For these reasons, early recognition, prevention, and treatment of coagulopathy in COVID-19 patients are vital. In COVID-19 cases, C-reactive protein (CRP) levels begin to rise before the computed tomography findings are detected[6]. On admission, low serum albumin levels indicate a more severe disease course and increased mortality risk[7]. Recently, a few studies reported that the ratio of CRP to albumin (CAR) might be a significant parameter for early diagnosis of severe COVID-19[7-9]. In these studies, patients with severe COVID-19 had significantly higher CAR levels than patients with a mild course[7-9].

CAR and D-dimer alone are significant predictors for disease severity in COVID-19 patients[5,9]. We hypothesized that CAR might predict D-dimer levels in COVID-19 patients. But there has been limited data regarding the relationship between CAR and D-dimer. This study aimed to investigate the possible relationship between CAR and D-dimer levels in COVID-19 patients. And also to assess the role of CAR in predicting high D-dimer levels in COVID-19 patients.

MATERIALS AND METHODS

Study design and participants

Patients admitted to infectious diseases inpatient clinic of Sakarya University Training and Research Hospital diagnosed with mild/moderate COVID-19 between 1 November 2020 and 31 December 2020 were included in this retrospective study. Patients older than 18 years were included in the study. Patients with malignancies, using anticoagulant drugs or steroids, pregnancy, thrombosis such as deep vein thrombosis (DVT) and pulmonary embolism (which was proved on admission or in the past three months), and with diseases that can reduce serum albumin levels such as malnutrition, nephrotic syndrome, and liver cirrhosis were excluded from the study. Besides, patients in need of intensive care due to the conditions such as bacterial infection, sepsis, septic shock, acute respiratory distress syndrome (ARDS), cytokine storm, disseminated intravascular coagulation (DIC), multiorgan failure, respiratory failure, and severe pneumonia were also excluded from the study. Initially, 170 patients were included in the study. Twenty patients were excluded for various reasons (3 liver cirrhosis, 5 anticoagulant use, 2 DVT, 3 steroid use, 4 sepsis, 3 ARDS, and 5 missing data). As a result, the study included 145 patients who fully met the criteria. On admission, patients with a D-dimer level higher than the upper limit of normal (D-Dimer > 500 ugFEU/L) were considered group 1. On admission, patients whose D-dimer levels were within the normal range (D-dimer 0-500 ugFEU/L) were considered group 2[4]. Clinical parameters, CAR, and the other laboratory parameters were compared between Group 1 and Group 2.

Power analysis and sample size of the study were performed with G power software. When the error type 1, study power, and margin of error were determined as 0.05, 0.80, and 0.20, respectively, 59 patients were calculated for each group. In our study, the patients with elevated D-dimer group included 66 patients, and those with normal D-dimer group included 79 patients.

Data collection and laboratory assays

Patients were diagnosed with COVID-19 with a positive real-time reverse transcription-polymerase chain reaction test using nasopharyngeal and oropharyngeal swabs. According to WHO's interim guidance, patients were diagnosed with mild/moderate COVID-19 according to WHO's interim guidance[10]. The pre-treatment laboratory data of the patients at the time of admission were collected from the patient files and the hospital data processing system. Patients' age, gender, comorbid diseases, demographic characteristics, medical history, physical examination findings, and laboratory tests were recorded from the patient files and the hospital data processing system. Data of the study were collected with the same researchers.

Within the scope of the study, serum sodium level was measured by ion-selective electrode (ISE) method; albumin, lactate dehydrogenase (LDH),

creatinine levels were measured by spectrophotometric method, and CRP was measured by an immunoturbidimetric method in autoanalyzer. Ferritin level was measured by chemiluminescence method, hemogram parameters were measured by laser measurement and LED Flow Cell method in CELL-DYN 3700 CD-3700SL device. Prothrombin time (PT) was measured by optical technique, and D-Dimer was measured by latex agglutination method in Diagon CoagXL (Budapest, Hungary) device. This study was approved by the Sakarya University Medical School Ethical Committee (Date 29.01.2021, no of approval E-71522473-050.01.04-608159).

Statistical analysis

Continuous variables with a normal distribution (on Kolmogorov–Smirnov test) were reported as mean and standard deviation, whereas median and 25th percentile-75th percentile were used for non-normally-distributed data. Categorical variables were expressed as numbers and percentages. While comparisons between groups with parametric conditions were performed using Student's t-test, comparisons between groups without parametric conditions were made using the Mann–Whitney U-test. Spearman's correlation coefficients were computed to assess the correlation between CAR and other variables. A binary logistic regression model investigated potential determinants of elevated D-dimer levels. CAR value in predicting high D-dimer levels was analyzed using receiver operating characteristics (ROC) curve analysis. When a significant cut-off value was observed, sensitivity, specificity, positive, and negative predictive values were presented. A P-value of < 0.05 is considered statistically significant. SPSS version 19.0 (SSPS Inc., Chicago, IL, USA) was used to conduct the statistical analysis.

RESULTS

Of the 145 patients included in the study, 76 were male, 69 were female, and the mean age was 52.9±17.9 years. The demographic and clinical parameters of the patients with normal D-dimer levels and elevated D-dimer levels are shown in Table 1. While there was no difference in gender between the groups, the patients with high D-dimer levels were older than the patients with normal D-dimer levels ($p=0.230$ and $p<0.001$, respectively). The patients in group 1 had more comorbidities than those in group 2 ($p=0.013$). Among the comorbid diseases, hypertension and diabetes mellitus were significantly more commonly seen in group 1 ($p=0.047$ and $p=0.001$, respectively). Headache, one of the symptoms patients could present with on admission, was more commonly seen in patients with elevated D-dimer levels ($p<0.001$).

Table 1. Demographic characteristics and presenting complaints of patients with COVID-19

Variables	Patients with elevated D-dimer (n=66)	Patients with normal D-dimer (n=79)	All patients (n=145)	P value
Gender (male/female) (n/n)	31/35	45/34	76/69	0.230
Age (year) (mean±SD)	62.3±16.8	45.5±14.8	52.9±17.9	<0.001
Comorbidity n, (%)	24 (46.1)	28 (53.8)	52 (44)	0.013
Hypertension n, (%)	26 (59)	18 (40.9)	44 (30.3)	0.047
Diabetes n, (%)	19 (79.1)	5 (20.8)	24 (16.5)	0.001
Heart failure n, (%)	4 (66.6)	2 (33.3)	6 (4.1)	0.411
Chronic kidney diseases n, (%)	4 (80)	1 (20)	5 (3.4)	0.177
Asthma n, (%)	3 (37.5)	5 (62.5)	8 (55.1)	0.728
Smoking n, (%)	8 (42.1)	11 (57.8)	19 (30.1)	0.748
Headache n, (%)	12 (32.4)	25 (67.5)	37 (44)	<0.001
Sore throat n, (%)	7 (36.8)	12 (63.1)	19 (22.6)	0.077
Cough n, (%)	28 (54.9)	23 (45)	51 (56.6)	1.000
Dyspnea n, (%)	18 (60)	12 (40)	30 (35.7)	0.869
Fever n, (%)	25 (67.5)	12 (32.4)	37 (44.5)	0.114
Myalgia n, (%)	10 (32.2)	21 (67.7)	31 (54.3)	0.612
Ageusia n, (%)	7 (38.8)	11 (61.1)	18 (31.5)	1.000
Anosmia n, (%)	3 (25)	9 (75)	12 (21)	0.504

Table 2. Laboratory results of the COVID-19 patients

Parameters	Patients with elevated D-dimer (n=66)	Patients with normal D-dimer (n=79)	P value
CAR	134.1 (30-357.1)	20.7 (9.7-105)	<0.001
CRP, mg/L	48.4 (11.2-111.7)	8.5 (3.3-37.2)	<0.001
Albumin, g/dL	3.3 (3-3.6)	3.8 (3.6-4.1)	<0.001
Creatinine, mg/dL	0.8 (0.6-1)	0.7 (0.6-0.9)	0.160
Sodium, mmol/L	137±3	138±3	0.035
Procalcitonin, ng/mL	0.09 (0.04-0.21)	0.04 (0.02-0.09)	0.045
LDH, U/L	299 (234-377)	241 (198-293)	0.000
Ferritin, µg/L	230 (93-596)	140 (58-304)	0.026
PT, sn	12.7±1.3	12.3±1.2	0.116
D-dimer, ugFEU/L	887 (626-1522)	188 (117-315)	<0.001
Fibrinogen, mg/dL	360 (316-426)	307 (263-380)	0.016
WBC, K/uL	5.615 (4.237-8.287)	4.860 (3.740-5.950)	0.003
Neutrophils, K/uL	3.760 (2.600-5.751)	2.640 (2.010-3.490)	<0.001
Lymphocytes, K/uL	1.200 (831-1.865)	1.510 (1.090-1.970)	0.039
Platelets, K/uL	182 (150-262)	178 (138-215)	0.046
NLR	3.4 (1.6-5.6)	1.7 (1.4-2.6)	<0.001

CAR: C-reactive protein to albumin ratio; CRP: C-reactive protein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; LDH: Lactate dehydrogenase; PT: Prothrombin time; APTT: Activated partial thromboplastin time; INR: International normalized ratio; WBC: White blood cells; NLR: Neutrophil to lymphocyte ratio. Data were expressed as mean ± SD or median (25 percentile-75 percentile).

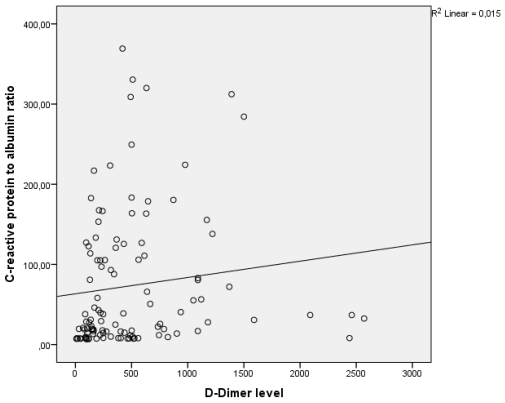

Figure 1. Positive correlation between C-reactive protein to albumin ratio (CAR) and d-dimer level in patients with Covid-19 (r=-0.470; p<0.001).

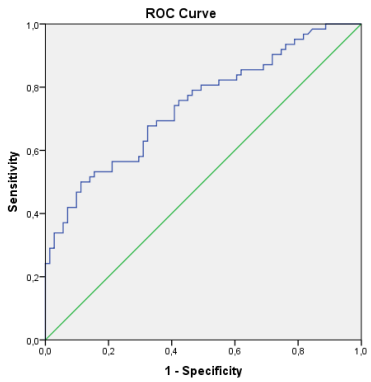

Figure 2. Receiver operating characteristic (ROC) curve of C-reactive protein to albumin ratio (CAR) for predicting elevated D-dimer levels in patients with Covid-19 (95 % CI: 0.657–0.825, AUC 0.741, p<0.001).

Laboratory parameters of the patients with normal D-dimer levels and elevated D-dimer levels are shown in Table 2. The median of CAR was 134.1 in group 1, whereas it was 20.7 in group 2, and this difference was statistically significant (p<0.001). Among other laboratory parameters, CRP, procalcitonin, LDH, ferritin, and fibrinogen were found to be higher in group 1 (p=0.000, p=0.045, p<0.001, p=0.026, and p=0.016, respectively). Among the complete blood count parameters, leukocyte, neutrophil, platelet counts, and neutrophil/lymphocyte ratio (NLR) were found to be higher, while lymphocyte counts were lower in the group with elevated D-dimer levels (p=0.003,

p=0.000, p<0.001, p=0.046, p<0.001 and p=0.039, respectively) (Table 2).

A highly significant positive correlation was found in the correlation analysis between CAR and D-Dimer (r=0.470, p<0.001, Figure 1). In addition, CAR had a significant correlation with PT, fibrinogen, procalcitonin, LDH, neutrophil, and lymphocyte (p=0.001, p<0.001, p<0.001, p<0.001, p<0.001 and p<0.001 respectively). Binary logistic regression analysis revealed that CAR was a significant determinant for elevated D-dimer levels (OR: 1.007, 95% CI: 1.004–1.011, p<0.001). A ROC curve was used to verify the optimum cut-off point of CAR for predicting elevated D-dimer levels. The area under the ROC curve (AUC) was 0.741 for CAR (95 % CI: 0.657–0.825, p<0.001) (Figure 2). The verified cut-off value of CAR for predicting elevated D-dimer levels in patients with COVID-19 was 81.89 with a sensitivity of 58 % and a specificity of 70 %.

DISCUSSION

CAR was significantly higher in COVID-19 patients with higher D-dimer levels in the present study. Furthermore, there is a highly significant positive correlation between CAR and D-dimer. CAR seems effective in predicting the severity of elevated D-dimer levels in patients with COVID-19. CAR can predict coagulability with a cut-off value of 81.8, with a sensitivity of 58% and a specificity of 70% in patients with mild/moderate COVID-19. The current study also revealed that acute phase reactants such as CRP, procalcitonin, ferritin, fibrinogen, leukocyte count, neutrophil count, and NLR are significantly higher in patients with high D-dimer. DM and HT as comorbidities in patients with COVID-19 were found as risk factors for elevated D-dimer levels in the present study.

Albumin is a vital serum protein that has been associated with systemic inflammation and reflects nutritional status. Low serum albumin level indicates the risk of developing renal and hepatic dysfunctions and reduced survival in critically ill patients. Decreased albumin level is an independent risk factor that negatively affects recovery in COVID-19 patients[11]. CRP is a proinflammatory biomarker and a prognostic factor related to the underlying disease course[1]. It has been documented that CRP level increases while albumin level decreases secondary to inflammation and immune response in COVID-19 patients[8,9,12,13]. Some studies reported that CAR was associated with poor prognosis and mortality not only in patients with COVID-19 but also in patients with gastric cancer, pancreatic cancer, and non-small cell lung cancer[8,14,15]. Various studies are conducted to identify the patient profile that will show a severe course in COVID-19[16-19]. However, the parameters that can predict coagulopathy are still limited.

Few studies have investigated the relationship between the severity of COVID-19 and CAR until now[7-9]. The pre-treatment CAR values were evaluated in these studies. In all three studies, the CAR was significantly higher in severe COVID-19 patients than patients with mild/moderate COVID-19[7-9]. It has also been reported that CAR alone might be a surrogate marker to predict the severity of COVID-19[8]. In the present study, it was found that there is a significant correlation between CAR and ferritin, LDH, fibrinogen, troponin, PT, and procalcitonin. Also, the current study revealed that CAR could predict elevated D-dimer levels in COVID-19 patients, and this association was reported for the first time to our knowledge.

Many studies have reported that neutrophil count, NLR, CRP, procalcitonin, CAR, AST, LDH, troponin, ferritin, and PT levels are higher in patients with severe COVID-19 compared to patients with mild/moderate COVID-19[5,20,21]. In the present study, CRP, CAR, procalcitonin, LDH, ferritin, D-dimer, fibrinogen, leukocyte count, neutrophil count, and NLR values were significantly higher in the group with elevated D-dimer levels compared to the group normal D-dimer levels. Advanced age, multiple comorbid diseases, DM, HT, cardiovascular disease, chronic lung disease, and obesity have been reported as risk factors for severe COVID-19[22]. In the current study, the mean age was significantly higher in the group with elevated D-dimer levels. Moreover, the group with elevated D-dimer levels had more comorbidities such as HT and DM.

The association between elevated D-dimer levels and mortality/morbidity in patients with COVID-19 has been frequently reported[1,4,23,24]. D-dimer level on admission has been a predictor of death, intubation, and VTE[5,20]. In the studies conducted in Wuhan at the beginning of the pandemic, D-dimer levels were higher in COVID-19 patients, and the mortality rate was found to be much lower in patients treated with heparin[1].

There are some limitations of the present study. First, there were a relatively small number of patients and a

mild/moderate COVID-19 patient population. Comparisons could also be made with those who needed intensive care unit support or died. The second is that the study was a single-center study. In addition, a method of evaluation with CAR could be performed in patients with and without proven thrombosis.

The early recognition and prevention of coagulopathy, a poor prognostic factor, has become necessary in COVID-19 patients. The present study revealed that CAR was highly positively correlated with D-dimer level in patients with COVID-19. Moreover, CAR can predict elevated D-dimer levels. The use of CAR as a new biomarker that can predict high D-dimer levels in COVID-19 patients might be beneficial.

Yazar Katkıları: Çalışma konsepti/Tasarımı: GKK, TK; Veri toplama: GKK, TK, Kİ, EG, OK; Veri analizi ve yorumlama: GKK, TK, Kİ, EG, OK; Yazı taslağı: GKK, TK, Kİ; İçeriğin eleştirel incelenmesi: TK, EG. OK; Son onay ve sorumluluk: GKK, TK, Kİ, EG, OK; Teknik ve malzeme desteği: GKK, TK, Kİ, EG, OK; Süpervizyon: TK, EG, OK; Fon sağlama (mevcut ise): yok.
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