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Research Article

Evaluation of fetuin-A, CRP, and CRP/fetuin-A values in COVID-19 patients

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Abstract

Objectives: Fetuin-A, a glycoprotein with several functions, is also a negative acute phase reactant. The purpose of this study was to investigate levels of serum fetuin-A in coronavirus disease 2019 (COVID-19) patients, its association with disease severity, and whether it has superiority over C-reactive protein (CRP).

Methods: The research comprised 56 individuals with COVID-19(+) and 30 healthy controls. The COVID-19(+) patient population was split into three subgroups: mild, moderate, and severe. All participants' serum concentrations of fetuin-A, tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) were measured using ELISA commercial test kits. In addition, CRP and other biochemical values from biochemistry laboratory data were gathered, and the CRP/fetuin-A ratio was calculated.

Results: The fetuin-A concentration of the COVID-19(+) patient group was shown to be statistically lower than that of the healthy control group. TNF-α and IL-6 levels were found to be significantly different in both groups. While fetuin-A had a higher area under the curve (AUC) value than CRP (0.875 and 0.800, respectively), CRP/fetuin-A had the strongest AUC (0.933).

Conclusion: Low serum fetuin-A concentrations in COVID-19 patients suggest that fetuin-A is a negative acute phase reactant for severe acute respiratory syndrome coronavirus 2. Furthermore, fetuin-A alone and CRP/fetuin-A value are both contenders for being more remarkable markers than CRP.

Keywords: Acute phase reactant, COVID-19, CRP, fetuin-A

Coronaviruses are enveloped RNA viruses that belong to the Coronaviridae family and the Nidovirales order. Although they have been isolated from a variety of species, bats are often recognized as the main source [1]. Coronavirus is responsible for acute respiratory tract illnesses and outbreaks. Severe acute respiratory syndrome (SARS) is a respiratory disorder caused by an infection with an airborne coronavirus [2]. On January 31, 2021, the World Health Organization issued a worldwide public health emergency for severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), a novel coronavirus that initially originated in Wuhan, China [3]. Infection severity in coronavirus disease 2019 (COVID-19) can range from asymptomatic to severe [4].

Fetuin-A (α-2-Heremans-Schmid glycoprotein, AHSG) is a glycoprotein possessing a molecular weight of 60 kDa. Fetuin-A has a normal serum value of 300-600 g/L and is a negative acute-phase reactant (APR) that lowers inflammation by 30%-50% [5]. It has been observed that neutrophils operate as a

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modulator in the activation of bacterial macrophages and that cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) inhibit the expression of fetuin-A [6]. Fetuin-A, which has a variety of biological roles, has been proposed to be an opsonin due to its two N-linked and three O-linked oligosaccharide chains, which may bind biological cationic ions and anti-inflammatory compounds (such as spermine) [7]. In the presence of elevated spermine, macrophages avoid excessive inflammation by downregulating cytokine production with fetuin-A [8]. Low fetuin-A levels are associated with an uncontrolled increase in proinflammatory cytokines [5, 9]. C-reactive protein (CRP) is a nonspecific positive acute phase reactant produced in the liver. It is a biomarker that is elevated under circumstances of inflammation, infection, and tissue injury [10]. Serum CRP values were observed to increase in COVID 19(+) individuals [11, 12].

Because SARS-CoV infection is related to severe inflammation, it can cause life-threatening symptoms. According to one research that investigated the relationship between SARS-CoV and fetuin-A, fetuin-A binds with the SARS nucleocapsid and inhibits the effect of the virus [13]. The objective of this study was to examine the levels of fetuin-A in COVID-19 patients. In addition, the importance of the ratio of a positive acute phase reactant (CRP) to a negative acute phase reactant (fetuin-A) in evaluating the severity of the disease was investigated.

Materials and Methods

Study design

The study required permission from the local ethics committee (B.30.2.ATA.0.01.00/369). Patients who applied to Ataturk University Research Hospital Infectious Diseases clinics between June and July 2021, as well as healthy adults with similar demographics, were included in the study. All potential participants were informed about the study, and those who agreed to participate provided informed consent. Real-time polymerase chain reaction (PCR) analysis was performed on nasopharyngeal and oropharyngeal samples collected from participants for COVID-19 testing. Based on this test result, the study included 56 patients with COVID-19(+) (PG) and 30 healthy controls with COVID-19(−). Diagnostic criteria were determined according to the adult COVID-19 patient diagnosis and treatment guidelines and literature published by the Ministry of Health of the Republic of Türkiye [14]. The COVID-19(+) patient group was divided into three subgroups: noncomplicated group (NCG) (no respiratory distress, fever, cough, sore throat, and muscle pain symptoms), moderate group (MG) (pneumonia finding in lung tomography image, spO_2 >90 in room air, fever, cough, sore throat, and myalgia), and severe (SG) (bilateral diffuse pneumonia on lung tomography image, spO_2 >90 in room air, fever, cough, sore throat, and myalgia). The patients in the NCG group had blood drawn on the first day after being diagnosed with COVID-19. Patients in this group were those who did not return to the hospital within 14 days of being diagnosed. On the first day of their service, the patients in the MG and SG groups had their blood taken. These patients had also received several antiviral drugs (Tamiflu, Plaquenil, and Favipiravir). Of the patients, 2 had diabetes, 7 had hypertension, 4 had chronic obstructive pulmonary disease, and 5 had coronary artery disease. Others did not have a history of chronic disease. Adults over the age of 18 years who were of age comparable to the patient age group, had no health concerns, were not pregnant, and did not have a chronic ailment were considered healthy volunteers.

Biochemical analysis

In specimens obtained from all participants, fetuin-A (Fetuin A ELISA Kit; Ref No. DK0128, DiaMetra, Italy, CV ≤11.3%), TNF-α (Hu TNF-α ELISA Kit; Cat. No. KHC3011, Thermo Scientific, Belgium, CV ≤ 8.5%), and IL-6 (Hu IL-6 ELISA Kit; Cat. No. KHC0061, Thermo Scientific, Belgium, CV ≤7.9%) concentrations were measured by a microplate reader spectrophotometer (XS Powerwave, BioTEK, USA) using commercial ELISA kits. A quantity of 100 µL serum samples was used, and measurements were made according to the instructions in the kit booklet, using the solutions in the kit. In addition, the results of biochemical analytes such as ALT, AST, LDH, GGT, and CRP and CBC (WBC, PLT, Hb, NE%, LY%) were recorded from the laboratory data. Hematological analyses were performed using the Sysmex XN-1000 Hematology System (Sysmex Corporation, Kobe, Japan), and biochemical analyses were performed using the Beckman Coulter Olympus AU2700 Plus Chemistry Analyzer (Beckman Coulter, Tokyo, Japan).

Statistical analysis

Statistical analysis was performed using the statistical software program, SPSS, for Windows (IBM, Inc. Version 20.0 Chicago, IL, USA). The variables were investigated using the Shapiro-Wilk test to determine their normal distribution. Descriptive analyses were presented using mean and standard deviation (mean±SD) or median, minimum, and maximum (med (min-max)). The differences in parametric and nonparametric data between PG and HCG were calculated using Student's t-test and the Mann-Whitney U test. Also, the Kruskal-Wallis test was used for statistical analysis of the COVID-19(+) subgroups. The correlations were calculated using Spearman's rank test. Differences were considered as significant at $p<0.05$. A receiver operating characteristic (ROC) analysis test was applied to determine whether the continuous variable could be used in the diagnosis and to determine the cutoff value, positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC). The statistical significance level for all data was taken as $p<0.05$.

Results

The research included 86 participants, of whom 44 were females and 42 were males. The mean age of the participants in the patient group and the healthy control group was the

Table 1. Demographic characteristics and radiologic image of the healthy control group and patients with COVID-19(+)

Variables	PG				HCG (n=30)
	Noncomplicated group (n=18)	Moderate severe group (n=25)	Severe group (n=13)	Total PG (n=56)	
Age (year)	39.4±14.1	56.8±17.2	58.7±13.3	49.8±17.1	49.7±15.1
Gender					
Female	6	14	4	24	14
Male	12	11	9	32	16
Hospital stay (day)	11±3	12±3	16±5	13±4	-
Radiological finding					
ULI	-	19	1	20	-
BLI	-	6	12	18	-
Fever	3	10	10	22	-
Cough	4	16	11	30	-
Exitus	-	-	6	6	-

PG: COVID-19(+) patient group; HCG: Healthy control group; ULI: Unilateral involvement in the lung; BLI: Bilateral involvement in the lung.

Table 2. Biochemical values of the healthy control group and patients with COVID-19(+)

Variables	PG (n=56) (mean±SD) or med (min-max)	HCG (n=30) (mean±SD) or med (min-max)	p
Fetuin-A (µg/L)	300±152	500±156	0.000*
CRP (mg/L)	10.8 (3.0-192.0)	2.5 (1.0-6.1)	0.000*
CRP/fetuin-A	0.036 (0.02-0.42)	0.005 (0-0.009)	0.000*
TNF-α (pg/mL)	26.8±12.6	19.4±6.8	0.000*
IL-6 (pg/mL)	27.5 (7.1-70.7)	16.4 (7.1-35.0)	0.000*
WBC ($\times10^3$)	6.8±2.4	8.1±2.5	0.001*
PLT ($\times10^6$)	229±69	275±119	0.013*
NE%	65.9±11.2	62.8±8.7	0.357
LY%	23.8±6.1	25.6±8.9	0.373
Hb (g/dL)	14.8±1.7	13.6±2.1	0.005*
ALT (U/L)	20 (8-80)	20 (11-93)	0.562
AST (U/L)	28 (16-48)	19 (13-85)	0.184
LDH (U/L)	273 (15-623)	205 (100-301)	0.002*
GGT (U/L)	28 (9-61)	18 (11-211)	0.290

*: Statistically significant. PG: COVID-19(+) patient group; HCG: Healthy control group; CRP: C-reactive protein; TNF-α: Tumor necrosis factor-alpha; IL-6: Interleukin-6; WBC: White blood cell; PLT: Platelet; NE: Neutrophil; LY: Lymphocyte; Hb: Hemoglobin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; LDH: Lactate dehydrogenase; GGT: Gamma-glutamyl transferase; SD: Standard deviation; min-max: Minimum-maximum.

same (p=0.984). Table 1 shows the demographic data of all participants.

The COVID-19(+) patient group had lower fetuin-A concentrations than the healthy control group (Fig. 1a). TNF-α and IL-6 levels were found to be significantly different in both groups (p<0.05). WBC and PLT counts were significantly lower in the COVID-19(+) patient group although Hb levels were higher (p<0.05). NE% and LY% were similar in both groups (p>0.05). Similarly, CRP and LDH levels increased dramatically in the patient group, whereas ALT, AST, and GTT activities were unchanged from the control group. On the other hand, CRP/fetuin-A ratios, derived from laboratory data, were found to be higher in the COVID-19(+) patient group than in the control group. Table 2 shows the variables of the patient and control groups.

When the COVID-19(+) subgroups were compared, a statistically marked increase in IL-6, TNF-α, and CRP levels ($p < 0.05$) was detected in the severe group. Similarly, the severe group had substantially greater LDH and GGT values than the other two groups (p<0.05). However, there was no significant difference in fetuin-A (Fig. 1b), WBC, NE%, LY%, Hb, procalcitonin, ALT, and AST levels among these three subgroups (p>0.05).

Table 3. Biochemical values of patient subgroups with COVID-19(+)

Variables	Noncomplicated group (mean±SD) or med (min-max) (n=18)	Moderate severe group (mean±SD) or med (min-max) (n=25)	Severe group (mean±SD) or med (min-max) (n=13)	p
Fetuin-A (µg/L)	220±176	328±124	335±145	0.125
CRP (mg/L)	3.7 (3.1-53.1)	3.8 (3.1-66.1)	30.5 (3.0-192.0)[a]	0.000*
TNF-α (pg/mL)	16.9±5.6	25.8±8.9	42.4±9.8	0.892
IL-6 (pg/mL)	16.2 (7.1-33.8)	29.8(17.2.8-57.2)	51.1 (37.5-70.1)[a]	0.040*
WBC Counts ($\times10^3$)	7.6±3.3	6.7±2.5	6.1±1.2	0.169
PLT Counts ($\times10^6$)	244±57	253±74	195±62	0.100
NE%	60.6±7.1	65.12±1.9	70.7±10.4	0.069
LY%	26.1±8.3	26.0±10.5	19.7±7.1	0.155
Hb (g/dL)	15.4±2.2	14.8±1.9	14.6±0.9	0.567
ALT (U/L)	18 (10-79)	21 (8-80)	20 (10-43)	0.903
AST (U/L)	26.9±10.3	26.4±6.2	30.9±9.1	0.810
LDH (U/L)	286 (145-623)	234 (198-366)	303 (224-609)[a]	0.012*
GGT (U/L)	18.6±8.4	31.7±16.8	32.2±10.7[a]	0.013*
Procalcitonin	0.04±0.01	0.04±0.02	0.04±0.01	0.811

*: Statistically significant. Comparing the three groups, the ones marked with the superscript letter "a" are statistically significant when compared with other groups in pairs. CRP: C-reactive protein; TNF-α: Tumor necrosis factor-alpha; IL-6: Interleukin-6; WBC: White blood cell; PLT: Platelet; NE: Neutrophil; LY: Lymphocyte; Hb: Hemoglobin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; LDH: Lactate dehydrogenase; GGT: Gamma-glutamyl transferase; SD: Standard deviation; min-max: Minimum-maximum.

Table 4. Data of ROC analysis for fetuin-A, CRP, and CRP/fetuin-A

Variables	AUC (CI%)	p	Sensitivity%	Specificity%	PPV (CI%)	NPV (CI%)
Fetuin-A	0.875 (83.2-94.7)	0.000*	66	90	90.2 (48.1-95.9)	57.9 (48.1-66.9)
CRP	0.800 (72.2-92.2)	0.000*	44	96	82.4 (68.5-90.9)	46.2 (38.4-54.1)
CRP/fetuin-A	0.933 (88.5-98.2)	0.000*	89	73	94.0 (84.2-97.8)	79.4 (65.7-88.6)

*: Statistically significant. ROC: Receiver operating characteristic; CRP: C-reactive protein; AUC: Area under the curve; PPV: Positive predictive value; NPV: Negative predictive value; CI: Confidence interval.

Table 3 shows the values related to the COVID-19(+) subgroups.

ROC analysis was performed to evaluate the diagnostic utility of fetuin-A for COVID-19(+) patients. A greater AUC value was obtained for fetuin-A than for CRP by ROC analysis. The ROC curve was drawn for CRP/fetuin-A and determined a higher AUC for CRP/fetuin-A than for CRP. The PPV and NPV were calculated for the cutoff values of 380 µg/mL for fetuin-A, 6 mg/mL for CRP, and 0.007 for CRP/fetuin-A. The results of the ROC analysis are presented in Table 4 and Figure 2a, b.

Correlation analysis of fetuin-A with other laboratory findings was also performed. Fetuin-A had a significantly negative correlation with CRP when all participants were included (r=-0.264, p=0.015). A significant negative correlation was observed with WBC only in the patient group (r=-0.436, p=0.001) (Fig. 3a, b).

Discussion

Apart from PCR testing, no biomarker has been discovered for the diagnosis of COVID-19 during the SARS-CoV-2 pandemic, which has been ongoing since December 2019. While the majority of participants infected with the virus have severe health problems, others are asymptomatic. While chronic diseases are assigned to the underlying causes in severe cases, there is still uncertainty in circumstances when there is no chronic disease, but the course is severe. In the current investigation, fetuin-A concentrations were evaluated in COVID-19(+) patients and healthy controls. We found a drop in the serum level of fetuin-A, an APR, in the patient group. Low levels, on the other hand, were unrelated to the severity of the disease. While there was a difference in TNF-α and IL-6 levels between COVID-19 patients and healthy controls, the highest increase was found in severe COVID-19 patients. CRP, Hb, and LDH levels in the patient group were considerably higher; however, WBC and PLT levels were significantly lower. The severity of the disease was associated with an increase in CRP, LDH, and GGT levels.

Ischemia and infectious toxins cause an increase in plasma LDH, a cytoplasmic enzyme [15]. Wan et al. [16] found statistically higher LDH readings in the severe group in a research comparing mild and severe COVID-19 patients. WBC, CRP, and IL-6 levels were higher in severe COVID-19 patients than in moderate COVID-19 patients in a meta-analysis of 29 studies assessing immune-inflammatory markers in COVID-19 cases [17]. CRP synthesized by the liver has an important role in

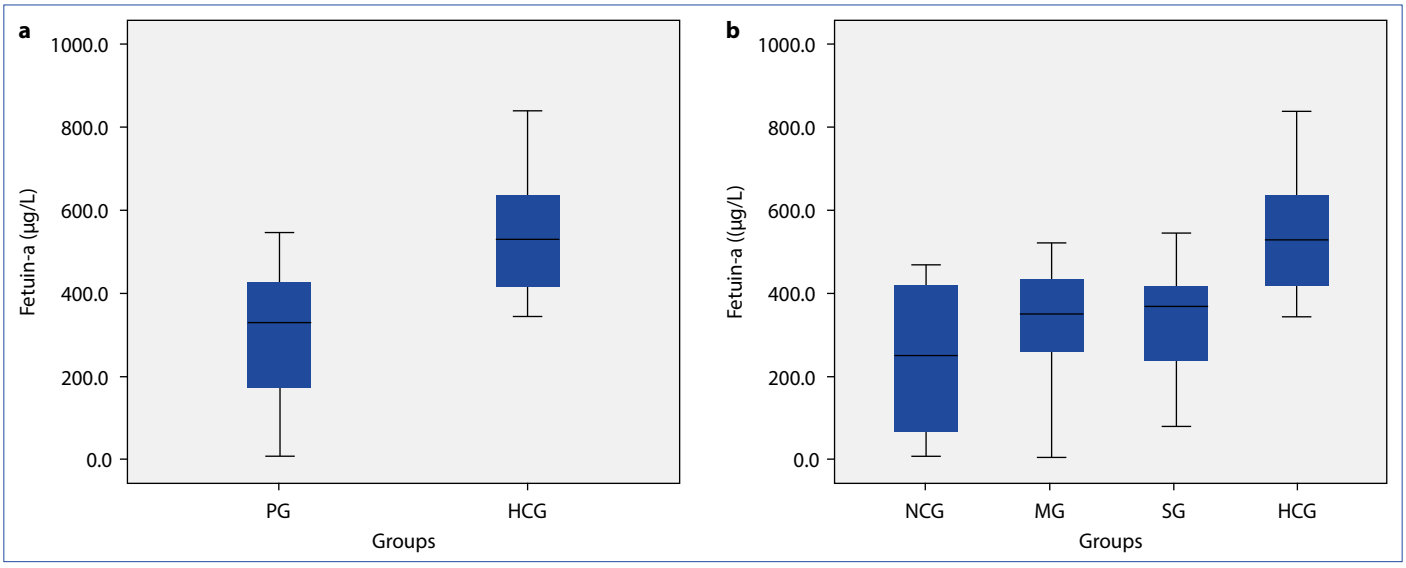

Figure 1. (a) Change of fetuin-A concentration in COVID-19(+) patients and healthy control group. (b) Change of fetuin-A concentration in COVID-19(+) subgroup patients (noncomplicated, moderate, and severe).

PG: COVID-19(+) patient group; HCG: Healthy control group; NCG: Noncomplicated group; MG: Moderate group; SG: Severe group.

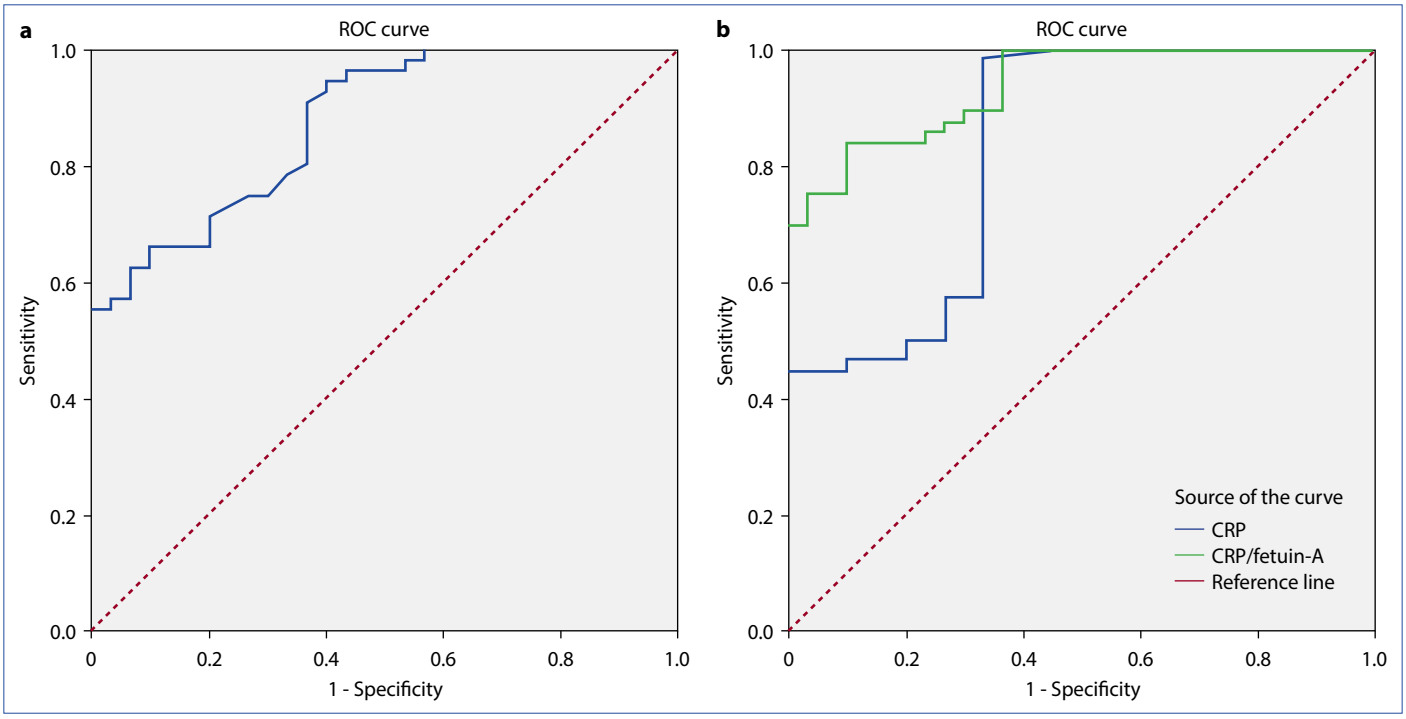

Figure 2. (a) ROC analysis of fetuin-A. (b) ROC analysis of CRP and CRP/fetuin-A.

ROC: Receiver operating characteristic; CRP: C-reactive protein.

protecting against infection, preventing autoimmunity, and regulating the inflammatory response. The SARS-CoV-2-induced cytokine storm, as well as interstitial pneumonia and ARDS found in severe COVID-19 patients, are all expected to be mediated by IL-6. According to Zhu et al., [18] elevated serum IL-6 and CRP levels are independent risk factors for determining the severity of COVID-19. TNF-α, a proinflammatory cytokine produced by immune cells in response to severe inflammatory and autoimmune diseases, stimulates the production of IL-6 [19]. In a meta-analysis of 24 articles involving patients with COVID-19, the levels of several cytokinins, including IL-6 and TNF-alpha, were evaluated, and it was found that IL-6 was considerably higher in patients with COVID-19 [20]. In our current study, in parallel with the literature, cytokine levels were found to be higher in COVID-19 patients compared with healthy controls.

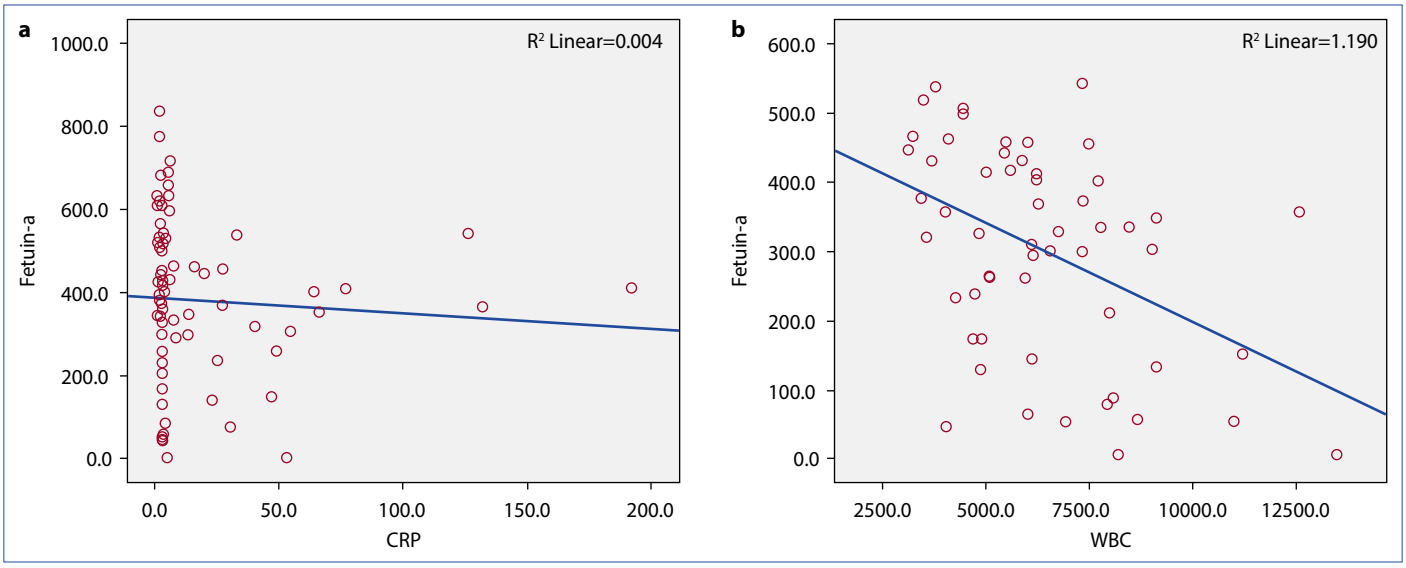

Figure 3. (a) Correlation between fetuin-A and CRP in all participants. (b) Correlation between fetuin-A and WBC in COVID-19(+) patient group.
PG: COVID-19(+) patient group; CRP: C-reactive protein; WBC: White blood cell.

According to recent findings, the majority of COVID-19 patients develop various degrees of liver disease [21]. The local and systemic impacts of this infection's inflammatory response may produce an irregularity in hepatokine production and affect the synthesis of various APRs in response to liver inflammation [22]. Although fetuin-A is known to be a negative acute phase reactant, it has been shown to increase in some cases [23]. Low blood fetuin-A levels have been reported in several experimental animals to promote uncontrolled proinflammatory cytokine production, and mice lacking in fetuin-A are hypersensitive to LPS-induced inflammation [5, 24]. In addition, low fetuin-A levels have also been associated with increases in proinflammatory cytokines. Simultaneously, increased TNF-α and IL-6 levels suppress fetuin-A expression [5, 9].

Zhu et al. [13] conducted a case-control research after first defining the relationship between SARS-CoV nucleocapsid and fetuin-A. According to this study, a single nucleotide polymorphism in the fetuin-A gene produces low serum fetuin-A concentration, which leads to the development of SARS-CoV. Individuals with the AA genotype were shown to have a 41% reduced chance of developing SARS than those with the TT/AT genotype.

Kukla et al. [25] reported the first and only study examining fetuin-A in COVID-19 patients, finding reduced fetuin-A levels in COVID-19 patients compared with the control group. They also observed that fetuin-A levels were lower in patients with pneumonia and COVID-19 who required critical care, indicating that low fetuin-A levels may be associated with a predisposition for severe COVID-19 prognosis. In accordance with the above-mentioned study, we detected reduced serum fetuin-A concentrations in COVID-19 patients in our investigation. The AUC value obtained in our ROC analysis identifies serum fetuin-A as a biomarker for COVID-19 patients, which might be a significant finding. Furthermore, as compared with CRP, another APR, a higher AUC, and better diagnostic PPV and NPV were observed. A stronger AUC CRP/fetuin-A ratio might be a highly useful biomarker for COVID-19.

The correlation between these two biomarkers, one positive and one negative APR, was strongly negative, as predicted. In COVID-19 patients, a very significant negative relationship was identified between higher WBC counts and fetuin-A. In contrast to the previous study, no association was observed between the severity of COVID-19 disease and fetuin-A levels in our investigation. This might be related to the small sample size in the COVID-19 patient subgroups. Another issue is the lack of a comparison with a control group with the same clinical finding to assess its prognostic value.

In conclusion, our current study's finding of decreased serum fetuin-A concentrations in COVID-19 patients suggests that fetuin-A is a negative APR for SARS-CoV-2. It can be thought that high cytokine levels suppressed the synthesis of fetuin-A. Therefore, low fetuin-A appears to be caused by inflammation. Furthermore, fetuin-A alone and the CRP/fetuin-A ratio are also potentials for being better biomarkers than CRP in inflammation.

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Conflict of Interest: The authors declare that there is no conflict of interest.

Ethics Committee Approval: The study was approved by The Ataturk University Faculty of Medicine Clinical Research Ethics Committee (No: B.30.2.ATA.0.01.00/369, Date: 24/06/2021).

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