Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Can Fetuin-A Deficiency Predict the Severity of COVID-19 Disease in Kidney Transplant Recipients?

Musa Pinar[a], Hamad Dheir[a], Aysel Tocoglu[b], Hande Toptan[c], Taner Demirci[d], Selcuk Yaylaci[b], Gozde Cakirsoy Cakar[e], Necattin Firat[f], Emrah Akin[f], Mahmud İslam[a]*, and Oguz Karabay[g]

[a]Division of Nephrology, Sakarya University Faculty of Medicine, Sakarya, Turkey; [b]Department of Internal Medicine, Sakarya University Faculty of Medicine, Sakarya, Turkey; [c]Department of Microbiology, Sakarya University Faculty of Medicine, Sakarya, Turkey; [d]Department of Endocrinology, Sakarya University Faculty of Medicine, Sakarya, Turkey; [e]Department of Pathology, Sakarya University Faculty of Medicine, Sakarya, Turkey; [f]Department of General Surgery, Sakarya University Faculty of Medicine, Sakarya, Turkey; and [g]Department of Infectious Diseases and Clinical Microbiology, Sakarya University Faculty of Medicine, Sakarya, Turkey

ABSTRACT

Background. This study aims to investigate whether fetuin A deficiency predicts the prognosis of COVID-19 disease in kidney transplant recipients (KTRs).

Method. The study was conducted on 35 hospitalized KTRs with COVID-19 pneumonia between November 2020 and June 2021. Serums were collected for fetuin-A measurement at admission and after six months of follow-up. The demographic and laboratory data of the patients were recorded and analyzed with the appropriate statistical method.

Results. A total of 35 KTRs, 23 of which (65.7%) were men, were included in the study. The mean age of the patients was 51.6 ± 14.0 years. Seventeen (48.6%) patients had severe disease criteria and required intensive care (ICU) support. Biopsy-proven acute rejection developed in 6 (17.1%) patients in the follow-up. At admission, the median fetuin-A value was 173.5 mcg/mL (143.5-199.25) in the moderate disease group and 126.0 mcg/mL (89.4-165.5) in the severe patient group ($p = 0.005$). While the Median fetuin-A value at the time of diagnosis was 173.5 mcg/mL (143.5-199.25), and in the 6th month was 208 mcg/mL [184-229] ($p<0.001$). By ROC analysis, the effect of serum fetuin-A level in predicting the severity of COVID-19 disease was significant (AUC: 0.771, $p = 0.006$, 95% CI: 0.615-0.927). When serum fetuin-A cut-off value was taken as 138 mcg/mL to determine disease severity, it was shown to have 83.3% sensitivity and 64.7% specificity.

Conclusions. Serum fetuin-A level can predict disease severity in kidney transplant recipients in the presence of active COVID-19 disease.

THE mortality rates associated with COVID-19 in kidney transplant recipients (KTRs) are several times higher than in the normal population [1]. Especially if COVID-19 occurs with comorbidities, the risk of morbidity and mortality increases even more. Many inflammatory biomarkers have been reported to determine the severity of COVID-19 disease in the normal population [2,3]. The deterioration of inflammatory predictors such as elevated serum ferritin, D-dimer, interleukin-6, lactate dehydrogenase, and decreased lymphocyte and thrombocyte counts detected in KTRs with COVID-19 may present differently from non-transplanted patients with COVID-19 [4]. For the first time, fetuin-A deficiency has been shown to be the most accurate biomarker to determine the severity of COVID-19 in nontransplant patients [5,6]. To our knowledge, no study has investigated fetuin-A levels and disease severity in immunocompromised patients with COVID-19. We aim to investigate whether the fetuin-A levels determine disease severity in KTRs with COVID-19 pneumonia.

*Address correspondence to Mahmud İslam, Sakarya University Hospital, Sirinevler, Adnan Menderes Street, Saglik Sokak No:195, 54100 Adapazari, Sakarya, Turkey. E-mails: drisleem@gmail.com, mislam@sakarya.edu.tr

0041-1345/20
https://doi.org/10.1016/j.transproceed.2023.01.040

MATERIALS AND METHODS

A cohort of KTRs hospitalized for COVID-19 pneumonia was identified from a single center between November 1, 2020 and June 30, 2021. COVID-19 was diagnosed in patients with clinical symptoms, positive reverse transcriptase-polymerase chain reaction results on nasopharyngeal swab specimens, and typical lung lesions on chest computed tomography scans. Inclusion criteria were age >18 years at diagnosis of COVID-19, having radiologic findings of COVID-19 pneumonia, and >6-month history of transplantation. Cases with a history of active coinfections, those who died during the 6-month study period, those having chronic obstructive pulmonary disease, those on high-dose steroids for acute rejection, those with increasing doses of immunosuppressive drugs, or those on biological therapies in the month preceding hospitalization were excluded from the study. Disease severity was categorized as follows: moderate disease requiring hospitalization but without an oxygen requirement or an oxygen need of <6 L/min and severe disease requiring hospitalization with an oxygen need of >6 L/min or mechanical ventilation. Serum was collected for fetuin-A measurement at admission and after 6 months of follow-up. Clinical and laboratory parameters for the disease were prospectively collected and analyzed concerning outcomes. Our study was approved by the Sakarya University Ethical Committee on April 29, 2022 (no. E-16214662-050.01.04-128231-67).

Statistical Analysis

Data analysis was performed using SPSS version 22 (IBM SPSS, Inc, Armonk, NY, United States). The variables were investigated using visual (histograms, probability plot) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether they were normally distributed. Categorical variables are described as frequencies and percentages. Categorical features and relationships between groups were assessed using an appropriate χ^2 test. The continuous variables are expressed as mean and SD or as the median and IQR, depending on the normality of their distribution. In 2 different periods of the disease, the Wilcoxon test was preferred to compare nonparametric variables, whereas the paired Student *t* test was used for variables with normal distribution. While evaluating the area under the curve, a 5% type 1 error level was used to accept a statistically significant predictive value of the test variables. The statistically significant 2-tailed *P* value was considered < .05.

RESULTS

The general characteristics of the 49 KTRs included in the study are shown in Table 1. A total of 35 KTRs were included in this study analysis. The median recipient age was 51.6 ± 14.0 years, and 65.7% were men. All patients received triple immunosuppressive therapy with steroids, tacrolimus, and antimetabolite at admission. On the first day of admission, antimetabolite treatment was discontinued in all patients, and the steroid dose was increased. At the time of diagnosis of COVID-19, the patients' median creatinine (IQR) value was 1.29 mg/dL (1.00-1.81), and the mean estimated glomerular filtration rate was 59.3 ± 22.8 mg/min per 1.73 m^2. Seventeen patients (48.6%) were critically ill, requiring intensive care unit support. During follow-up, biopsy-proven acute rejection developed in 6 (17.1%) patients, whereas 12 (34.3%) patients required dose reduction or interruption of calcineurin inhibitors (Table 1).

Table 1. Baseline Characteristics of KTRs with COVID-19

Characteristics	Patients (n = 35)
Age, y	51.6 ± 14.0
Sex, male (%)	23 (65.7)
Body mass index, kg/m^2	28.3 ± 4.4
Chronic diseases, n (%)	
Hypertension	21 (60.0)
Diabetes	10 (28.6)
ASCVD	7 (20.0)
Transplant duration, mo	38.8 (14.8-62.4)
Serum creatinine, mg/dL	1.29 (1.00-1.81)
Glomerular filtration rate, mL/min	59.3 ± 22.8
White blood cell count, 10^3/mm^3	5.6 (4.41-7.70)
Absolute neutrophil count, 10^3/mm^3	3.9 (3.1-7.08)
Absolute lymphocyte count, 10^3/mm^3	0.92 (0.60-1.70)
Albumin, g/L	3.8 ± 0.4
ALT, IU/L	24 (16-41)
AST, IU/L	25 (18-42)
C-reactive protein, mg/L	19.0 (4.4-65.0)
Procalcitonin, ng/mL	0.08 (0.04-0.13)
Fibrinogen, mg/dL	378 ± 96
D-dimer, ng/mL	362 (180-645)
Disease severity, n (%)	
Moderate	18 (51.4)
Critical	17 (48.6)
Post-COVID acute rejection, n (%)	
Yes	6 (17.1)
No	29 (82.9)
Calcineurin inhibitor withdrawal or tapering, n (%)	
Yes	12 (34.3)
No	23 (65.7)

Descriptive results for continuous variables were expressed as mean and SD or as median and IQR, depending on the normality of their distribution.

ALT, alanine transaminase; ASCVD, atherosclerotic cardiovascular disease; AST, aspartate transaminase; KTR, kidney transplant recipient.

The fetuin-A median (IQR) value was 173.5 μg/mL (143.5-199.25) in the moderate patient group at the time of diagnosis of COVID-19, whereas it was 126.0 μg/mL (89.4-165.5) in the severe patient group (*P* = .005; Fig 1). There was no significant correlation between fetuin-A measured at diagnosis and other acute phase indicators measured simultaneously. The fetuin-A median (IQR) value at the time of diagnosis of COVID-19 was 173.5 (143.5-199.25), which was statistically significantly lower than the fetuin-A level 6 months after diagnosis (208

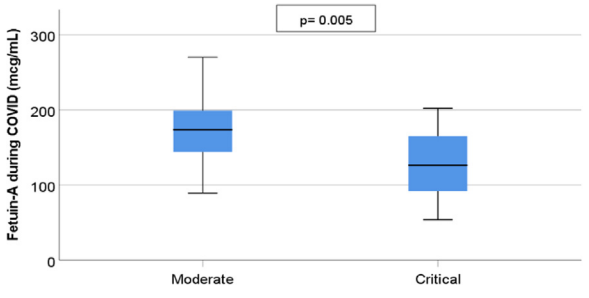

Fig 1. Comparison of fetuin-A levels according to disease severity in kidney transplant recipients with COVID-19 at admission.

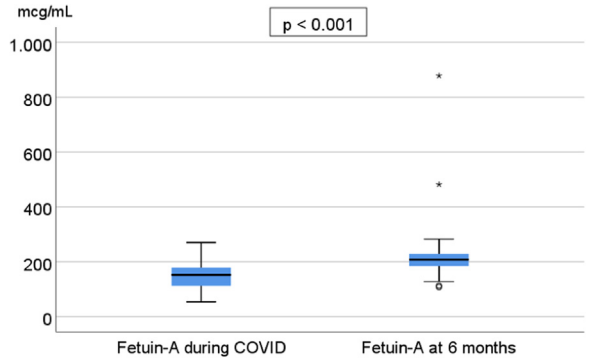

Fig 2. Comparison of fetuin-A levels at admission and month 6 in kidney transplant recipients with COVID-19 disease.

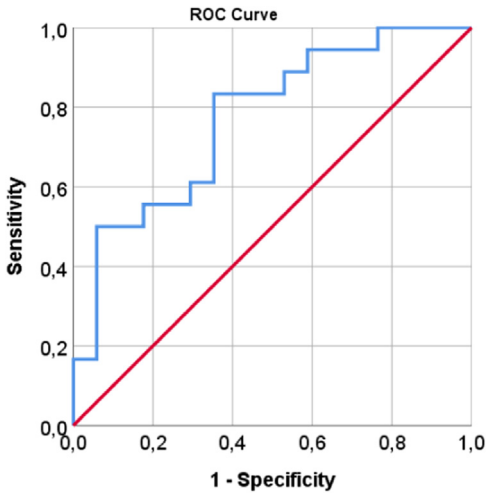

Fig 3. The receiver operating characteristic curve of serum fetuin-A predicts severe SARS-CoV-2 infection at admission. ROC, receiver operating characteristic.

[184-229]; $P < .001$; Fig 2). With receiver operating characteristic analysis, the effect of serum fetuin-A level in predicting the severity of COVID-19 disease was significant (area under the curve: 0.771; $P = .006$; 95% CI, 0.615-0.927; Fig 3). When the serum fetuin-A cutoff value is taken as 138 μg/mL to determine disease severity, it has 83.3% sensitivity and 64.7% specificity.

DISCUSSION

The mechanical pathways leading to immune dysregulation and the morbidities caused by severe uncontrolled COVID-19 disease remain significant challenges for physicians. For the first time, we have shown that serum fetuin-A deficiency can confirm disease severity in hospitalized KTRs with COVID-19. In addition, we showed that fetuin-A levels were significantly improved in patients who recovered from the disease 6 months after the COVID-19 attack. Recently, fetuin-A deficiency has been shown to predict the disease severity in non-transplanted patients with COVID-19. [5,6]. Fetuin-A is a negative acute phase reactant to various inflammatory stimuli and injuries. Depending on the stimulation mode, fetuin-A can also work as a positive or negative acute phase protein. Previous studies showed that fetuin-A deficiency was detected in some bacterial and viral infections and predicted infection status [5−8]. It may indicate the crucial role of this hepatokine in COVID-19 pathogenesis in immunocompromised and normal populations.

Severely affected patients have a poor prognosis and a high mortality rate compared with more mildly and/or moderately affected patients [9]. The acute inflammatory response observed in patients with severe COVID-19 disease has been described as related to increased inflammatory markers such as C-reactive protein, ferritin, D-dimer, and elevated levels of some inflammatory cytokines and chemokines [9]. However, these indicators may not be specific to disease severity, especially in kidney transplant patients [4]. Our study found no significant correlation between fetuin-A measured at admission and inflammatory indicators. A new biomarker panel containing serum fetuin-A, inter-α-trypsin inhibitor 3, glutamic acid, and cholesteryl esters demonstrated accurate differentiation of mild COVID-19 from critical COVID-19 in nontransplant patients [5]. Similarly, in the present study, the fetuin-A level in severe KTRs was significantly lower than in moderately severe patients. The effect of serum fetuin-A level in predicting the severity of COVID-19 disease was significant (area under the curve: 0.771; $P = .006$; 95% CI, 0.615-0.927). Also, the cutoff value taken as $\geq$138 μg/mL has been a significant value for determining disease severity.

Fetuin-A has a pleiotropic role in biological processes such as immune response regulation and inflammation [10]. The serum concentration of fetuin-A decreases during the acute inflammatory response and returns to typical values when the infection is successfully treated. Similar to the literature, we also found that low fetuin-A levels on the first day of hospitalization increased significantly after recovery from the infection.

This study had several limitations because it was a descriptive, single-center study with a small sample size. However, this study questions the specificity and whether fetuin-A determines disease severity in kidney transplant patients with COVID-19, and the topic has not been previously described.

In conclusion, the COVID-19 disease in KTRs may have a different inflammatory pattern. We found that fetuin-A deficiency predisposes to a more severe COVID-19 course in KTRs. According to our small study results, fetuin-A may be the most confirmatory biomarker for the severity of COVID-19 disease in transplant patients. Larger studies with immunocompromised patients are needed to assess the extent of these inflammation biomarkers more robustly for COVID-19 infection.

DISCLOSURES

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

REFERENCES

[1] Caillard S, Chavarot N, Francois H, Matignon M, Greze C, Kamar N, et al. Is COVID-19 infection more severe in kidney transplant recipients? Am J Transplant 2021;21:1295–303.

[2] Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med 2020;58:1021–8.

[3] Ji P, Zhu J, Zhong Z, Li H, Pang J, Li B, et al. Association of elevated inflammatory markers and severe COVID-19: a meta-analysis. Medicine 2020;99:e23315.

[4] Molina M, Burgos E, Cacho J, Juega J, Cañas L, Taco O, et al. Routine biomarkers for the severity of COVID-19 pneumonia may present differently in kidney transplant recipients. Transplant Proc 2021;53:2476–80.

[5] Reverté L, Yeregui E, Olona M, Gutiérrez-Valencia A, Buzón MJ, Martí A, et al. Fetuin-A, inter-α-trypsin inhibitor, glutamic acid and ChoE (18:0) are key biomarkers in a panel distinguishing mild from critical coronavirus disease 2019 outcomes. Clin Transl Med 2022;12:e704.

[6] Kukla M, Menżyk T, Dembiński M, Winiarski M, Garlicki A, Bociąga-Jasik M, et al. Fetuin-A deficiency but not pentraxin 3, FGF-21, or irisin, predisposes to more serious COVID-19 course. Biomolecules 2021;11:1422.

[7] Low serum fetuin-A as a biomarker to predict pneumococcal necrotizing pneumonia and hemolytic uremic syndrome in children: erratum. Medicine (Baltimore) 2018;97:e9684.

[8] Li L, Gu X, Fang M, Ji J, Yi C, Gao C. The diagnostic value of serum fucosylated fetuin A in hepatitis B virus-related liver diseases. Clin Chem Lab Med 2016;54:693–701.

[9] Laing AG, Lorenc A, Del Molino Del Barrio I, Das A, Fish M, Monin L, et al. A dynamic COVID-19 immune signature includes associations with poor prognosis. Nat Med 2020;26:1623–35.

[10] Wang H, Sama AE. Anti-inflammatory role of fetuin-A in injury and infection. Curr Mol Med 2012;12:625–33.