TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Original Article

Factors Affecting Kidney Functions in One-year Follow-up After COVID-19 in Kidney Transplant Patients

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ABSTRACT

Background Coronavirus disease (COVID-19) is more severe, and mortality is higher in kidney transplantation (KTx) patients; it is still unclear how renal functions progress and the conditions affecting renal functions in the post-COVID-19 period. We aimed to investigate the changes in kidney functions and the factors affecting this change after COVID-19.

Material and Methods Forty-one kidney transplantation patients who were hospitalised for COVID-19 were included in this retrospective study. The patient's personal information, examination, and treatment information regarding their hospitalisation and follow-ups were obtained from the hospital system.

Results Patients with elevated serum creatinine in the first year post-COVID had higher baseline proteinuria and systemic immune inflammation index (SII). Proteinuria increased more in patients with a long transplantation period, hypertension, high basal creatinine, and SII. Also, proteinuria was higher in patients who developed AKI during the COVID period. In addition, baseline SII was an independent predictor of the change in serum creatinine and proteinuria.

Conclusions We found that patients with signs of increased inflammation, such as high SII were more fragile regarding renal functions. Therefore, the post-COVID-19 follow-up process of KTx patients with COVID-19 should be individualised.

Turk J Int Med 2023:5(2);124-134
DOI: 10.46310/tjim.1165344

Keywords: *COVID-19, kidney functions, kidney transplantation, proteinuria, systemic immune inflammation index.*

Received: August 22, 2022; Accepted: January 12, 2023; Published Online: April 29, 2023

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INTRODUCTION

Although the primary affected system of the coronavirus disease - 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the respiratory system, the condition also frequently affects other organ systems. Renal involvement is commonly reported in patients hospitalised with COVID-19 and may be detected from isolated hematuria and proteinuria to acute kidney injury (AKI) requiring renal replacement therapy.[1] Many mechanisms thought to cause renal involvement have emerged in COVID-19. Some of these mechanisms are direct viral cytopathic effect on the kidney, dehydration, tissue hypoxia, systemic inflammation (cytokine storm), immune complex deposition, and diffuse intravascular coagulation. Tubular, glomerular, or vascular damage may occur in the kidney. In histopathology studies, acute tubular necrosis is the most common type of injury. Tubular and vascular damage occurs mainly in the form of AKI, and glomerular damage occurs in the form of proteinuria, while co-occurrence of these findings is a typical and expected situation.[2-4]

Considering the multiple comorbidities and immunosuppressive treatments of kidney transplant patients (KTx), a more severe disease course is inevitable during COVID-19. KTx patients are more likely to develop AKI and need haemodialysis (HD) than the average population.[5] However, it is thought that the immunosuppressive state in KTx patients may also have protective effects against the systemic inflammatory response responsible for the severe disease in the course of COVID-19.[6]

Derived inflammation markers such as neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) are more sensitive inflammatory markers than leukocytes, neutrophils or lymphocytes.[7] While the systemic immune inflammation index (SII) was a significant prognostic indicator used only in malignant patients initially, it has become an essential indicator of inflammation in different patient groups, recently in Ktx patients and COVID-19.[8,9] SII is an independent predictor of albuminuria in the general population.[10]

Although it is well known that the course of COVID-19 is more severe and mortality is higher in KTx patients, it is still not clear how kidney function progresses in the post-COVID-19 period and the conditions that affect its course. Immune dysregulation and increased proinflammatory cytokine levels occurring during the response to SARS-CoV-2 are considered the primary cause of tissue damage. Considering the negative effect of increased inflammation on graft functions, the impact of the hyperinflammatory state in the COVID period on long-term renal functions is also a matter of interest. Based on this idea, we aimed to investigate the changes in renal functions and the factors affecting this change one year after COVID-19.

MATERIAL AND METHODS

Ethics committee approval was obtained from our institution for this retrospective study. The data of 75 kidney transplant patients hospitalised with the diagnosis of COVID-19 between January 1 and March 31, 2021, were scanned retrospectively from our hospital system. Twenty patients with negative COVID-19 PCR results, five who died during hospitalisation, and nine whose data for the first year could not be reached after the COVID-19 diagnosis date were excluded from the study. Forty-one patients whose data could be entirely determined were the study group. A review of medical records (including information on age, sex, weight, medications, duration of the disease, and laboratory results) was done. Inclusion criteria were: 1) Being a KTx patient aged 18-60. 2) Having a positive COVID-19 PCR result. 3) Having hospital records in the 1st year after the diagnosis of COVID-19. Exclusion criteria were: 1) being under 18 and over 60, 2) Negative COVID-19 PCR result, 3) Presence of pregnancy, 4) history of acute rejection in the last three months or positive donor-specific antibody test (DSA), 5) presence of previously detected proteinuria over 500 mg/day. The patients included in the study were divided into two groups according to their creatinine levels and proteinuria levels based on the 1st year post-COVID-19 data. In these groups, those whose creatinine level increased and non-increased; were divided into those whose proteinuria level increased and non-increased.

Obtaining Baseline Data and Post-COVID First Year Data

Basal values were accepted on the day when the COVID-19 PCR test of the patients was positive or on the day of treatment was started by hospitalisation. The control performed at least one year after the diagnosis of COVID-19 was accepted as the first year of control examinations. The treatments applied to the patients during the hospitalisation, and the changes made in the immunosuppressive therapies were obtained by scanning the hospital registry system. All patients included in the study had negative DSA tests

before and after COVID-19. DSA test positivity was taken as an exclusion criterion as it would cause suspicion of graft rejection.

Biochemical Analyses

Venous blood samples were drawn after an overnight fast and stored at -80 °C for biochemical analyses in patients. All biochemical studies were undertaken in the Central Biochemistry Laboratory of our hospital. Serum creatinine was measured with Jaffe Method. Using an automated clinical chemistry analyser, serum C-reactive protein (CRP) levels were measured with an immunoturbidimetric assay (Diasis Diagnostic System). Serum levels of calcium, phosphate, and intact parathyroid hormone (iPTH) were measured. iPTH was measured using the Elecsys PTH assay.

24-hour Urinary Proteinuria

The 24-hour urinary proteinuria levels detected within the first three days of hospitalisation were recorded as initial proteinuria. Total protein concentration levels were measured by a turbidometric assay using benzethonium chloride. The results were expressed as mg/L.

Calculation of the Systemic Immune Inflammation Index

The SII value was calculated according to the basal blood values of the patients. The NLR x platelet count formula was used to calculate SII.11

Statistical Analyses

The data obtained were evaluated using the Statistical Package for Social Sciences for Windows 21.0 (SPSS Inc. Chicago, Illinois, USA) statistical program. Descriptive statistics were determined for each variable. Data were expressed as mean±standard deviation or median and interquartile range (IQR). The $\chi 2$ test for categorical variables determined a statistically significant difference between the groups. Non-parametric statistics (Mann-Whitney U test) and parametric statistics (independent sample t-test) were all used for continuous variables. Associations between the variables were explored using Spearman's rho test. Binary logistic regression analysis was performed to determine independent predictors for increased proteinuria and serum creatinine levels. Factors with a *p* - value of < 0.2 were included in the univariate analysis in the regression test, while those significant in the univariate analysis were included in the multivariable evaluation. A statistically significant difference was considered when the *p* - value <0.05.

RESULTS

Demographic Characteristics of Patients and Pre-COVID-19 Data

A total of 41 kidney transplantation patients, 14 (34%) female and 27 (66%) male, with a mean age of 45.96 ± 9.46 years, who met all inclusion and exclusion criteria, were included in the study. The most common comorbidity was hypertension (n: 26, 61.9%). Of 41 patients, 9 (22%) were transplanted from deceased donors and 32 (78%) from living donors. Before COVID-19, mean creatinine values were 1.45 mg/dL, and 24-hour urinary proteinuria averages were 285 mg/L. The demographic characteristics of the patients and the initial data for the diagnosis of COVID-19 and pre-hospitalization were in Table 1.

Characteristics of Patients during Treatment of COVID-19

All patients whose diagnosis was confirmed by the COVID-19 PCR test were included in the study.

Table 1. Demographic, clinical characteristics, and biochemical parameters of 41 kidney transplant patients with COVID-19

Parameters	Values
Age (years)	45.96 ± 9.46
Gender (Female/Male)	14/27
Body mass index (kg/m^2)	25.26 ± 3.76
Posttransplant period (years)	7.5 (7)
History of diabetes mellitus	7 (16.7%)
History of hypertension	26 (61.9%)
History of coronary artery disease	6 (14.3%)
COVID-19 associated AKI	14 (34.1%)
Sistolic blood pressure (mmHg)	128.41 ± 11.96
Diastolic blood pressure (mmHg)	76.46 ± 10.2
Creatinine (mg/dL)	1.45 (0.55)
White blood count (10^3/uL)	7.37 (4.13)
Haemoglobin (g/dL)	12.75 ± 2.07
Platelet count (10^3/mm^3)	220.27 ± 77
Albumin (g/L)	4.17 ± 0.52
Alanine aminotransferase (U/L)	15.5 (11.3)
Proteinuria (mg/L)	285 (431)
Lactate dehydrogenase (U/L)	147 (74)
Ferritin (mg/dL)	220 (898.09)
C-reactive protein (mg/L)	10.79 (34.42)
SII	684.5 (683.19)

Data were expressed as mean±SD, median (IQR) or frequency. AKI: acute kidney injury, SII: systemic immune inflammation index.

Table 2. Changes in immunosuppressive therapies during COVID-19.

Medications	Continued	Stopped or reduced	Total
Glucocorticoids	41 (100%)	0	41 (100%)
Tacrolimus	24 (75%)	8 (25%)	34 (82%)
Cyclosporin	2 (50%)	2 (50%)	4 (10%)
Mycophenolic acid analogue	7 (19%)	29 (81%)	36 (87%)
m-TOR inhibitor	0	4 (100%)	4 (10%)
Azathioprine	0	2 (100%)	2 (5%)

Data were expressed as n (%). m-TOR: mammalian target of rapamycin.

When evaluated with thorax computed tomography, 11 (26%), patients did not have any involvement in the lung, while 30 (72%) patients had different degrees of involvement. All of the patients were receiving various immunosuppressive treatments before COVID-19, and multiple changes were made in their treatments during the disease period. Treatment changes of all patients were shown in Table 2. Of the 41 patients included in the study, 26 (63%) were receiving angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) treatments. Treatments of 16 (61%) patients, including 14 patients who developed AKI, were stopped during their hospitalisation. ACEi/ARB treatment was started again in all patients at least one month after discharge. The mean hospital stay of the patients was 11.09 days, and 9 (22%) patients required follow-up in the intensive care unit for varying periods. The treatments for COVID-19 during their hospitalisation were also evaluated. Hydroxychloroquine in 16 (39%) patients, favipiravir in 39 (95%) patients, pulse steroid in 27 (66%) patients, tocilizumab in 11 (27%) patients, and plasma infusion in 13 (32%) patients were used.

Characteristics of Patients Developing Acute Kidney Injury during COVID-19

During the hospitalisation period, acute kidney injury (AKI) developed in 14 (34.1%) 41 patients in our

Table 3. Comparison of demographic, clinical characteristics and biochemical parameters of patients according to increase in serum creatinine value.

Parameters	Increased creatinine (n: 29)	Stable creatinine (n: 12)	P value
Age (years)	44.93 ± 9.3	48.5 ± 9.75	0.277
Gender (Female/Male)	12/17	2/10	0.129
Body mass index (kg/m^2)	25.16 ± 4.09	25.52 ± 2.96	0.787
Post-transplant period (year)	7.5 (5)	8 (8)	0.667
History of diabetes mellitus	6 (20.6%)	1 (8.3%)	0.339
History of hypertension	18 (62%)	8 (66.6%)	0.781
History of coronary artery disease	5 (17.2%)	1 (8.3%)	0.463
COVID-19 associated AKI	11 (38%)	3 (25%)	0.427
Sistolic blood pressure (mmHg)	129.31 ± 12	126.25 ± 12.08	0.463
Diastolic blood pressure (mmHg)	77.07 ± 11.14	75 ± 7.68	0.561
Creatinine (mg/dL)	1.34 (0.67)	1.6 (0.69)	0.339
White blood count (10^3/uL)	7.37 (4.04)	5.97 (4.6)	0.623
Haemoglobin (g/dL)	12.45 ± 2	13.53 ± 2.1	0.125
Platelet count (10^3/mm3)	229.31 ± 80.6	198.42 ± 65.48	0.247
Albumin (g/L)	4.07 ± 0.55	4.4 ± 0.36	0.065
Alanine aminotransferase (U/L)	16.85 (12.8)	14.7 (9.7)	0.501
Proteinuria (mg/L)	320 (601.8)	161.5 (282.8)	0.046
Lactate dehydrogenase (U/L)	147 (74)	142 (119.8)	0.311
Ferritin (mg/dL)	230.5 (533.25)	145 (1339.6)	0.423
C-reactive protein (mg/L)	3.11 (34.32)	10.8 (50.43)	0.770
SII	823.14 (730.91)	412.39 (352.86)	0.013

Data were expressed as mean ± SD, median (IQR) or frequency. AKI: acute kidney injury, SII: systemic immune inflammation index.

Table 4. Comparison of demographic, clinical characteristics and biochemical parameters of patients according to increase in amount of proteinuria.

Parameters	Increased proteinuria (n: 25)	Stable proteinuria (n: 16)	*P* value
Age (years)	46.68 ± 10	44.87 ± 8.62	0.558
Gender (Female/Male)	8/17	6/10	0.717
Body mass index (kg/m^2)	25.19±3.68	25.37 ± 4.02	0.883
Post-transplant period (year)	9 (5)	4 (7)	0.001
History of diabetes mellitus	5 (20%)	2 (12.5%)	0.534
History of hypertension	20 (80%)	6 (37.5%)	0.006
History of coronary artery disease	5 (20%)	1 (6.25%)	0.224
COVID-19 associated AKI	13 (52%)	1 (6.25%)	0.003
Sistolic blood pressure (mmHg)	131.6 ± 10.17	123.44 ± 13.13	0.031
Diastolic blood pressure (mmHg)	79.2 ± 8.74	72.19 ± 11.1	0.03
Creatinine (mg/dL)	1.67 (1.88)	1.17 (0.58)	0.001
White blood count (10^3/uL)	7.8 (16.23)	5.18 (2.91)	0.024
Haemoglobin (g/dL)	12.49 ± 2.1	13.16 ± 2.01	0.317
Platelet count (10^3/mm3)	235.72 ± 83.75	196.13 ± 59.74	0.109
Albumin (g/L)	4.07 ± 0.58	4.32 ± 0.38	0.110
Alanine aminotransferase (U/L)	23 (19.5)	13.1 (5)	0.058
Proteinuria (mg/L)	311 (545)	280 (233)	0.066
Lactate dehydrogenase (U/L)	147 (58.5)	145 (109)	0.135
Ferritin (mg/dL)	291 (969)	189 (421)	0.658
C-reactive protein (mg/L)	13.2 (63.09)	7 (17.17)	0.046
SII	868.44 (829.46)	529.96 (448.93)	0.050

Data were expressed as mean±SD, median (IQR) or frequency. AKI: acute kidney injury, SII: systemic immune inflammation index.

study. According to the KDIGO AKI classification, 4 (28%) patients were evaluated as stage-1, 3 (21%) patients as stage-2, and 7 (50%) patients as stage-3 AKI. 7 (50%) of the 14 patients who developed AKI needed HD. The mean HD session duration was 3.77 sessions. None of the patients who developed AKI needed HD at discharge.

First-Year Data after COVID-19

In the post-COVID first year, 29 (70.7%) patients with increased serum creatinine compared to the pre-COVID period and 12 (29.3%) patients with a stable course were detected. The two groups had no significant difference regarding age, gender, body mass index, time spent post-transplant, diabetes mellitus, hypertension, history of coronary artery disease, and blood pressure (Table 3).

Interestingly, no significant difference was observed between the two groups regarding basal creatinine levels and AKI development during the COVID-19 process. AKI developed during the period of COVID-19 in 11 (38%) patients in the patient

Table 5. Binary logistic regression analysis with other parameters of the increase in amount of proteinuria in kidney transplant patients with COVID-19.

Parameters	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P value	OR (95% CI)	*P* value
Post-transplant period (years)	1.469 (1.14-1.89)	0.003	1.204 (0.86-1.67)	0.269
History of hypertension	6.667 (1.63-27.27)	0.008	1.562 (0.19-12.76)	0.677
COVID-19 associated AKI	16.250 (1.85-142.46)	0.012	6.244 (0.53-73.19)	0.145
Sistolic blood pressure (mmHg)	1.066 (1.003-1.133)	0.039	1.036 (0.91-1.17)	0.590
Diastolic blood pressure (mmHg)	1.094 (1.004-1.192)	0.040	0.996 (0.86-1.15)	0.959
White blood count (103/uL)	1.00 (1.00-1.00)	0.059	-	-
Creatinine (mg/dL)	16.940 (1.56-183.06)	0.020	3.789 (0.28-49.68)	0.310
C-reactive protein (mg/L)	1.023 (0.99-1.05)	0.087	-	-
SII	1.002 (1.00-1.003)	0.012	1.001 (1.00-1.002)	0.048

CI: confidence interval, AKI: acute kidney injury, SII: systemic immune inflammation index.

Table 6. Binary logistic regression analysis with other parameters of the increase in serum creatinine values in kidney transplant patients with COVID-19.

Parameters	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Gender (Male/Female)	0.785 (0.257-0.890)	0.043	0.283 (0.052-1.53)	0.143
Haemoglobin (g/dL)	0.764 (0.54-1.08)	0.129	-	-
Albumin (g/L)	0.225 (0.04-1.16)	0.075	-	-
Proteinuria (mg/L)	1.002 (0.999-1.004)	0.180	-	-
SII	1.004 (1.001-1.007)	0.028	1.002 (1.00-1.005)	0.039

CI: confidence interval, SII: systemic immune inflammation index.

group with increased serum creatinine and 3 (25%) patients in the other group, but it was not statistically significant ($p = 0.427$). While the mean of basal creatinine in the group with stable serum creatinine was 1.6 mg/dL, it was 1.34 mg/dL in the other group ($p = 0.339$). The mean basal proteinuria in the group with increased serum creatinine was 320 mg/L, while the other group had 161.5 mg/L ($p = 0.046$). While there was no significant difference in the peripheral blood variables (haemoglobin, white blood count, platelet count) of the two groups, the SII value was found to be significantly higher in the group with increased creatinine level (823.14 vs 412.39, $p = 0.013$) (Table 3).

Patients were divided into two groups according to the increase and stability of proteinuria in the first year of follow-up after COVID. There were 25 (60.9%) patients in the group with increased proteinuria and 16 (39.1%) patients in the other group. The two groups had no significant difference regarding age, gender, body mass index, and basal proteinuria. In the group with increased proteinuria, the time elapsed after KTx was longer ($p = 0.001$), the history of hypertension was more common ($p = 0.006$), and systolic and diastolic blood pressures were higher ($p = 0.031$ and 0.03, respectively). While the mean basal creatinine was 1.67 mg/dL in the increased proteinuria group, it was 1.17 mg/dl in the other group ($p = 0.001$). In addition, 13 (52%) patients in the increased proteinuria group and 1 (6.25%) patient in the other group developed AKI during the COVID-19 period ($p = 0.003$). When inflammatory markers were evaluated, both CRP (13.2 vs 7 mg/L) and SII (868.44 vs 529.96) were found to be higher in the increased proteinuria group ($p = 0.046$ and $p = 0.05$, respectively) (Table 4).

Evaluation of Factors Associated with Increase in Proteinuria and Serum Creatinine

Parameters associated with an increase in proteinuria at one-year post-COVID were evaluated. In the univariable analysis, the time elapsed post-KTx, history of hypertension, AKI developed during COVID-19, systolic and diastolic blood pressure elevations, serum creatinine, and SII, were associated with post-COVID increased proteinuria. However, only SII was associated with increased proteinuria in the multivariable analysis ($p = 0.048$) (Table 5). Also, associated factors with increased serum creatinine were evaluated in the multivariable analysis. SII alone was an independent predictor of the change in serum creatinine value ($p = 0.039$) (Table 6).

DISCUSSION

The study investigated the changes in renal functions and the factors affecting this change in the one-year follow-up of KTx patients diagnosed with COVID-19. Patients with elevated serum creatinine in first-year post-COVID had higher baseline proteinuria and SII. We found that patients with long transplantation time, hypertension and high basal creatinine and SII values had higher proteinuria increases in the follow-up. The development of AKI during the COVID period increased the risk of proteinuria in the long term. Finally, we showed that baseline SII was an independent predictor of the change in serum creatinine and proteinuria.

In COVID-19, renal damage can be seen in a wide range, from hematuria and proteinuria to developing severe AKI that may require RRT. While the prevalence of acute kidney injury (AKI) is approximately 17% in all populations during the COVID-19 period[12], publications are reporting that it is very high, such as 45-83% in KTx patients.[13-15] AKI developed during hospitalisation in 34.1% of our patient group, and HD need in 50% of these patients. In COVID-19, the risk of developing AKI and the need for HD are higher in KTx patients than in the normal population.[5] The frequency of proteinuria in patients followed up for

COVID-19 has been reported as 10-45%, and the severity of proteinuria is directly related to mortality.[13,16] In our study, the rate of patients with newly developed proteinuria was 60%. This difference between studies is due to the severity of COVID-19. While severe disease, predominantly with tubular damage, may cause more moderate proteinuria and accompanying higher creatinine levels, higher proteinuria levels may be detected in patients with milder disease.[17] In our study group, it was impossible to differentiate tubular or glomerular damage due to the failure of any patient to undergo a kidney biopsy.

Knowing the mechanisms that cause renal damage in COVID-19 is essential for what we should pay attention to in the follow-up of renal functions. While systemic inflammation (cytokine storm) and immune dysregulation are the primary factors causing organ damage, acute tubular injury is the most common histopathological finding.[2-4] The association of inflammatory markers with COVID-19 has always been of interest, as systemic inflammation and immune dysregulation are significant causes of renal injury during COVID-19. Inflammatory markers have been used to diagnose the disease or predict its prognosis, but there is no study on how they can predict damage in any organ system in the long term. SII is a stronger predictor of inflammatory status than traditional inflammatory markers such as NLR, PLR, and monocyte/lymphocyte ratio (MLR).[11,18,19] In COVID-19, it has been determined that the prognostic value of SII is stronger than inflammation indicators such as NLR, derived NLR (d-NLR), MLR, and PLR.[20,21] The usefulness of SII in identifying COVID-19 patients at higher risk of death is attributed to the different roles played by lymphocytes, neutrophils, and platelets during the disease response.[22]

Our study is the first to show that SII, an important indicator of systemic inflammation, is associated with increased creatinine and proteinuria in the long term after COVID-19. Kidney injury during COVID-19 results from increased local and systemic inflammation and microthrombotic events on both tubules and glomeruli.[3,4] The relationships between tubular injury markers with increased interleukin 6 (IL-6) level, collapsing glomerulopathy and inflammatory cytokine production, and systemic inflammation markers such as NLR and CRP with the severity of renal injury are findings that draw attention to the role of inflammation in renal injury in COVID-19. Considering all these findings, SII, one of the strong indicators of systemic inflammation, may also be an important predictor in the relationship between COVID-renal dysfunction.[23,24] Patients with high SII values may be exposed to more renal inflammation and have worse renal functions in the long term. Many studies are showing that, in COVID-19, SII is a useful indicator to predict the development of AKI, that patients with AKI have higher white blood cell and CRP levels than patients without AKI, and patients with evidence of renal involvement, have higher white blood cell counts and lower lymphocyte count. All these studies support our hypothesis.[18,25,26]

Neutrophil-related endothelial damage is the other mechanism thought to cause renal injury in COVID-19 patients.1[2,25,27,28] Tumor necrosis factor (TNF) overactivation increases the oxidative stress of the glomeruli in addition to direct renal endothelial damage. Cytokines such as interferons (IFN: alpha and beta) also cause podocyte dysfunction and glomerulosclerosis.[29] The increased neutrophil activity also causes platelet activation, increasing inflammatory cytokine production and microthrombus formation.[30] Evidence of extensive endothelial inflammation, inflammatory cell deposits, and endotheliitis in post-mortem autopsies supports this theory.[30] Proteinuria is a consequence of this hyperinflammatory state.[31] Over time, the increased expression of all these cytokines and the role of local tissue inflammation in renal cells have become more evident in COVID-19.[32] Since high SII is an indicator of increased neutrophil and platelet counts and indirectly increased activity of these two cells, it can be considered an indirect indicator of endothelial damage.

SII is helpful with other inflammatory markers to predict prognosis after kidney transplantation.[33] In addition, when studies reporting the relationship between delayed graft function and the development of acute rejection and inflammatory markers[34] and the relationship between high NLR-PLR and the development of immunological damage are evaluated, SII may be an important indicator of both renal and overall survival in KTx patients. The role of SII in predicting renal survival in KTx patients includes neutrophilia and thrombocytosis that occur during ischemia-reperfusion injury, which contributes to the formation of immunogenic microthrombi in renal vascular structures.3[5,36]

Regardless of allograft function and underlying renal allograft histology, the level of proteinuria at any time after transplantation is one of the main deter-

minants of graft survival.[37] Bajpai *et al*.[13] found that basal proteinuria level is an independent predictor of renal survival in the follow-up of renal functions after COVID-19. Our study found that creatinine increases were higher in the first year in patients with higher initial proteinuria. In addition, it was determined that transient proteinuria due to post-COVID febrile disease resolved within three weeks. It is also known that the increase in proteinuria in the follow-up indicates increased long-term mortality in KTx patients.[16] Therefore, proteinuria detected in the COVID-19 period should be followed up, and transient proteinuria should be differentiated from long-term proteinuria in the early period.

We found that patients with increased proteinuria during long-term follow-up developed more AKI during COVID-19. AKI, proteinuria, and hematuria developing during COVID-19 are independently associated with a higher risk of death.[26,38] This can be explained by the increase in the severity of the disease and the increase in organ dysfunctions. The demonstration that patients who develop proteinuria during hospitalisation have a worse prognosis can also be interpreted as the renal reflection of the systemic inflammatory state. Although publications report that 35-60% of patients who develop AKI during COVID-19 have permanent deterioration in renal function during follow-up[13,39], there are also studies showing all patients who develop AKI return to their initial kidney functions.[15] This difference is because the severity of the disease differs between studies.

As in our study group, hypertension is the most common co-morbidity in COVID-19 patients and is a risk factor for severe illness and death. Impaired hypertension regulation is also an independent predictor of the development of AKI.40 We found that creatinine and proteinuria increases were higher in patients with a history of hypertension during follow-up. The relationship between hypertension and COVID-19 is explained by the interaction of the virus with ACE2, the gateway to hosting cells[41], and endothelial dysfunction.[42] Tubular and glomerular visceral epithelial cells of the kidney are the main targets of SARS-CoV-2. The resulting inflammatory state increases endothelial damage while the endothelium is not expected to be directly infected with SARS-CoV-2.[28] Our patient group also found that blood pressures were higher than basal levels at the end of follow-up in groups with both proteinuria and creatinine increases. Other reasons for the deterioration in blood pressure regulation in our patients may be the discontinuation of RAS blocker drugs in the early stages of the epidemic, with the belief that ACEi or ARB drugs adversely affect the course of the disease or the fact

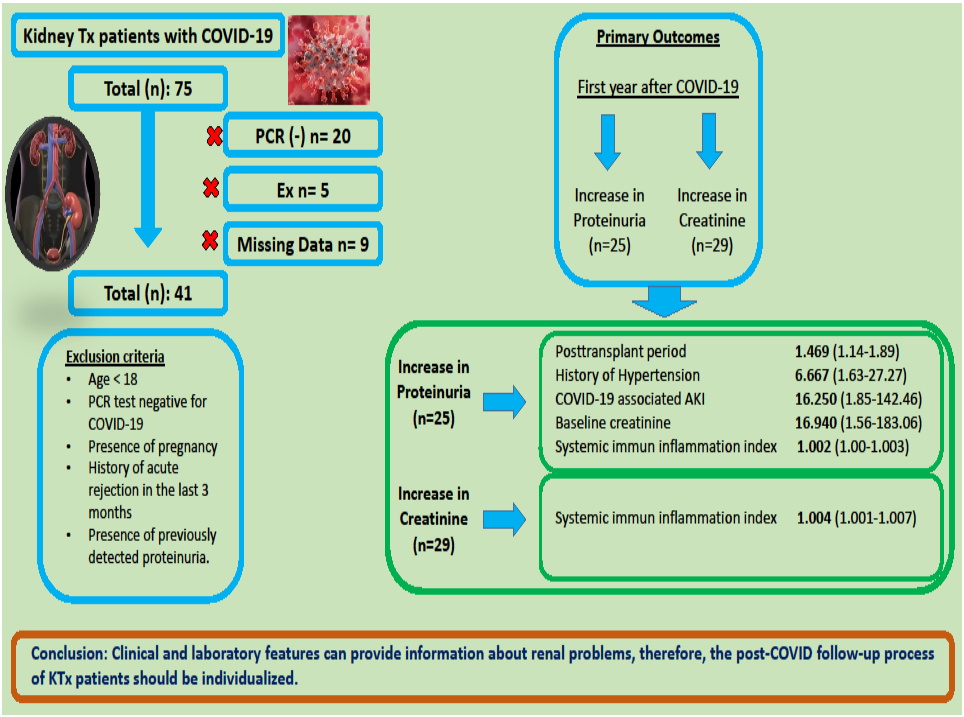

Figure 1. Study brief.

that the virus may change the homeostasis of the renin-angiotensin-aldosterone system (RAAS) with the ACE2 interaction.[43]

Longer transplantation time is associated with higher mortality and more frequent AKI during COVID-19.[5] We found that patients with a long transplantation period have more proteinuria after COVID-19. This is due to the advanced age of the graft being more prone to renal injury.

In the long term, one of the critical factors affecting renal functions is the immunosuppressive treatments reduced during COVID-19. All of our patients' immunosuppressive therapies were returned to the basal levels within two weeks at the latest after COVID. In a study evaluating the effects of reduced immunosuppressive treatments on renal functions in the early post-COVID period (within the first three weeks), it was observed that patients with reduced immunosuppression had better graft function in the early period, which was attributed to a temporary glomerular filtration rate elevation as a result of reduction of calcineurin inhibitors (CNI).[44] Immune dysregulation due to COVID-19 may trigger disease activation or acute T-cell-mediated graft rejection in patients with the underlying immune disease.[4] Studies, including histopathological evaluations, show that rejection frequency is very low in the early period, and reduced immunosuppression is well tolerated.[3,4,13-1]5 However, rejection should be considered in the differential diagnosis of patients with proteinuria or increased creatinine in long-term follow-up. Since a kidney biopsy was not performed on any patient in our study, we can't comment on this situation.

Our study has some limitations. One of the most important limitations of our study is the absence of a control group. The limited number of patients is another limitation. The fact that no biopsy was performed in any patient with proteinuria or increased creatinine prevents us from commenting on the type of renal dysfunction that developed. Although DSA test positivity was taken as an exclusion criterion since it would lead to suspicion of graft rejection, the most important limitation of this study is that kidney biopsy could not be performed in patients with increased creatinine or worsening proteinuria.

CONCLUSIONS

As a result, we have shown that clinical and laboratory features such as high SII, increased proteinuria, hypertension, development of AKI, and long post-transplant time can provide information about renal problems we may encounter in the long term (Figure 1). Therefore, the post-COVID follow-up process of KTx patients should be individualised.

Highlights

- Patients with high SII were more fragile regarding renal functions after COVID-19.
- SII was an independent predictor of the change in serum creatinine and proteinuria after COVID-19.
- Post-COVID renal dysfunction may be more severe in patients with high initial proteinuria and creatinine level.
- Patients with a long transplantation period and hypertensive had higher renal dysfunction risk in the long term after COVID-19.

Conflicts of Interest

All authors declare that there is no conflict of interest in this study.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Necmettin ERBKAN University, Faculty of Medicine, Meram, Konya, Turkey. (Decision number: 2022-3845, date: June 2022).

Authors' Contribution

Study Conception: HÖ, KZ,; Study Design: HÖ, HZT,; Supervision: HÖ, İB, FY,; Literature Review: HÖ, İB, KT,; Critical Review: HZT, KT NYS,; Data Collection and/or Processing: YÖ, FY, İB,; Statistical Analysis and/or Data Interpretation: İB, NYS,; Manuscript preparing: HÖ, İB.

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