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ORIGINAL PAPER

Late Renal Effects of COVID-19 in Kidney Transplant Recipients: A Single-Center Study

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ABSTRACT

Introduction: During the coronavirus disease 2019 (COVID-19) pandemic, kidney transplant recipients had higher rates of hospitalization and mortality. However, data on the late renal effects of the infection are scarce. **Objectives:** This study aims to describe the evolution of renal function and proteinuria in kidney transplant recipients after the infection. **Methods:** Single-center prospective cohort study. A total of 321 kidney transplant recipients who survived COVID-19 from March 2020 to December 2022 were included. Data on renal function, proteinuria, and immunosuppression were analyzed pre-infection, 3 and 6 months post-infection. **Results:** Most patients were male (58.9%), with a mean age of 50 years, recipients of kidneys from deceased donors (79.4%), and with a median time after transplant of 6.6 years. There was a reduction in the level of immunosuppression, from a pre-infection Vasudev score of 4.66 to 4.50 ($p < 0.001$) in the 3rd month and 4.54 ($p = 0.016$) 6 months post-infection. The glomerular filtration rate (GFR) remained stable at around 60 mL/min/1.73 m^2. The percentage of patients with proteinuria ≥ 1.0 increased from 9.6% pre-infection to more than 13% ($p < 0.001$) in the 3rd and 6th months after infection. Higher proteinuria levels were observed in recipients with longer follow-up post-transplant, previous rejection episodes, lower estimated GFR, and higher prevalence of donor-specific anti-HLA antibodies. **Conclusion:** Kidney transplant recipients with COVID-19 had an increase in proteinuria within 6 months after the infection despite a stable GFR.

Descriptors: Kidney transplantation; COVID-19; SARS-CoV-2; Post-Acute COVID-19 Syndrome; Proteinuria.

Efeitos Renais Tardios de Covid-19 *em Receptores de Transplante Renal: Estudo Unicêntrico*

Introdução: Durante a pandemia causada pela doença do coronavírus 2019 (COVID-19), os receptores de transplante renal apresentaram maiores taxas de hospitalização e mortalidade. No entanto, os dados sobre os efeitos renais tardios da infecção são escassos. **Objetivos:** Este estudo tem como objetivo descrever a evolução da função renal e proteinúria em receptores de transplante renal após a infecção. **Métodos:** Estudo de coorte prospectivo unicêntrico. O total de 321 receptores de transplante renal que sobreviveram à COVID-19 de março de 2020 a dezembro de 2022 foi incluído. Dados sobre função renal, proteinúria e imunossupressão foram analisados pré-infecção, 3 e 6 meses após a infecção. **Resultados:** A maioria dos pacientes era do sexo masculino (58,9%), com média de idade de 50 anos, receptor de rins de doadores falecidos (79,4%) e com mediana de tempo pós-transplante de 6,6 anos. Houve redução do nível de imunossupressão, de um escore de Vasudev pré-infecção de 4,66 para 4,50 ($p < 0,001$) no 3º mês e 4,54 ($p = 0,016$) 6 meses pós-infecção. A taxa de filtração glomerular (TFG) permaneceu estável, em torno de 60 mL/min/1,73 m^2. A porcentagem de pacientes com proteinúria ≥ 1,0 aumentou de 9,6% pré-infecção para mais de 13% ($p < 0,001$) nos 3º e 6º meses após a infecção. Níveis mais elevados de proteinúria foram observados em receptores com maior tempo de seguimento pós-transplante, episódios de rejeição prévios, menor TFG estimada e maior prevalência de anticorpos anti-HLA doador-específicos. **Conclusão:** Os receptores de transplante renal com COVID-19 tiveram um aumento na proteinúria em 6 meses após a infecção, apesar de apresentarem TFG estável.

Descritores: Transplante de Rim; COVID-19; SARS-CoV-2; Síndrome de COVID-19 Pós-Aguda; Proteinúria.

INTRODUCTION

Kidney transplant recipients are a highly vulnerable population to viral infections, with high morbidity and mortality, because of immunosuppressive therapy, low levels and short persistence of antibody titers after vaccination or infection, a procoagulant state caused by chronic kidney disease (CKD), and a higher need for hospitalization and medical assistance.[1] During the coronavirus disease 2019 (COVID-19) pandemic, kidney transplant recipients were considered at high risk for poor outcomes, which was confirmed by high rates of hospitalization and mortality.[2,3]

Acute kidney injury (AKI) is a common complication of COVID-19, even in patients with normal renal function.[4] In a previous meta-analysis, 28% of hospitalized COVID-19 patients had AKI, with 9% requiring renal replacement therapy.[5] The impact of COVID-19 on renal function can persist even after the acute phase. Within 30 days, patients who survived the infection had a higher risk of AKI, a significant decrease in the glomerular filtration rate (GFR), and a higher prevalence of end-stage renal disease, particularly among those who required hospitalization and intensive care unit (ICU) admission.[6] Several mechanisms contribute to renal dysfunction in COVID-19, including tubular injury, endothelial damage, thrombotic microangiopathy, complement activation, podocyte injury, and collapsing glomerulopathy.[1]

Despite increasing evidence of renal involvement in the post-acute phase of COVID-19, few studies have examined the late renal effects of COVID-19 among kidney transplant recipients. This study aimed to analyze renal function and proteinuria evolution in kidney transplant recipients within 6 months after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

METHODS

A single-center prospective cohort study including kidney transplant recipients older than 18, with a positive molecular diagnostic assay for COVID-19 from March 2020 to December 2022. The local ethics committee approved the study. Demographic data collected at the time of diagnosis of COVID-19 included gender, age, body mass index (BMI), type of donor, etiology of CKD, comorbidities, maintenance immunosuppression, level of immunosuppression, baseline renal function, and proteinuria. At 3 and 6 months post-infection, the following data were analyzed: maintenance immunosuppression, immunosuppression level (Vasudev scale),[7] renal function, proteinuria, and donor-specific anti-HLA antibodies (DSA). Regarding COVID-19, the data collected included hospitalization, need for ICU admission, mechanical ventilation (MV), length of hospitalization, serum creatinine levels at discharge, and immunosuppression management during and after the infection.

To evaluate the baseline renal function, the average of the last three serum creatinine (mg/dL) values was considered, and the estimated GFR (eGFR mL/min/1.73 m^2) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[8] Proteinuria was computed as the average of the last three urine protein-to-creatinine ratio (UPCR) values. Renal function and proteinuria were evaluated in the 3rd and 6th months after infection. For DSA evaluation, HLA was typed by polymerase chain reaction (PCR) amplification of genomic DNA samples, and anti-HLA antibodies were screened with solid-phase tests, as previously described.[9]

Statistical analysis

Numerical data were expressed as the median and interquartile range (IQR) and evaluated by the Mann-Whitney *U* test or by the mean and standard deviation (SD) and evaluated by the Student's *t* test for paired samples. Categorical variables, expressed as frequency and percentage, were analyzed using Pearson's chi-square test or McNemar test for paired samples. Values of $p < 0.05$ were considered statistically significant. Statistical analysis was performed using the Jamovi software (version 2.3).

RESULTS

From March 2020 to December 2022, 402 out of 1,257 kidney transplant recipients (31.9%) presented laboratory-confirmed COVID-19, with an overall lethality of 20.1% (n = 81). A total of 321 survived and were included in the study. Most included patients were male (n = 189, 58.9%), with a median age of 50.4 (40.4-58.8) years, recipients from a deceased kidney donor (n = 255, 79.4%), presenting a median post-transplant follow-up of 6.6 (3.3-13) years, and a median BMI of 27.8 kg/m^2 (24.8-30.8). The most prevalent etiologies of CKD were chronic glomerulonephritis (24.6%), hypertensive nephrosclerosis (19.9%), diabetes mellitus (12.1%), and unknown (22.1%). A high prevalence of comorbidities was observed, mainly systemic hypertension (83.5%), diabetes mellitus (37.1%), and cardiovascular diseases (10.9%).

Sixteen (4.9%) patients presented preformed DSA, and most persisted with detected DSA after infection (n=13, 81.2%). Twenty-four patients developed *de novo* DSA after infection. About 5% of the patients had a graft rejection episode before infection. The hospitalization rate for COVID-19 was 30.5%, with an average hospital stay of 17 days. Admission to ICU was required in 29.6%, and MV in 18.4%. In most patients (n = 272, 84.7%), immunosuppressive therapy was maintained; in 49 (15.3%), immunosuppression was reduced or withdrawn. At hospital discharge, mean serum creatinine was 1.67 ± 0.92 mg/dL, with a mean eGFR of 60.3 ± 30.9 mL/min.

During the 6 months post-infection, there was a reduction in immunosuppression, from a Vasudev score of 4.66 pre-infection to 4.50 ($p < 0.001$) at 3 months and 4.54 ($p = 0.016$) after 6 months. Before infection, 259 (80.7%) patients received a calcineurin inhibitor (CNI), mainly tacrolimus (n = 215, 83%). In the 3rd month, 206 (65.4%) patients received tacrolimus, 53 (16.8%) cyclosporine, and 62 (19.7%) received non-CNI immunosuppressive therapy. In the 6th month, the number of patients treated with a CNI remained stable (n = 259, 80.7%), the majority on tacrolimus (n = 204, 78.7%). The blood CNI levels were not evaluated in this series. The eGFR remained stable at around 60 mL/min/1.73 m^2, and there was no significant change in proteinuria during follow-up. The percentage of patients with UPCR in the range 1.0-3.5 increased from 9% pre-infection to 13% ($p < 0.001$) at 3 and 6 months, and the percentage of patients with UPCR ≥ 3.5 rose from 0.6% pre-infection to 3.4% ($p < 0.001$) at 3 months and 2.1% ($p < 0.001$) at 6 months (Table 1).

Table 1. Immunosuppressive treatment and evolution of immunosuppression, renal function, and proteinuria 3 and 6 months after COVID-19.

	Pre-infection (n = 321)	3 months (n = 321)	*p*-value*	6 meses (n = 313)	*p*-value*
Medication, n (%)					
Prednisone	319 (99.4)	319 (99.4)		311 (99.4)	
Cyclosporin	44 (13.7)	54 (16.8)		55 (17.6)	
Tacrolimus	215 (67.0)	207 (64.5)		204 (65.2)	
Mycophenolate	213 (66.4)	200 (62.3)		197 (62.9)	
Azathioprine	77 (24.0)	76 (23.4)		77 (24.6)	
Sirolimus	17 (5.3)	15 (4.7)		12 (3.8)	
Vasudev score	4.66 ± 1.83	4.50 ± 1.73	< 0.001†	4.54 ± 1.73	0.016†
Renal function					
Serum creatinine, mg/dL	1.46 ± 0.59	1.49 ± 0.75		1.53 ± 0.87	0.039†
eGFR	60.5 ± 23.1	61.3 ± 24.3		60.1 ± 24.0	
Proteinuria					
UPCR	0.21 (0.03-7.27)	0.21 (0.03-11.30)	0.663‡	0.19 (0.03-9.31)	0.927‡
UPCR range, n (%)					
0.2-1.0	163 (50.8)	153 (53.6)		142 (48.6)	
1.0-3.5	29 (9.0)	38 (13.1)	< 0.001§	38 (13.0)	< 0.001§
≥ 3.5	2 (0.6)	10 (3.4)	< 0.001§	6 (2.1)	< 0.001§

Source: Elaborated by the authors. *Compared to the pre-infection values. †Student's *t* test. ‡Mann-Whitney *U* test. §Pearson's chi-square test.

After 6 months of follow-up, proteinuria was available in 292 patients. Comparing groups presenting proteinuria < 1 and ≥ 1 6 months post-infection, we observed that the group with higher values of proteinuria had a longer post-transplant follow-up (11.3 vs. 6.3 years, $p = 0.008$), a higher prevalence of previous acute rejection (18.4 vs. 3.1%, $p < 0.001$), a lower eGFR at COVID-19 diagnosis (38.2 vs. 61.1 mL/min, $p < 0.001$), and a higher prevalence of DSA pre-infection (17.9 vs. 4.1%, $p = 0.003$), as well as previous proteinuria. There was no difference between the groups related to the severity of the disease or the immunosuppressive therapy management (Table 2).

Table 2. Characteristics of kidney transplant recipients stratified by proteinuria 6 months after COVID-19.

	UPCR ≥ 1 (n = 38)	UPCR < 1 (n = 254)	*p*-value
Deceased donor, n (%)	26 (68.40)	204 (80.30)	0.09*
Time post-transplant, years	11.30 (4.80-16.70)	6.30 (3.00-12.20)	0.01†
Previous rejection, n (%)	7 (18.40)	8 (3.10)	< 0.01*
Hospitalization, n (%)	16 (42.10)	70 (27.60)	0.07*
ICU	5 (31.30)	22 (31.40)	0.99*
MV	4 (25.00)	13 (18.60)	0.56*
Hospital stay, days	15 (6-32)	12 (7-20)	0.69†
Immunosuppression management, n (%)			
Maintenance	32 (84.20)	216 (85.00)	
Reduction/withdraw	6 (15.80)	38 (15.00)	0.92*
Renal function			
Serum creatinine, mg/dL	1.77 (1.32-2.63)	1.29 (1.07-1.66)	< 0.01†
eGFR, mL/min	38.20 (25.80-58.90)	61.10 (43.80-75.30)	< 0.01†
UPCR			
Before infection	1.01 (0.53-1.65)	0.17 (0.09-0.30)	<0.01†
After infection	2.08 (1.23-2.97)	0.16 (0.10-0.31)	< 0.01†
DSA, n (%)			
Before infection	5 (17.90)	9 (4.10)	<0.01*
After infection	8 (21.10)	27 (11.10)	<0.01*

Source: Elaborated by the authors. *Pearson's chi-square test. †Mann-Whitney *U* test.

DISCUSSION

There are few available data about the long-term effects of COVID-19 in renal transplant recipients, including risk for development of *de novo* DSA, increased risk for rejection or progression of graft dysfunction, and long-term proteinuria.

The development of *de novo* DSA is associated with an increased risk of antibody-mediated rejection, glomerulopathy, and graft failure.[10] Previous studies have also associated *de novo* DSA with the onset of post-transplant proteinuria.[11] Risk factors *de novo* DSA include a high HLA mismatch, inadequate immunosuppression or nonadherence, and graft inflammation caused by viral infection, cellular rejection, or ischemic injury.[10]

A study by Masset et al.[12] found that 4% of kidney transplant recipients presented DSA after COVID-19, were associated with younger age, had a transplant follow-up of less than 1 year, and had preformed DSA. The severity of COVID-19 was not related to the development of DSA, and only two patients presented proteinuria. A study by Basic-Jukic et al.[13] including 104 kidney transplant recipients followed for 6 months after COVID-19 infection showed that, despite stable GFR in most patients after the acute phase, eight (7.7%) had graft dysfunction, most presenting proteinuria, and six (5.8%) developed *de novo* DSA. A previous study from our group, including 267 kidney transplant recipients diagnosed with COVID-19 who survived for more than 3 months after the disease and had been screened for anti-HLA antibodies before or after kidney transplantation, showed that 8.2% of patients presented *de novo* DSA, being more frequent in patients without pre-transplant anti-HLA antibodies, without association with changes in immunosuppression during the disease.[14] In this series, the immunosuppression level was estimated using a scale from Vasudev et al.[7] with one unit of immunosuppression assigned for each of the following daily doses of immunosuppressive drugs: cyclosporine 100 mg, tacrolimus 2 mg, mycophenolate mofetil 500 mg, prednisone 5 mg, sirolimus 2 mg, and azathioprine 100 mg.[7] Although most patients continued to take habitual immunosuppressive drugs during COVID-19, we observed a significant reduction in their doses within the first 3 months after COVID-19, without a significant difference in the Vasudev score at the 6th-month post-disease compared to the baseline.

Proteinuria is an independent risk factor for cardiovascular disease and mortality among kidney transplant recipients, as well as a predictor of graft dysfunction and failure.[15] Several factors may be related to the development of post-transplant proteinuria, including recurrent or *de novo* glomerular diseases, acute or chronic rejection, arterial hypertension, and AKI. The occurrence of

proteinuria after a kidney transplant varies between 7.5 and 45%, depending on the method, threshold values, and the duration of post-transplant follow-up.[16]

In this series, during a 6-month follow-up after COVID-19, we observed an increased number of transplant recipients with proteinuria ≥ 1 g despite maintaining a preserved eGFR. The exact incidence of proteinuria associated with COVID-19 is unknown because of the variability in how frequently proteinuria is assessed in affected patients.[17] COVID-19 can cause hemodynamic changes, cytokine-mediated effects, and immune responses that may damage the glomerular and tubulointerstitial compartments, resulting in proteinuria.[17,18] Some individuals of African ancestry who carry the high-risk apolipoprotein L1 (APOL1) genotype may develop collapsing glomerulopathy, which presents with AKI and new-onset nephrotic range proteinuria.[17] In addition, COVID-19 can also worsen an existing immune-mediated glomerular condition, such as membranous nephropathy, lupus nephritis, and anti-glomerular basement membrane disease.[18] In patients undergoing kidney transplants, COVID-19 can worsen tissue damage in the graft, especially with longer post-transplant follow-up, lower eGFR prior to infection, and previous acute rejection episodes. In this series, we observed a higher prevalence of proteinuria in the 3rd month following COVID-19 compared to the 6th month after the disease. This finding may indicate the impact of the acute phase of COVID-19 on tissue damage and the subsequent recovery of reversible changes.

CONCLUSION

COVID-19 infection in kidney transplant recipients may lead to increased proteinuria and the development of *de novo* DSA in the post-acute phase of the disease. A better understanding of the long-term effects of COVID-19 in this population may help prevent complications and mortality. Further studies with long-term follow-up are needed.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Conception and design: Mazzali M. **Data analysis and interpretation:** Sousa MV, Mazzali M. **Article writing:** Sousa MV, Gomes BT. **Critical revision:** Gomes BT, Sousa MV, Bressanin FG, Rossi MR, Mazzali M. **Final approval:** Sousa MV.

DATA AVAILABILITY STATEMENT

Data will be provided upon request.

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