HOSPITAL DE CLÍNICAS DE PORTO ALEGRE

PROGRAMA DE RESIDÊNCIA MÉDICA

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LATE IMPACT OF EARLY-PHASE COVID-19 ON OUTCOMES OF KIDNEY TRANSPLANT RECIPIENTS THAT SURVIVED THE ACUTE INFECTION

Porto Alegre

2025

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Trabalho de Conclusão de Residência apresentado ao Programa de Residência Médica do Hospital de Clínicas de Porto Alegre como requisito parcial para a obtenção do título de especialista em Nefrologia.

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Porto Alegre

2025

CIP - Catalogação na Publicação

Manfro, Arthur Gus
Late impact of early-phase COVID-19 on outcomes of kidney transplant recipients that survived the acute infection / Arthur Gus Manfro. -- 2025.
25 f.
Orientador: Roberto Ceratti Manfro.

Trabalho de conclusão de curso (Especialização) -- Universidade Federal do Rio Grande do Sul, Hospital de Clínicas de Porto Alegre, Residencia Medica em Nefrologia, Porto Alegre, BR-RS, 2025.

1. Transplante Renal. 2. COVID-19. I. Manfro, Roberto Ceratti, orient. II. Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os dados fornecidos pelo(a) autor(a).

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Lista de Abreviaturas

AKI – Acute Kidney Injury

ANOVA – Analysis of Variance

COVID-19 – Coronavirus disease 2019

eGFR – estimated Glomerular Filtration Rate

GAMMs – Generalized Additive Mixed Models

KTR – Kidney Transplant Recipient

P/C – Protein-to-Creatinine Ratio

RT-PCR – Real-Time Polymerase Chain Reaction

Capítulo 1 – Introdução

A pandemia de COVID-19 causou grande impacto e determinou mudanças drásticas no panorama da saúde do século XXI. A alta taxa de mortalidade foi observada principalmente em populações de risco – na qual os transplantados de órgãos sólidos estavam incluídos. A população de transplantados renais foi desproporcionalmente atingida em relação às já altas taxas de morbimortalidade na população geral. Estudos de coortes de transplantados identificaram taxas de óbito de até 30% dos pacientes que se contaminavam com COVID-19 nas primeiras fases da pandemia, principalmente na era pré-vacinal.

Os pacientes transplantados renais que sobreviveram ao quadro agudo apresentaram em estudos populacionais maiores taxas de insuficiência renal aguda e rejeições do enxerto – muito em decorrência da necessidade de descontinuação temporária do esquema de imunossupressão nos pacientes que desenvolveram COVID-19 moderado e grave. Apesar dos impactos negativos em morbimortalidade aguda estarem bem descritos, a literatura científica atualmente carece de evidências mais sólidas sobre os potenciais desfechos de longo prazo dos pacientes transplantados que sobreviveram à fase aguda da infecção por COVID-19. Desta forma, o acompanhamento longitudinal destes pacientes é capaz de fornecer informações importantes sobre os desfechos duros de sobrevida do paciente e enxerto, além de marcadores funcionais – como a taxa de filtração glomerular estimada e a proteinúria.

O entendimento destes fatores é fundamental, considerando ainda a significativa prevalência de pacientes transplantados ainda sob acompanhamento das equipes transplantadoras que apresentaram infecções agudas por COVID-19 nos anos iniciais da pandemia.

Capítulo 2 – Artigo Original

Late impact of early-phase COVID-19 on outcomes of kidney transplant recipients that survived the acute infection.

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Author's Contributions

AGM participated in research design, manuscript writing and statistical analyses. ETS participated in data collection and manuscript writing. LLAB participated in data collection and manuscript writing. GP participated in data collection and manuscript writing. RFF participated in study design and data collection. CEOC participated in study design and data collection. ACB participated in study design and manuscript writing. RCM participated in study design and manuscript writing.

Conflicts of Interest

The authors declare no conflict of interest for this work.

Funding

This work was performed without any private or government specific funding.

Abstract

Background: The COVID-19 pandemic has significantly affected global health, particularly among high-risk populations such as kidney transplant recipients (KTR), who have exhibited elevated morbidity and mortality rates. Long term impact of COVID-19 in KTR who survived the infection is unknown.

Objective: This study aims to evaluate the long-term effects of early-phase COVID-19 on patient and graft survival, as well as graft function in KTRs who survived the acute phase of the COVID-19 infection.

Methods: We conducted a prospective, single-center cohort study involving KTRs who survived COVID-19 from June 2020 to January 2022. Patients were stratified by disease severity and followed for 24 months. Data on renal function (estimated glomerular filtration rate [eGFR] and urinary protein-to-creatinine ratio [P/C]) were collected at multiple time points. Statistical analyses were based on Chi-Square tests, ANOVA, Generalized Additive Mixed Models, and Kaplan-Meier analyses.

Results: Among 1,477 KTRs, 233 (15.8%) contracted COVID-19, with 60 (25.8%) fatalities. Of the 173 survivors, 50 (28.9%) had mild, 102 (59%) moderate, and 21 (12.1%) severe disease. Severe cases showed significant declines in eGFR and higher rates of renal replacement therapy and acute rejection compared to mild and moderate cases. Mean loss of glomerular filtration rate in two years of the severe COVID group was 9mL/min/m2. Graft and patient survival rates were also worse in moderate and severe COVID groups.

Conclusions: KTRs with moderate and severe COVID-19 experience significant long-term declines in renal function, increased graft loss, and mortality. Understanding these impacts is critical for optimizing care for this population.

Key-words:

COVID-19, renal transplantation, survival, glomerular filtration rate

Introduction

The COVID-19 pandemic has profoundly impacted global health, resulting in unprecedented mortality rates in the modern era[1]. Among high-risk populations, the morbidity and mortality associated with the disease were particularly severe, especially prior to the widespread availability of vaccines[2,3]. Solid organ transplant recipients, notably kidney transplant recipients (KTR), experienced significant adverse outcomes during the pandemic. Mortality rates in KTR populations ranged from 20% to 30% across various cohorts[4,5]. Compared to the general population, KTR patients exhibited higher mortality rates, even when accounting for similar disease severity[6]. Furthermore, among KTR patients who survived the infection, there are ongoing concerns regarding long-term outcomes, particularly given that many experienced acute kidney injury (AKI) and were required to taper or temporarily discontinued their immunosuppressive medications[7,8].

While the acute effects of COVID-19 KTR are well-documented, the long-term consequences of the infection in this population remain under-evaluated. Notably, the short-term impact on graft function is significant; reports indicate that 44% of KTR patients experienced AKI, 12% required renal replacement therapy, and 8% faced graft loss[9]. However, the literature has yet to comprehensively address late survival and graft outcomes. In this study, we present data on patient and graft survival, as well as the effects on graft function, in a single-center cohort of KTR who survived the early stages of the COVID-19 pandemic.

Patients and methods

Study Design and Population

The present study is a prospective, single-center cohort investigation involving KTRs at the Hospital de Clínicas de Porto Alegre, a large tertiary teaching hospital located in southern Brazil. This research included all KTR patients who survived the acute phase of COVID-19 between June 2020 and January 2022. Confirmation of COVID-19 infections was achieved through real-time polymerase chain reaction (RT-PCR) or specific antigen testing. Patients were followed for a period of 24 months after the COVID-19 diagnosis. The study received approval from the Institutional Review Board of the Hospital de Clínicas de Porto Alegre and the local ethics committee (CAEE number: 30631820.0.2012.5327).

Demographic and clinical information for the patients was obtained from clinical records or directly from patients during follow-up appointments. Baseline measurements of creatinine, estimated glomerular filtration rate (eGFR) using the CKD-EPI equation[10], and urinary spot protein-to-creatinine ratio (P/C) were collected one month prior to COVID-19 diagnosis. Follow-up assessments of creatinine, eGFR, and P/C were conducted at 6-, 12-, 18-, and 24-months post-diagnosis. Kidney transplant recipients (KTRs) were stratified according to the severity of COVID-19 as follows: (a) Mild disease patients who did not require hospital admission; (b) Moderate disease patients admitted to a clinical ward for COVID-19 treatment without the need for invasive ventilation; (c) Severe disease patients admitted to the intensive care unit and requiring mechanical ventilation support. Survival of acute infection was defined as symptom recovery and dehospitalization of those admitted to hospital care in the acute infection episode.

Statistical analysis

The study utilized three sets of statistical analyses: (a) Chi-Square tests and Analysis of Variance (ANOVA) were employed to compare demographic characteristics

and clinical outcomes among COVID-19-affected KTRs stratified by disease severity. Post-hoc analyses were performed to adjust for multiple comparisons using Tukey's tests; (b) Generalized Additive Mixed Models (GAMMs) were applied to estimate and compare the smoothed trajectories of eGFR and urinary P/C across severity groups over time - this analysis combines the flexibility of the generalized additive models with the ability to consider random effects; By evaluating repeated assessments, the model constructs a loess trajectory curve for each patient – after, it combines these individual trajectories in a regression model accounting for group differences; (c) Kaplan-Meier models were utilized to evaluate patient and graft survival. All statistical analyses were conducted using R software[11], incorporating the "tidygam," "ggplot2," and "survival" packages[12–14]. A p-value of less than 0.05 was adopted for statistical significance.

Results

Demographic traits and clinical outcomes

During the study period, a total of 1,477 KTRs were followed at our center. Among these, 233 patients (15.8%) developed confirmed COVID-19 infections, with 60 individuals (25.8%) succumbing to the disease. Among the 173 survivors, 50 (28.9%) were classified as having mild disease, 102 (59%) as having moderate disease, and 21 (12.1%) as experiencing severe COVID-19. All deaths occurred in patients classified in the severe disease group. Most patients were middle-aged, predominantly white, and had undergone transplantation approximately seven years prior to their COVID-19 diagnosis. Demographic and clinical characteristics of this cohort are detailed in Table 1.

On average, patients with mild disease exhibited higher eGFRs and lower urinary P/C ratios compared to those with more severe disease. Clinical outcomes varied

significantly among the groups, as anticipated: the requirement for renal replacement therapy was notably higher in the severe disease group compared to moderate and mild cases (67%, 5%, and 0%, respectively; $\chi^2 = 76.63$, $p < 0.001$). Additionally, the incidence of acute cellular rejection was greater in patients with severe forms of the disease (14%, 2%, and 0%, respectively; $\chi^2 = 10.80$, $p = 0.005$). All acute cellular rejections were confirmed by kidney biopsies. Furthermore, the frequency of immunosuppression tapering was significantly influenced by disease severity, with rates of 100%, 81%, and 36% for severe, moderate, and mild cases, respectively ($\chi^2 = 43.22$, $p < 0.001$). Two patients in the severe disease group presented biopsy confirmed recurrence of native kidney diseases, one with focal and segmental glomerulonephritis and the other with pauci immune vasculitis.

Trajectories of eGFR and P/C

The evaluation of eGFRs revealed that both the moderate and severe groups exhibited lower baseline renal function. Notably, only the severe group demonstrated a marked decline in eGFR during the follow-up period, particularly within the first six months post-infection. Patients in the severe group experienced a median loss of eGFR of -7 mL/min/1.73 m², whereas the mild and moderate groups maintained stable eGFRs. Generalized additive mixed models indicated a significant interaction between eGFR, severity group, and time ($F = 1.26$, $p = 0.01$). Conversely, the interaction of urinary P/C ratio, severity group, and time was not statistically significant ($F = 0$, $p = 0.58$). The eGFR and proteinuria trajectories are illustrated in Figure 1 (Panels A and B).

Graft and patient survival

Uncensored graft survival rates over the 24-month follow-up period differed significantly across severity groups. In the mild group, 100% of grafts remained

functional, compared to 83% in the moderate group and 81% in the severe group (p = 0.009). A similar behavior was observed for patient survival, with rates of 100% in the mild group, 93% in the moderate group, and 83% in the severe group (p = 0.012). These results are illustrated in Figure 2 (Panels A and B).

Of the 11 KTRs who died during follow-up, five cases (45%) were due to non-COVID-related sepsis, one due to a cardiovascular event, another due to malignancy, and four due to unknown causes. There were also 11 death-censored graft losses: nine due to end-stage allograft kidney disease, and two due to graft rejection.

Discussion

In this study, we demonstrated that acute early-phase COVID-19 infection has distinct late effects on KTR, largely influenced by disease severity. While mild cases were associated with neither significant acute distress nor long-term complications, severe cases resulted in a temporary increase in proteinuria, long-term deterioration of renal function, and a higher incidence of graft loss and death. Previous studies have already highlighted the severe outcomes of acute COVID-19 infection in KTR, with mortality rates reaching 20-30% in several cohorts[15]. Shorter follow-up studies of COVID-19 affected KTR also showed generally good outcomes for survivors with mild to moderate disease and more detrimental recovery for those affected with severe COVID-19[16]. To our knowledge, our study is the longest follow-up cohort study of COVID-19-infected KTR. Our findings contribute to the body of knowledge, showing that medium- to long-term consequences of the pandemic persist in KTR who survive the acute phase of infection.

Our data demonstrate that late clinical outcomes in KTR who survived the acute COVID-19 infection episode were profoundly influenced by the acute disease severity. Mild cases exhibited stable outcomes, with no episodes of rejection, stable eGFR, and no graft losses or deaths, behaving almost as if unaffected by the disease. Patients with moderate disease severity showed intermediate outcomes, characterized by a low frequency of acute rejection and stable eGFR, but a notable incidence of graft failure and post-infectious mortality. As hypothesized, recipients with severe COVID-19 experienced the worst outcomes, including a significantly higher incidence of rejection, graft loss, and mortality, along with substantial eGFR decline over two years compared to the mild group. These findings may be attributed not only to the direct effects of the disease, such as cytokine storms, immunomodulation, and the need for advanced life support (e.g., mechanical ventilation, vasoactive drugs, and hemodialysis), but also to alterations in immunosuppressive regimens that were indicated in the acute phase of the disease. In virtually all severe cases, immunosuppression was greatly reduced or even discontinued, potentially triggering alloimmune responses that contributed to subsequent rejection and graft loss[17,18].

Extensive research has demonstrated significant long-term detrimental effects of COVID-19 on mortality and morbidity within the general population. Survivors of COVID-19, particularly those who experienced severe disease requiring hospitalization, face markedly higher risks of adverse outcomes compared to uninfected individuals. For instance, one study indicated that individuals discharged after hospitalization for COVID-19 had a 2.2-fold increased risk of rehospitalization or death and a 4.8-fold increase in all-cause mortality compared to controls from the general population[19]. Another investigation revealed that nearly 30% of hospitalized patients succumbed within six months, with higher mortality rates observed among older patients and those requiring

mechanical ventilation[20]. In the survivor of acute disease, loss of renal clearance was observed in general population infected by COVID-19 [21,22]. Additionally, the increasingly recognized post-COVID syndrome, or long COVID, presents a significant concern[23]. This syndrome has also been studied in KTR, showing significant prevalence and impact in morbidity and labor activities[24].

Our study produced relevant information in the subject, among its strengths are the prospective evaluation of a cohort of KTR affected by COVID-19, the multiple measurements of renal function and the follow-up over an extended period. However, there are some limitations that include being a single-center cohort, which may limit the generalizability of the findings. Nonetheless, the data were collected at an established transplant center that employs updated KTR management practices, suggesting that the results are likely applicable to broader populations. Also, the observations were made prior to the widespread availability of COVID-19 vaccines and the emergence of less pathogenic variants of the virus, which is significantly different from the present scenario. The reported cases were analyzed between 2020-2022, period when the most prevalent variants were Alpha, Beta, and Gamma. Despite this, a considerable proportion of KTRs worldwide were infected under similar conditions, and many are still under medical care, potentially presenting comparable outcomes.

In conclusion, our cohort study demonstrates that KTR with moderate and severe COVID-19 infections experience significant declines in renal function, with higher rates of graft loss and mortality. Given that many KTR were infected during the early stages of the pandemic, understanding the long-term impacts on these patients may be important for informing clinical practice and optimizing their care.

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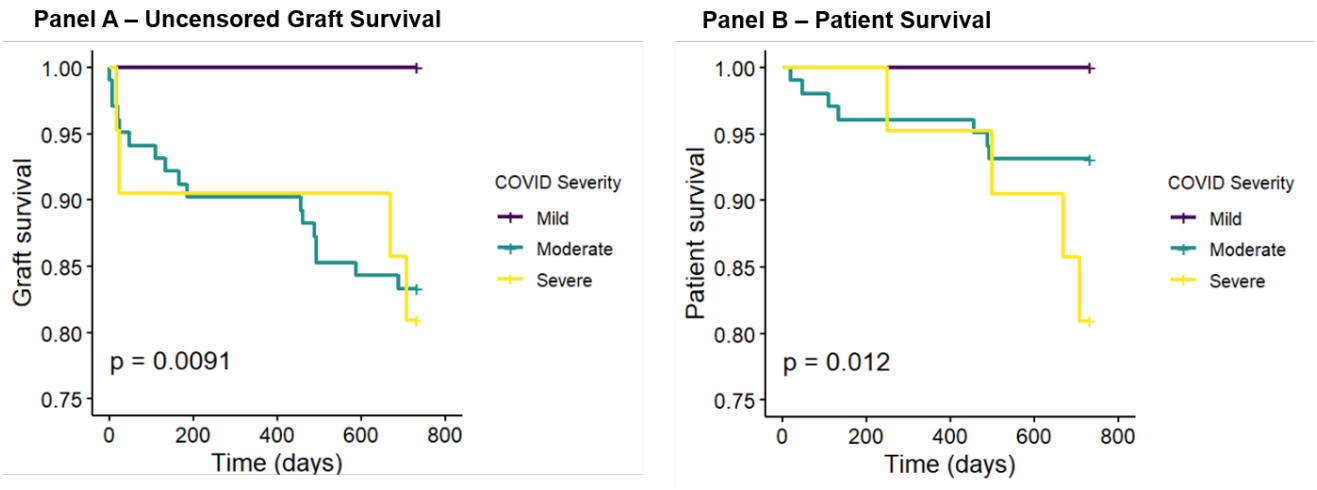
Table 1: Demographic and clinical characteristics of the kidney transplant recipient's cohort

	Mild COVID	**Moderate COVID**	**Severe COVID**	**ANOVA**		**Mild vs Moderate**		**Mild vs Severe**		**Moderate vs Severe**	
	Mean (SD)	Mean (SD)	Mean (SD)	Z	p	MD	p	MD	p	MD	p
Demographics											
*Age (years, m*ean ± SD)	48.4 (12.6)	51.9 (12.0)	53.4 (11.8)	1.8	0.168	-3.4	0.230	-5.0	0.256	-1.5	0.855
*BMI (m*ean ± SD)	27.5 (5.8)	30.0 (5.8)	29.8 (5.7)	1.6	0.211	-1.5	0.295	-2.3	0.282	-0.8	0.835
Years after transplantation	6.9 (5.7)	7.2 (5.7)	6.9 (7.4)	0.1	0.928	-0.3	0.937	0.0	0.999	0.3	0.964
Baseline serum creatinine	1.3 (0.5)	1.7 (0.9)	1.6 (0.8)	4.3	0.015*	-0.4	0.010*	-0.3	0.407	0.1	0.738
Baseline eGFR	65.5 (22.8)	54.2 (24.4)	54.2 (20.0)	4.9	0.009*	13.2	0.007*	11.3	0.166	-1.9	0.941
Baseline P/C	0.2 (0.2)	0.5 (0.7)	0.6 (1.2)	3.7	0.028*	-0.3	0.067	-0.4	0.052	-0.2	0.622
	n (%) Std. Residual	n (%) Std. Residual	n (%) Std. Residual	Chi-Squares							
Demographics											
Sex (male)	25/50 (50.0) -0.3	52/102 (51.0) -0.3	15/21 (71.4) 1.1	x2 = 3.21, p = 0.201							
Race (white)	43/50 (86.0) 0.1	87/101 (86.1) 0.1	16/21 (76.2) -0.4	x2 = 1.41, p = 0.494							
Comorbidities											
Hypertension	43/50 (86.0) 0.0	87/102 (85.3) 0.0	18/21 (85.7) 0.0	x2 = 0.01, p = 0.993							
Diabetes	14/50 (28.0) -0.8	40/102 (39.2) 0.8	6/21 (28.6) -0.5	x2 = 2.26, p = 0.324							
Cardiovascular Disease	6/50 (12.0) -0.8	18/102 (17.6) 0.2	5/21 (23.8) 0.8	x2 = 1.62, p = 0.445							
Liver Disease	2/50 (4.0) -0.4	6/102 (5.9) 0.3	1/21 (4.8) -0.1	x2 = 0.25, p = 0.882							
Lung Disease	2/50 (4.0) -0.4	7/102 (6.9) 0.7	0/21 (0.0) -1.0	x2 = 1.87, p = 0.393							
Autoimune Disease	3/50 (6.0) 1.0	3/102 (2.9) -0.3	0/21 (0.0) -0.9	x2 = 1.79, p = 0.407							
Cancer	2/50 (4.0) 0.2	4/102 (3.9) 0.2	0/21 (0.0) -0.9	x2 = 0.86, p = 0.651							
Etiology of CKD											
Hypertensive	3/50 (6.0)	7/102 (6.9)	4/21 (19.0)	x2 = 3.89, p = 0.143							

	-0.5	-0.4	1.8	
Diabetes	7/50 (14.0) -0.5	20/102 (19.6) 0.7	2/21 (9.5) -0.8	x2 = 1.65, p = 0.437
Glomerulopathy	11/50 (22.0) 0.8	17/102 (16.7) -0.2	2/21 (9.5) -0.9	x2 = 1.68, p = 0.431
Polycystic	4/50 (8.0) -0.4	12/102 (11.8) 0.6	1/21 (4.8) -0.7	x2 = 1.23, p = 0.541
Urologic	4/50 (8.0) 0.1	9/102 (8.8) 0.5	0/21 (0.0) -1.3	x2 = 1.97, p = 0.3732
Unknown / Other	21/50 (42.0) 0.2	37/102 (36.3) -0.7	12/21 (57.1) 1.2	x2 = 3.22, p = 0.200
Transplant Characteristics				
Donor (deceased)	40/50 (80.0) -0.2	83/102 (81.4) -0.1	20/21 (95.2) 0.6	x2 = 2.68, p = 0.262
Immunosuppression				
FK + AZA	2/50 (4.0) -0.2	4/102 (3.9) -0.3	2/21 (9.5) 1.0	x2 = 1.30, p = 0.522
FK + MPA	41/50 (82.0) 0.1	82/102 (80.4) 0.0	16/21 (76.2) -0.2	x2 = 0.32, p = 0.854
FK + mTOR	0/50 (0.0) -0.8	2/102 (2.0) 0.8	0/21 (0.0) -0.5	x2 = 1.41, p = 0.494
CsA + MPA	3/50 (6.0) 0.1	6/102 (5.9) 0.0	1/21 (4.8) -0.2	x2 = 0.05, p = 0.977
MPA + mTOR	1/50 (2.0) 0.6	1/102 (1.0) -0.2	0/21 (0.0) -0.5	x2 = 0.58, p = 0.746
Other	3/50 (6.0) -0.3	7/102 (6.9) 0.0	2/21 (9.5) 0.5	x2 = 0.29, p = 0.867
Outcomes				
Hemodialysis	0/50 (0.0) -2.3	5/102 (4.9) -1.9	14/21 (66.7) 7.7	x2 = 76.63, p < 0.001*
Graft Rejection	0/45 (0.0) -1.2	2/99 (2.0) -0.6	3/21 (14.3) 3.0	x2 = 10.80, p = 0.005*
Immunosuppression Tapering	18/50 (36.0) -2.9	83/102 (81.4) 1.3	21/21 (100.0) 1.6	x2 = 43.22, p < 0.001*

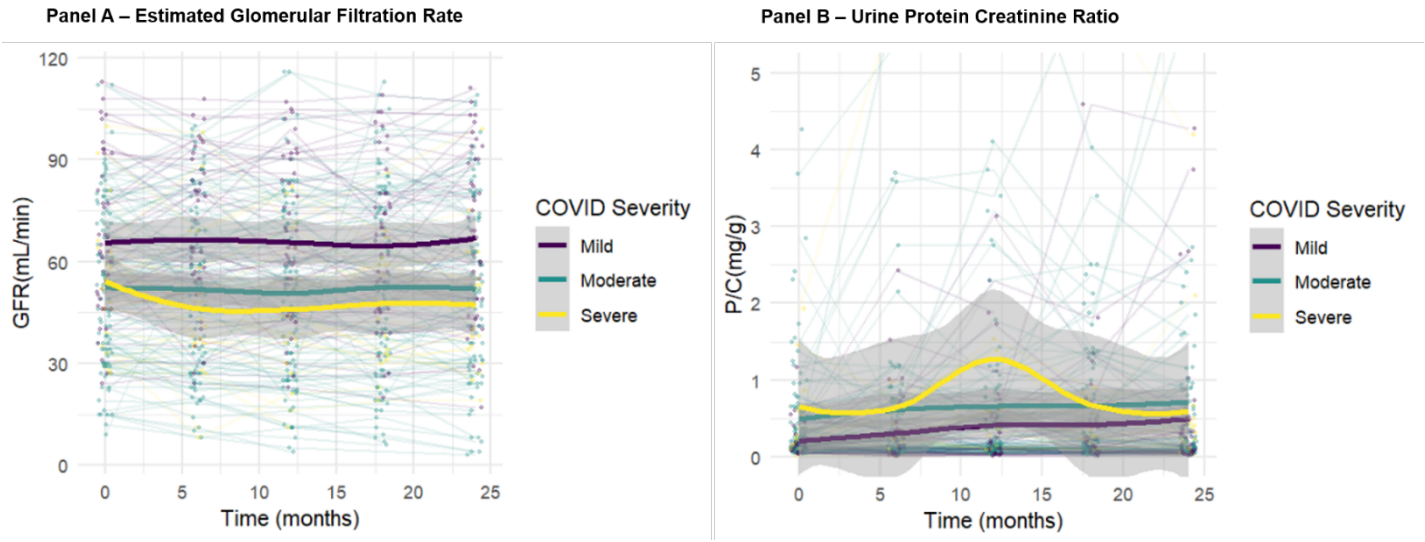
Abbreviatures: SD – Standard Deviation, MD – Mean Difference; eTFG – Estimated Glomerular Filtration Rate; P/C – Proteinuria and Creatinuria ratio; CKD – Chronic Kidney Disease; FK – Tacrolimus; AZA – Azthioprine; MPA – Mycophenolic Acid; mTOR - Mammalian Target of Rapamicyn Inhibitors; CsA - Ciclosporine

Figure 1 – Kaplan-Meir survival of kidney grafts and KTR patients in follow-up



Legend: Kaplain-Meier survival statistics for graft (Panel A) and KTR patients (Panel B) in follow-up, showing higher rates of graft loss and patient mortality in KTR with moderate and severe COVID. Graft losses are not censored for death in the present analysis and Kaplain-Meier graphics are censored in p75. P values are depicted in the lower left of each panel.

Figure 2 – Distinct trajectories of glomerular filtration rate and urine protein creatinine ratio over time



Legend: Generalized Mixed-Effects Model graphics for estimated glomerular filtration rate (Panel A) and urine protein-to-creatinine ratio (Panel B), stratified by COVID-19 severity. Each line represents an individual patient's exams in multiple follow-up assessments. The bold line represents the loess regression of each severity group – demonstrating glomerular filtration loss in patients with severe COVID-19.

Capítulo 3 – Considerações finais

O estudo apresentado como trabalho de conclusão da residência médica em Nefrologia apresenta dados que evidenciam aumento de morbimortalidade em pacientes transplantados renais que tiveram infecções moderadas e graves por COVID-19 no início da pandemia. Os dados demonstram piores desfechos de sobrevida tanto dos enxertos quanto dos pacientes, em relação aos transplantados renais que tiveram COVID-19 sem critério de gravidade. Além disso, a avaliação longitudinal destes pacientes mostrou que aqueles que foram acometidos por COVID-19 grave apresentaram perda progressiva de taxa de filtração glomerular estimada no primeiro semestre após a infecção, sem apresentar recuperação deste declínio após seguimento de 24 meses.

Os achados deste estudo evidenciam a necessidade de acompanhamento próximo e regular de pacientes transplantados renais que tiveram infecção por COVID-19. Apesar de o momento atual ser caracterizado por menor circulação viral, além de cepas menos virulentas e impactos clínicos atenuados pela vacinação em larga escala, os achados ainda são relevantes pela alta prevalência de transplantados acometidos pela infecção no início da pandemia. Estes pacientes, em especial aqueles que tiveram necessidade de internação de CTI, devem ser avaliados de forma mais próxima pelo risco de perda de função do enxerto.