The Mycophenolate-based Immunosuppressive Regimen Is Associated With Increased Mortality in Kidney Transplant Patients With COVID-19

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Background. The chronic use of immunosuppressive drugs is a key risk factor of death because of coronavirus disease 2019 (COVID-19) in kidney transplant recipients (KTRs), although no evident association between the class of immunosuppressive and outcomes has been observed. Thus, we aimed to compare COVID-19–associated outcomes among KTRs receiving 3 different immunosuppressive maintenance regimes. **Methods.** This study included data from 1833 KTRs with COVID-19 diagnosed between March 20 and April 21 extracted from the national registry before immunization. All patients were taking calcineurin inhibitor associated with mycophenolate acid (MPA, n = 1258), azathioprine (AZA, n = 389), or mammalian targets of rapamycin inhibitors (mTORi, n = 186). Outcomes within 30 and 90 d were assessed. **Results.** Compared with patients receiving MPA, the 30-d (79.9% versus 87.9% versus 89.2%; $P < 0.0001$) and 90-d (75% versus 83.5% versus 88.2%; $P < 0.0001$) unadjusted patient survivals were higher in those receiving AZA or mTORi, respectively. Using adjusted multivariable Cox regression, compared with patients receiving AZA, the use of MPA was associated with a higher risk of death within 30 d (adjusted hazard ratio [aHR], 1.70; 95% confidence interval [CI], 1.21-2.40; $P = 0.003$), which was not observed in patients using mTORi (aHR, 0.78; 95% CI, 0.45-1.35; $P = 0.365$). At 90 d, although higher risk of death was confirmed in patients receiving MPA (aHR, 1.46; 95% CI, 1.09-1.98; $P = 0.013$), a reduced risk was observed in patients receiving mTORi (aHR, 0.59; 95% CI, 0.35-0.97; $P = 0.04$) compared with AZA. **Conclusions.** This national cohort data suggest that, in KTRs receiving calcineurin inhibitor and diagnosed with COVID-19, the use of MPA was associated with higher risk of death, whereas mTORi use was associated with lower risk of death.

(*Transplantation* 2022;106: e441–e451).

Received 13 March 2022. Revision received 10 May 2022.

Accepted 23 May 2022.

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<zdoi;10.1097/TP.0000000000004231>

INTRODUCTION

Viral infections are associated with morbidity and mortality among kidney transplant recipients (KTRs), with the lifelong immunosuppressive drug exposure identified as the key risk factor.[1] Thus, early in the coronavirus disease 2019 (COVID-19) pandemic, KTRs were considered at higher risk for unfavorable outcomes,[2] ultimately confirmed by several reports demonstrating high hospitalization and high fatality rates.[3-5] Although the clinical outcomes seem to be similar comparing recipients of solid organ transplants and nontransplanted patients,[6,7] our previous analysis showed that KTRs presented a 6% per day increased risk of death during the first 30 d after the COVID-19 diagnosis, leading to a higher 30-d case fatality rate than patients undergoing dialysis.[8] Albeit the cumulative number of comorbidities are prevalent in both groups, the chronic use of immunosuppressive drugs is a determinant additional risk factor.

The risk of viral infection and the outcome of the disease is associated with the drug class and the net immunosuppressive effect of the combination regimen. Clinical trials consistently showed the lower immunosuppressive efficacy of azathioprine (AZA) than mycophenolate acid (MPA) or mammalian targets of rapamycin inhibitors (mTORi) for the prevention of acute rejection.[9-11] Furthermore, compared with AZA, the use of MPA is associated with an increased risk of virus-related events.[12,13] On the other hand, the use of mTORi has been associated with a reduced risk of virus infections.[14-16] Particularly for cytomegalovirus infection, mTORi interferes with critical viral replication pathways, preventing viral reactivation and restoring functional T-cells subsets, consequently improving the specific immune responses.[17-19]

The impact of the maintenance immunosuppressive regimen on the outcomes of the respiratory virus infection is unclear. For instance, in the previous influenza A H1N1 outbreak, the use of MPA was not associated with poor outcomes compared with other drugs.[20] In addition, no evident association between the class of immunosuppressive drug and the risk of inhospital death was observed in a large cohort of immunocompromised patients, including solid organ transplant recipients.[21] Nevertheless, in our previous preliminary analysis, although the use of MPA was associated with increased risk, the use of mTORi was associated with reduced risk of COVID-19–associated death.[22] Thus far, data on the impact of immunosuppressive regimens on COVID-19–clinical outcomes are lacking. Therefore, the present study seeks to compare COVID-19–associated outcomes among KTRs receiving calcineurin inhibitor (Cni) in combination with AZA, MPA, or mTORi.

MATERIALS AND METHODS

Study Design

This is a multicenter retrospective cohort study comprising data from 44 transplant centers included in the COVID-19-KT Brazil Study. The study was approved by the National Ethics Research Committee (approval number 4.033.525) and by the local ethics committee of each participating center, and it was registered at clinical trials.gov (NCT04494776). Informed consent or its exemption followed specific national legislation, local institutional review board recommendations, and the guidelines of the Declaration of Helsinki.

Inclusion and Exclusion Criteria

Adult KTRs (aged ≥18 y) with symptomatic COVID-19 diagnosed by reverse-transcription polymerase chain reaction between March 2020 and April 2021, before the COVID-19 immunization campaign were eligible. The final follow-up date was the date of death or 90 d after the COVID-19 diagnosis. For the present analysis, patients had to be receiving a maintenance immunosuppressive regimen based on Cni associated with AZA, MPA, or mTORi at the time of the COVID-19 diagnosis. Recipients of kidney combined with another solid organ transplant were excluded. Patients receiving other immunosuppressive drug combinations, with missing immunosuppression and primary outcome data, were also excluded.

Variables of Interest and Definitions

Demographic and baseline data comprised recipient age, sex, ethnicity, body mass index, chronic kidney disease (CKD) cause, comorbidities, time after transplantation, baseline renal function, and maintenance immunosuppressive regimen. For baseline renal function, the median value of the last 3 available serum creatinine was considered, and the estimated glomerular filtration rate (eGFR) was estimated by the CKD-epidemiology equation.[23] The following comorbidities were reported: hypertension, diabetes, cardiovascular, pulmonary, or liver diseases, current or previous neoplasia, and peripherical vascular disease. The COVID-19–attributable signs and symptoms were fever, cough, dyspnea, myalgia, headache, fatigue, asthenia, diarrhea, nausea, and vomiting. The criteria for hospitalization and the clinical management for COVID-19 treatments of patients who were allocated to home care or admitted to the hospital were defined by the investigators according to local practices. Similarly, immunosuppression was adjusted after diagnosis per local practices.

This study was partially funded by EMS, and it also received financial support from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES), Finance Code 88881.507066/2020-01, Edital 11/2020.

Trial registration: ClinicalTrials.gov NCT04494776.

L.R.R.-M., L.G.M.d.A., T.V.d.S.F., H.T.-S., and J.M.-P. contributed to research design. L.R.R.-M., L.G.M.d.A., T.V.d.S.F., and H.T.-S. involved in writing of the paper. L.R.R.-M., L.G.M.d.A., T.V.d.S.F., M.P.C., L.A.V., M.R.N., V.D.G., R.C.M., D.R.S., R.A.M.d.B.A., G.F.F., K.M.A.H.C., P.R.d.L., A.P.-S., I.M.M.F.C., L.M.D., T.C.A.F., M.M., C.A.C.C., R.B.O., H.T.-S., and J.M.-P. contributed to the performance of the research. L.R.R.-M., L.G.M.d.A., T.V.d.S.F., and H.T.-S. contributed to data analysis. L.R.R.-M., L.G.M.d.A., T.V.d.S.F., M.P.C., L.A.V., M.R.N., V.D.G., R.C.M., D.R.S., R.A.M.d.B.A., G.F.F., K.M.A.H.C., P.R.d.L., A.P.-S., I.M.M.F.C., L.M.D., T.C.A.F., M.M., C.A.C.C., R.B.O., H.T.-S., and J.M.-P. involved in approving the manuscript.

The authors declare no conflicts of interest.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantjournal.com).

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ISSN: 0041-1337/20/10610-e441

DOI: 10.1097/TP.0000000000004251

Outcome

The primary outcome was death by any cause within 30 and 90 d after the COVID-19 diagnosis. The intermediate outcomes were hospitalization, admission to intensive care unit (ICU), and requirement for mechanical ventilation.

Statistical Analyses

Analyses were conducted using the R Statistical language (version 3.6.3; R Core Team, 2020).

Groups

The cohort was stratified into 3 groups according to the baseline maintenance immunosuppressive regimen at the time of COVID-19 diagnosis: Cni associated with AZA (Cni-AZA), Cni associated with MPA (Cni-MPA), and Cni associated with the mTORi (Cni-mTORi).

Missing Data and Imputation

Details of missing data, mostly <1%, are presented in **Tables S1 and S2** (**SDC**, http://links.lww.com/TP/C485). The strategy for handling missing values was the multiple imputation by chained equations, generating plausible numbers derived from distributions of and relationships among observed variables in the data set, following 3 steps: (1) generating replacement values for missing data and repeating this procedure 10 times; (2) analyzing the 10 imputed data sets; and (3) pooling the results according to Rubin's rules.

Univariate Comparisons

Demographic data, comorbidities, COVID-19–attributable signs/symptoms, and intermediate outcomes were stratified by groups of baseline immunosuppressive regimen, and data were compared by Kruskal-Wallis for continuous variables and by χ^2 or the Fisher exact test for categorical variables or outcomes. Post hoc analyses based on Pearson's χ^2 test residuals for counting data or Dunn's nonparametric all-pairs comparison test for Kruskal-type ranked data were performed to identify significant differences for each group. The primary outcome was evaluated by Kaplan-Meier curves, stratified by groups, and compared by log-rank test, adjusted by a test for trend.

Cox Regression Analysis

The association between variables and the probability of death within 30 and 90 d after the COVID-19 diagnosis was analyzed by univariable and multivariable Cox regression. The variables that reached a P value <0.20 in the univariate analyses were included in the multivariate models. The proportional hazards assumption was tested with the Schoenfeld residuals, and the Cox models reached the proportionality in all analyses. Aiming to account for changes in clinical practices throughout the pandemic progression, time in months from COVID-19 diagnosis since the index case on March 3, 2020, was included as a covariate. In addition, owing to the potential variation in clinical management between the transplant centers, the multivariable Cox models were adjusted for centers and added as a random intercept. The group of patients receiving AZA was used as the reference group for Cox regression modeling because of its lower efficacy for the prevention of acute rejection (lower net immunosuppressive state) and the opposite effects of MPA and mTORi on the risk of viral infections.

Sensitivity Analyses

In a sensitivity analysis, the association between the baseline maintenance immunosuppressive regimen and death within 30 and 90 d after the COVID-19 diagnosis was investigated in the subgroup of patients who were hospitalized, admitted to ICU, and required mechanical ventilation, using multivariable Cox regression analysis adjusted for center effect.

RESULTS

Patient Disposition and Demographic Data

Between March 2020 and April 2021, 2225 patients enrolled in the COVID-19-KT Brazil Study were older than 18 y and had symptomatic COVID-19 diagnosed by reverse-transcription polymerase chain reaction. Fifty-four patients who had undergone a kidney combined with another solid organ transplant, 270 receiving any immunosuppressive regimen other than those of interest in the current analysis, 35 with no information about immunosuppression, and 33 with a missing outcome status were excluded. Thus, 1833 patients were analyzed: 389 receiving Cni-AZA, 1258 Cni-MPA, and 186 Cni-mTORi. The detailed patient flowchart is shown in Figure 1.

The demographic data, comorbidities, and COVID-19–attributable signs/symptoms according to the maintenance immunosuppressive regimen are shown in Table 1. There were no differences in age, sex, body mass index, and baseline eGFR according to groups, but glomerulonephritis as the CKD cause was slightly more frequent in the Cni-MPA and less frequent in the Cni-mTOR group. A higher proportion of patients received a transplant from a deceased donor in the Cni-MPA group, whereas the lower frequency occurred in the Cni-AZA group. Time after transplantation was longer among patients using Cni-AZA and shorter in the Cni-mTORi group. Although a higher proportion of patients were receiving cyclosporin in the Cni-AZA, a lower proportion of patients in the Cni-mTORi group were receiving steroids. Finally, diabetes was more frequent in the Cni-mTORi group. Despite that the combination of Cni and MPA has been the predominant regimen, there was a difference in the frequency of the maintenance immunosuppressive regimen according to the center, which is detailed in **Figure S1** (**SDC**, http://links.lww.com/TP/C485).

COVID-19 Clinical Presentation and Immunosuppressive Drug Changes

A bimodal distribution of COVID-19 cases during the study period was observed in all groups, in line with the first and second COVID-19 waves observed in the country (**Figure S2, SDC**, http://links.lww.com/TP/C485). Most COVID-19–attributable signs/symptoms were similar among the groups (Table 1), except for fever, which was more frequent in the Cni-mTORi group, for fatigue/asthenia, and for gastrointestinal symptoms, which were more frequent in the Cni-MPA and less frequent in the Cni-AZA groups.

Clinical management and supportive treatment were carried out according to local practices. A higher proportion of patients receiving Cni-MPA required immunosuppressive drug dose changes (36.0%, AZA versus 61.6%, MPA versus 38.2%, mTORi; $P < 0.001$). Although a lower

proportion of patients in the Cni-mTORi had all drugs completely withdrawn (19.3%, AZA versus 21.5%, MPA versus 12.9%, mTORi; $P = 0.02$), MPA dose reduction/discontinuation was higher than AZA or mTORi (13.9%, AZA versus 35.4%, MPA versus 22.0%, mTORi; $P < 0.001$). These results are detailed in **Table S3** (**SDC**, http://links.lww.com/TP/C485). In addition, **Table S4** (**SDC**, http://links.lww.com/TP/C485) shows the frequency of the immunosuppression changes after the COVID-19 diagnosis stratified by centers.

Outcomes

We observed a lower 30-d (79.9% versus 87.9% versus 89.2%; $P < 0.0001$, log-rank test for trend) and 90-d (75% versus 83.5% versus 88.2%; $P < 0.0001$, log-rank test for trend) patient survival in the Cni-MPA group than in the Cni-AZA and Cni-mTORi groups, respectively (Figure 2). The distribution of death within 30 d after COVID-19 diagnosis over time and stratified by groups are shown in **Figure S3** (**SDC**, http://links.lww.com/TP/C485). Following the number of cases, the number of deaths also presented a bimodal distribution.

The overall hospitalization rate was 65.5% and lower among patients in the Cni-AZA group than in the Cni-MPA (45.6% versus 66.7%; $P < 0.001$) and Cni-mTORi groups (45.6% versus 61.1%; $P = 0.001$; Figure 3). The overall admission rate to the ICU was 32.3%, higher in the Cni-MPA group than in the Cni-AZA (35.7% versus 25.8%; $P < 0.001$) and Cni-mTORi groups (35.7% versus 22.6%; $P < 0.001$). Finally, 23.5% of the patients required mechanical ventilation, a higher proportion in the Cni-MPA group than in the Cni-AZA (26.8% versus 17.8%; $P < 0.001$) and Cni-mTORi groups (26.8% versus 13.4%; $P < 0.001$).

After the COVID-19 diagnosis, 369 patients had the immunosuppression completely withdrawn. They represented 33% of patients who needed hospitalization (n = 367), 53% who were admitted to the ICU (n = 312), and 64% who required mechanical ventilation. Among them, the death rate was 50.1% (n = 185), which represented 57% of total deaths.

Because 35.4% of patients in the MPA group had the MPA dose reduced or discontinued, the patient survival stratified by the immunosuppression change after COVID-19 diagnosis was investigated in this group (Figure 4). The 30- and 90-d survival was lower in patients who continued the MPA on their usual dose (versus MPA dose reduced or discontinued): 78% and 72% versus 83% and 81%, respectively ($P < 0.001$).

Risk Factors Associated With Death Within 30 and 90 d After COVID-19 Diagnosis

Using multivariable Cox regression analysis adjusted for center effect, the use of Cni-MPA was associated

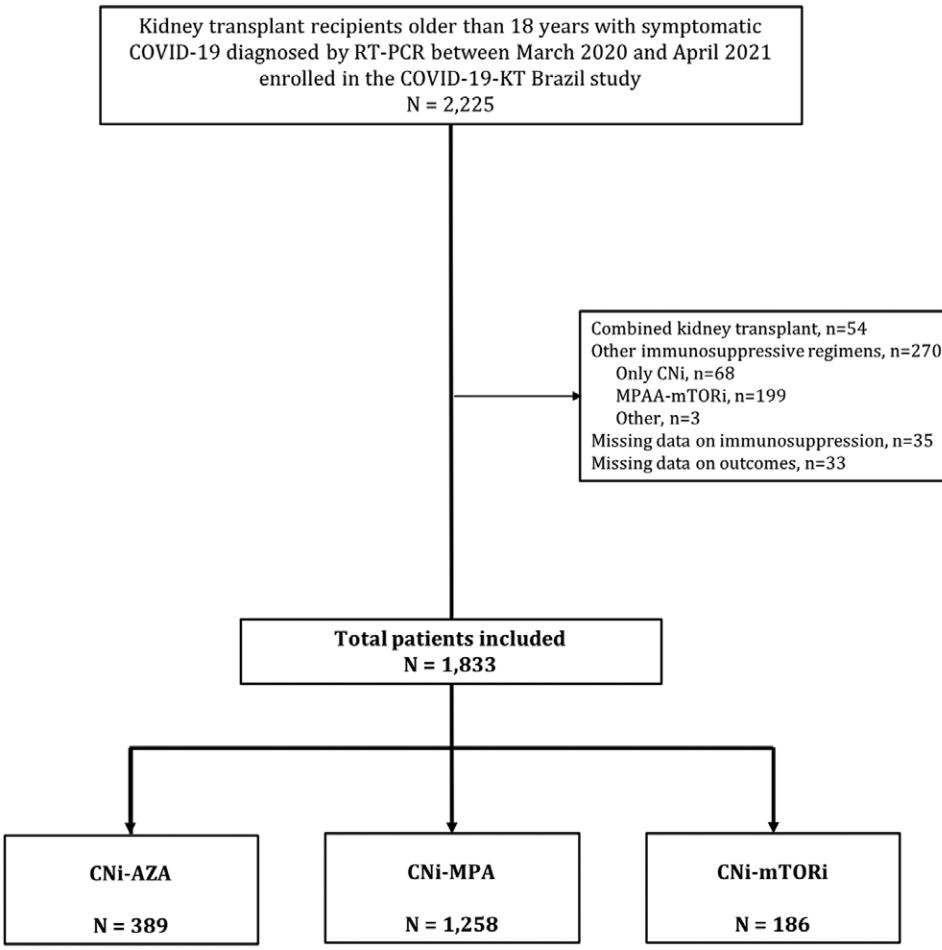

FIGURE 1. Detailed patient flowchart. AZA, azathioprine; CNi, calcineurin inhibitor; COVID-19, coronavirus disease 2019; KT, kidney transplant; MPA, mycophenolic acid; MPAA, MPA analogs; mTORi, mammalian target of rapamycin inhibitor; RT-PCR, reverse-transcription polymerase chain reaction.

TABLE 1.

Demographic data, comorbidities, and COVID-19–attributable symptoms stratified by the baseline maintenance immunosuppressive regimens

Characteristic	CNi-AZA N = 389	CNi-MPA N = 1258	CNi-mTORi N = 186	*P*
Demographic data				
Age, y	51 (41–60)	52 (42–60)	52 (42–61)	0.92
Ethnicity, n (%)				
White	265 (68)	775 (63)	108 (58)	0.01
Afro-Brazilian	116 (30)	457 (37)	74 (40)	
Other	7 (1.8)	7 (0.6)	4 (2.2)	
Male sex, n (%)	229 (59)	770 (61)	120 (65)	0.42
BMI, kg/m^2	27.0 (24.2–30.0)	26.6 (23.7–30.2)	26.2 (23.8–29.0)	0.23
Donor source, n (%)				
Living	202 (52)	326 (26)	65 (35)	<0.001
Deceased	187 (48)[a]	932 (74)[a]	121 (65)	
CKD cause, n (%)				
Diabetes	53 (18)	210 (19)	36 (22)	0.012
Glomerulonephritis	54 (18)	239 (22)[b]	17 (10)[b]	
Hypertension	41 (14)	176 (16)	32 (19)	
Other	147 (50)	467 (43)	82 (49)	
Time after transplantation, y	7.5 (3.8–12.6)	5.0 (1.9–9.4)[c]	3.4 (1.2–5.7)[c]	<0.001
eGFR, mL/min/1.73 m^2	50 (38–64)	48 (33–65)	50 (36–64)	0.53
Type of CNi, n (%)				
Cyclosporin	94 (24)[a]	89 (7.1)[a]	0 (0)[a]	<0.001
Tacrolimus	295 (76)[a]	1,169 (93)[a]	186 (100)[a]	
Use of steroids, n (%)	385 (99)[a]	1.195 (95)	162 (87)[a]	<0.001
Comorbidities, n (%)				
Hypertension	296 (76)	984 (78)	143 (77)	0.66
Diabetes	114 (29)	426 (34)	84 (45)[b]	<0.001
Cardiovascular disease	27 (6.9)	148 (12)	18 (9.7)	0.024
Liver disease	4 (1.0)	34 (2.7)	4 (2.2)	0.13
Lung disease	4 (1.0)	37 (2.9)	2 (1.1)	0.055
Peripherical vascular disease	0 (0)	4 (0.3)	0 (0)	0.73
Neoplasia	11 (2.8)	45 (3.6)	11 (5.9)	0.18
Use of ACEi or ARB	133 (35)	362 (29)	59 (32)	0.065
COVID-19–attributable symptoms, n (%)				
Fever	196 (50)	703 (56)	128 (69)[b]	<0.001
Cough	211 (54)	678 (54)	90 (48)	0.35
Dyspnea	123 (32)	413 (33)	48 (26)	0.16
Fatigue and or asthenia	57 (15)[a]	341 (27)[a]	35 (19)[a]	<0.001
Myalgia	176 (45)	526 (42)	81 (44)	0.48
Gastrointestinal	96 (25)[a]	487 (39)[a]	60 (32)	<0.001
Mental confusion	4 (1.0)	12 (1.0)	2 (1.1)	0.93

The values for continuous variables are presented as median (first and third interquartile range).
[a]$P < 0.001$: post hoc analyses based on Pearson's χ^2 test residuals for counting data.
[b]$P > 0.01$ and <0.05: post hoc analyses based on Pearson's χ^2 test residuals for counting data.
[c]$P < 0.001$: post hoc analysis based on Dunn's nonparametric all-pairs comparison test for Kruskal-type ranked data.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AZA, azathioprine; BMI, body mass index; CKD, chronic kidney disease; CNi, calcineurin inhibitor; COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; MPA, mycophenolate acid; mTORi, mammalian target of rapamycin inhibitor.

with a 70% increased risk of death within 30 d (adjusted hazard ratio [aHR], 1.70; 95% confidence interval [CI], 1.21-2.40; *P* = 0.003) compared with Cni-AZA. In addition, increasing age and body index mass and history of diabetes and cardiovascular disease were associated with increased risk of 30-d mortality, whereas higher baseline eGFR and time since the index case were associated with reduced risk of 30-d mortality (Table 2). Similarly, the use of MPA was associated with 46% increased risk of death within 90 d (aHR, 1.46; 95% CI, 1.09-1.98; *P* = 0.013), whereas the use of Cni-mTORi was associated with 41% reduced risk (aHR, 0.59; 95% CI, 0.35-0.97; *P* = 0.04) compared with Cni-AZA. Additional risk factors included increasing age and body index mass, deceased donor type, and history of diabetes and cardiovascular disease, whereas baseline eGFR and time since the index case were associated with reduced risk of 90-d mortality (Table 3).

Sensitivity Analyses

Using an indirect measure of disease severity and progression, we compared 30-d mortality stratified by immunosuppressive regimen among patients admitted to the hospital and to the ICU and those requiring mechanical ventilation (Figure 5 and **Table S5, SDC**, http://links.lww.com/TP/C485). The use of Cni-MPA was associated with a 44% higher risk of death within 30 d (aHR, 1.44; 95% CI, 1.02-2.04; $P = 0.039$) among patients requiring hospitalization than the use of Cni-AZA. Among those who required ICU admission, the use of Cni-MPA was associated with a 43% higher risk of death within 30 d (aHR, 1.43; 95% CI, 1.06-1.92; $P = 0.020$), whereas the use of Cni-mTORi was associated with a 44% reduced risk (aHR, 0.56; 95% CI, 0.34-0.93; $P = 0.026$) compared with Cni-AZA. No associations between maintenance immunosuppressive regimens and 30-d mortality were observed in those who required mechanical ventilation.

The lower risk of death in patients receiving Cni-mTORi was more evident in the sensitivity multivariable analysis for death within 90 d after the COVID-19 diagnosis. The use of Cni-mTORi was associated with a 50% reduced risk for patients admitted to the hospital (aHR, 0.50; 95% CI, 0.30-0.84; $P = 0.008$) and a 41% reduced risk of death for patients who required ICU admission (aHR, 0.59; 95% CI, 0.35-0.98; $P = 0.042$) compared with Cni-AZA.

DISCUSSION

In this study, we describe the association between the baseline maintenance immunosuppressive regimens and clinical outcomes among KTRs developing COVID-19. In addition to the traditional predictors of COVID-19–related death, such as comorbidities, obesity, and poor kidney function, also confirmed in this current analysis, the risk of death was increased among patients receiving MPA and decreased in patients receiving mTORi, compared with patients receiving AZA.

Immunosuppression in KTRs has been considered one predictor of unfavorable COVID-19–related outcomes, justified by the high hospitalization rate, critical illness progression, and risk of death among those patients[22]; however, some evidence has questioned the role of immunosuppression per se, considering that KTRs usually have a cumulative number of comorbidities, whereas few observational studies found similar outcomes for transplanted patients, compared with nontransplanted, when age and comorbidities were strictly matched.[6,7]

In a recent large American cohort, the immunosuppression did not increase the risk of mechanical ventilation or death for COVID-19 patients.[21] Of note, that study enrolled >220 000 individuals, 7% of them long-term immunosuppressed for different reasons (3423 due to solid organ transplantation), and the analyses were provided after a propensity score matching with robust adjustment. In addition, no independent impact of one immunosuppressive specific class on the risk of COVID-19 death was observed, excepting rituximab for rheumatological disease and cancer.[21] Transplant patients usually require a lifelong combination of 3 immunosuppressive agents to prevent renal allograft rejection with different mechanisms of action, and investigating the impact of different combinations on COVID-19 outcomes is valuable and has not previously been extensively investigated.

The available evidence on the effect of immunosuppressive drugs on coronaviruses replication is preliminary. In vitro studies demonstrated that thiopurine analogs and

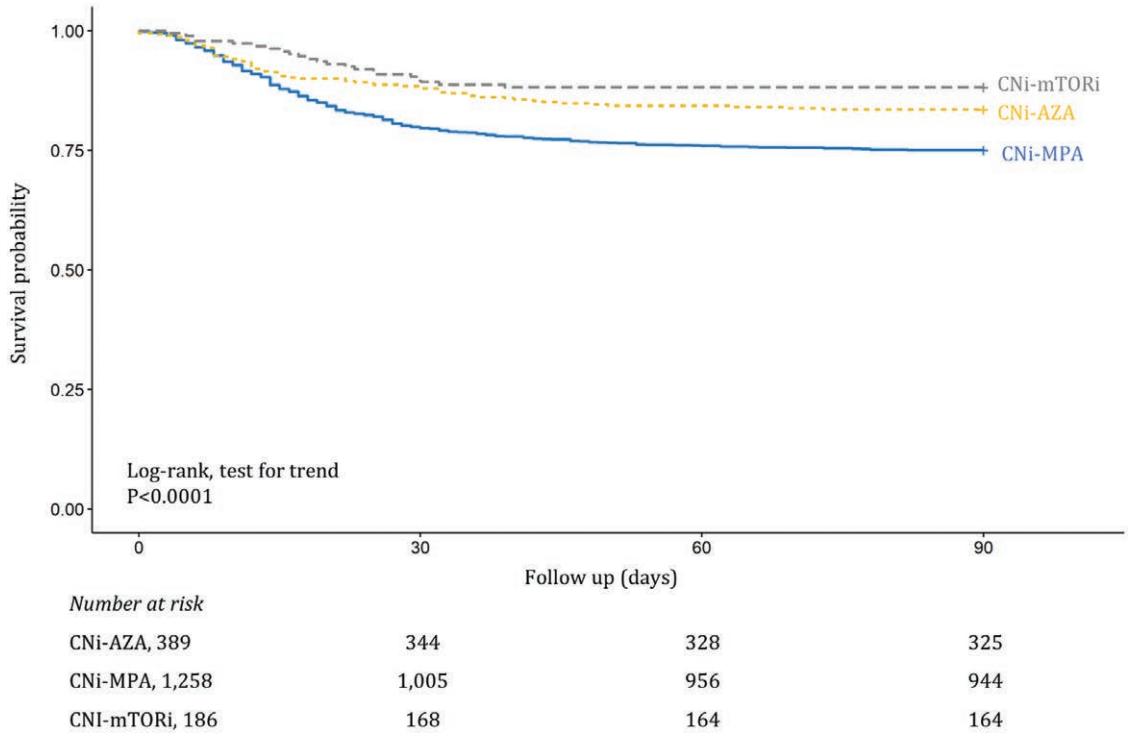

FIGURE 2. Patients' survival after the coronavirus disease 2019 diagnosis stratified by groups. AZA, azathioprine; CNi, calcineurin inhibitor; MPA, mycophenolate acid; mTORi, mammalian target of rapamycin inhibitor.

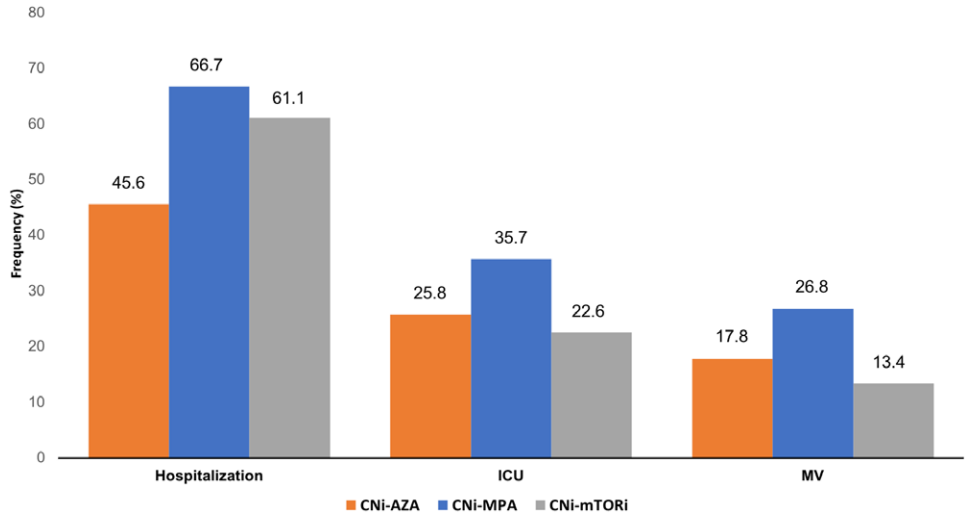

FIGURE 3. Intermediate outcomes stratified by groups. Overall differences among the 3 groups for hospitalization, admission to the ICU, and MV requirement: $P < 0.001$. For hospitalization: CNi-AZA vs CNi-MPA, $P < 0.001$; CNi-AZA vs CNi-mTORi, $P = 0.001$; CNi-MPA vs CNi-mTORi, $P = 0.13$. For admission to the ICU: CNi-AZA vs CNi-MPA, $P < 0.001$; CNi-AZA vs CNi-mTORi, $P = 0.40$; CNi-MPA vs CNi-mTORi, $P < 0.001$. For mechanical ventilation requirement: CNi-AZA vs CNi-MPA, $P < 0.001$; CNi-AZA vs CNi-mTORi, $P = 0.19$; CNi-MPA vs CNi-mTORi, $P < 0.001$. AZA, azathioprine; CNi, calcineurin inhibitor; ICU, intensive care unit; MPA, mycophenolate acid; mTORi, mammalian target of rapamycin inhibitor; MV, mechanical ventilation.

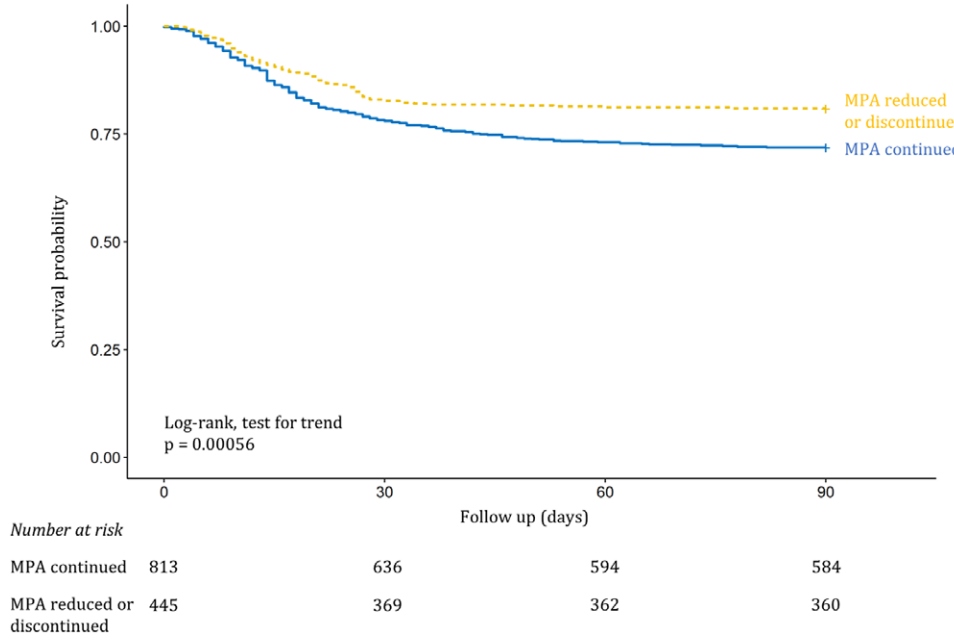

FIGURE 4. Patients' survival stratified by immunosuppression change after the coronavirus disease 2019 diagnosis in the MPA group. Thirty- and ninety-day survival in patients who continued the MPA on their usual dose: 78% and 72%, respectively; 30- and 90-d survival in patients with MPA dose reduced or discontinued: 83% and 81%, respectively ($P < 0.001$). MPA, mycophenolate acid.

mycophenolic acid inhibit the proteolytic activity of Middle East Respiratory Syndrome Coronavirus and Severe Acute Respiratory Syndrome Coronavirus,[24,25] potentially mitigating clinical complications. Nonetheless, MPA has potent cytostatic effects on T and B lymphocytes, contributing to lymphopenia and compromising the humoral immune response to the virus, which could explain the worst outcomes. In turn, mTORi inhibits the PI3K-AKT-mTOR pathway, required for intracellular virus replication, and increases the quality and functionality of memory T cells, ultimately modulating human innate response and mitigating immunosenescence.[24,26,27] An additional mechanism associated with modulation of COVID-19 severity and progression is the potential attenuation of the cytokine storm.[26,28] In a prospective randomized clinical trial in H1N1-infected patients, sirolimus was associated with less severe hypoxemia, reduced length on mechanical ventilation, and faster virus clearance.[29] In the context of coronaviruses, in vitro study demonstrated that sirolimus and everolimus reduce Middle East Respiratory Syndrome Coronavirus infection in a hepatocyte-derived cell live.[25] Of note, the mTORi is not typically used as a first-line regimen for de novo maintenance immunosuppression in kidney transplants, and the reasons why some patients were under a regimen based on this class were not explored in the present study. In addition, only in 3 centers was mTORi

TABLE 2.

Univariable and multivariable analysis for death within 30 d after COVID-19 diagnosis

	Univariable			Multivariable		
Variables	**HR**	**95% CI**	***P***	**aHR**	**95% CI**	***P***
Group						
CNi-AZA (reference)						
CNi-MPA	1.74	1.28-2.38	<0.001	1.70	1.21-2.40	0.003
CNi-mTORi	0.86	0.51-1.45	0.578	0.78	0.45-1.35	0.365
Age (each 10 y)	1.75	1.59-1.93	<0.001	1.58	1.42-1.76	<0.001
Ethnicity						
White (reference)						
Afro-Brazilian	0.99	0.79-1.25	0.945	–	–	–
Other	1.69	0.70-4.11	0.246	–	–	–
Sex (male vs female)	1.10	0.87-1.37	0.429	–	–	–
BMI (for each kg/m^2)	1.03	1.01-1.05	0.003	1.03	1.01-1.05	0.015
ACE/ARB (yes vs no)	1.07	0.85-1.35	0.569	–	–	–
Deceased donor (vs living)	1.75	1.34-2.27	0.001	1.23	0.91-1.66	0.184
Hypertension (yes vs no)	2.22	1.59-3.11	<0.001	1.38	0.97-1.95	0.072
Diabetes (yes vs no)	2.15	1.73-2.68	<0.001	1.39	1.09-1.76	0.007
Cardiovascular disease (yes vs no)	2.84	2.19-3.69	<0.001	1.58	1.18-2.11	0.002
Time of transplant (for each year)	1.01	0.99-1.03	0.225	1.01	0.99-1.04	0.194
eGFR (for each 10 mL/min/1.73 m^2)	0.83	0.79-0.88	<0.001	0.85	0.80-0.90	<0.001
Time since index case (for each month)	0.94	0.91-0.97	0.001	0.95	0.92-0.99	0.014

For the multivariable analysis, the variables were included after the multiple imputation. The results for multivariable Cox regression are adjusted for center.
ACE, angiotensin-converting enzyme inhibitor; aHR, adjusted hazard ratio; ARB, angiotensin II receptor blocker; AZA, azathioprine; BMI, body mass index; CI, confidence interval; CNi, calcineurin inhibitor; COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MPA, mycophenolate acid; mTORi, mammalian target of rapamycin inhibitor; –, not applicable.

TABLE 3.

Univariable and multivariable analysis for death within 90 d after COVID-19 diagnosis

	Univariable			Multivariable		
Variable	**HR**	**95% CI**	***P***	**aHR**	**95% CI**	***P***
Group						
CNi-AZ[a] (reference)						
CNi-MPA	1.59	1.21-2.08	0.001	1.46	1.09-1.98	0.013
CNi-mTORi	0.70	0.43-1.13	0.143	0.59	0.35-0.97	0.040
Age (each 10 y)	1.73	1.59-1.88	<0.001	1.58	1.43-1.74	<0.001
Ethnicity						
White (reference)						
Afro-Brazilian	0.96	0.78-1.18	0.706	–	–	–
Other	2.56	1.32-4.98	0.006	–	–	–
Sex (male vs female)	1.14	0.93-1.40	0.204	–	–	–
BMI (for each kg/m^2)	1.03	1.01-1.05	0.001	1.03	1.01-1.05	0.010
ACE/ARB (yes vs no)	1.05	0.85-1.30	0.672	–	–	–
Deceased donor (vs living)	1.85	1.46-2.35	<0.001	1.34	1.02-1.76	0.036
Hypertension (yes vs no)	2.03	1.52-2.71	<0.001	1.26	0.93-1.71	0.130
Diabetes (yes vs no)	2.13	1.75-2.59	<0.001	1.40	1.13-1.73	0.002
Cardiovascular disease (yes vs no)	2.85	2.25-3.61	<0.001	1.53	1.17-1.99	0.002
Time of transplant (for each year)	1.01	0.99-1.03	0.337	1.01	0.99-1.03	0.220
eGFR (for each 10 mL/min/1.73 m^2)	0.84	0.80-0.89	<0.001	0.87	0.82-0.91	<0.001
Time since index case (for each month)	0.93	0.90-0.96	<0.001	0.94	0.91-0.97	0.001

For the multivariable analysis the variables were included after the multiple imputation. The results for multivariable Cox regression are adjusted for center.
ACE, angiotensin-converting enzyme inhibitor; aHR, adjusted hazard ratio; ARB, angiotensin II receptor blocker; AZA, azathioprine; BMI, body mass index; CI, confidence interval; CNi, calcineurin inhibitor; COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MPA, mycophenolate acid; mTORi, mammalian target of rapamycin inhibitor. –, not applicable.

more frequent than MPA, representing a possible local policy for selected patients. Yet, MPA use is associated with lower rejection rates, and patients on second-line regimens may have had morbidity related to the immunological low risk that was not captured in this analysis.

In total, 400 events of death were reported in the present study (21.8%), 77 of them between 30 and 90 d after the COVID-19 diagnosis. Although the death within 30 d has been defined as the primary outcome, we extended the follow-up because we observed this residual but

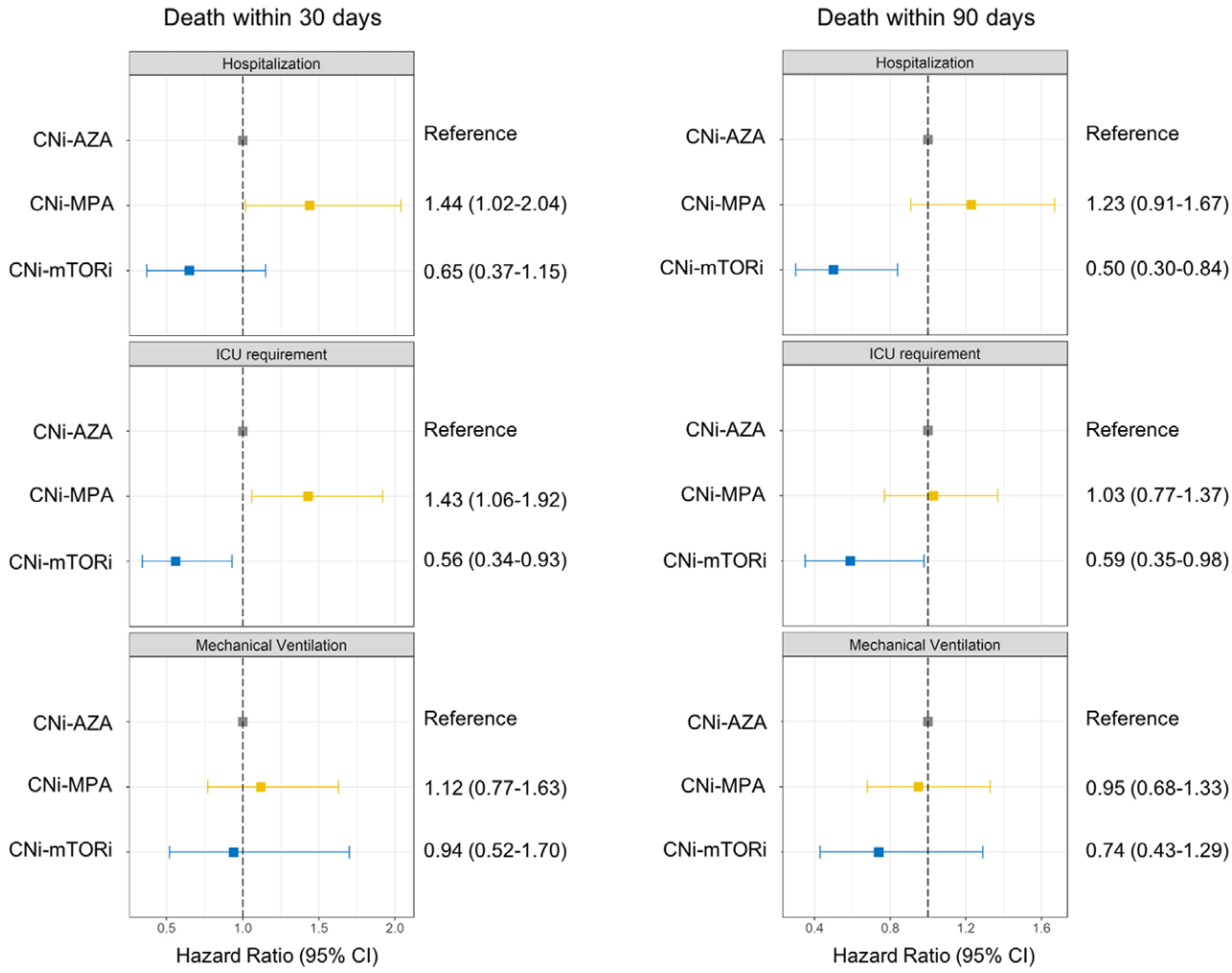

FIGURE 5. Sensitivity analyses for death within 30 and 90 d after coronavirus disease 2019 diagnosis stratified by hospitalization, ICU, and mechanical ventilation requirement status. AZA, azathioprine; CI, confidence interval; CNi, calcineurin inhibitor; ICU, intensive care unit; MPA, mycophenolate acid; mTORi, mammalian target of rapamycin inhibitor.

significant death rate after 30 d. Furthermore, the association between death and the use of MPA was consistently observed when the follow-up was extended, as well as in a sensitivity analysis considering only the more severe patients. Contrariwise, some results suggested that the maintenance regimen based on mTORi may be associated with a reduced risk of death, mainly in the extended follow-up and in the sensitivity analyses considering severe patients, that is, those who were hospitalized and those requiring ICU admission, suggesting that its effects are beyond viral replication and mitigation of initial clinical signs and symptoms.

To date, no clinical trial evaluating immunosuppressive drugs in Severe Acute Respiratory Syndrome Coronavirus-2–infected KRTs are available, and evidence is restricted to observational studies. In a cohort study, the risk of death among liver transplant recipients was 4-fold higher in those using mycophenolate.[30] Another cohort recently published by our group showed that mTORi (versus MPA or AZA) was protective for death within 30 d.[22] Some clinical trials evaluating the effect of mTORi on COVID-19 are ongoing. Interestingly, other mTOR inhibitors beyond sirolimus and everolimus have been considered promising for inhibiting COVID-19 infection. As an example, metformin, which activates 5-adenosine monophosphate–activated protein kinase via liver kinase B1 and also indirectly attenuates Akt activity through phosphorylation of insulin receptor substrate, was associated with a reduction in COVID-19–associated death in observational studies.[31,32,33]

The decision for reducing, changing, or withdrawing immunosuppression in the course of infection probably is an important confounding factor in our study. We could not capture the moment and the main reason for drug change, precluding to analyze the impact of this intervention on clinical outcomes. Despite that no robust evidence for a guide on managing the immunosuppression in COVID-19 is available, a recently published meta-analysis suggested that maintaining the baseline immunosuppressive regimen seemed to be safe, and changes would have potentially harmful effects.[34] Compared with mTORi, patients on MPA had more immunosuppression discontinuation following diagnosis in the present cohort. On the other hand, for patients in the MPA group, the 30- and 90-d survivals were lower in patients who continued the MPA on their usual dose than in those with the MPA dose reduced or discontinued. The discontinuation could lead to increased cytokine storm, which is an interesting

hypothesis. Yet, another point that should be considered is the clinical decision for immunosuppression withdrawal for patients who have more severe COVID-19. In this context, the whole immunosuppression discontinuation might be influenced by the clinical severity.

Our study has several limitations, some of them related to the retrospective and observational design. Despite our efforts in enrolling a representative number of Brazilian transplant centers, a potential bias of selection should be carefully considered. Furthermore, in the COVID-19 clinical management, the criteria for hospitalization and ICU admission were not standardized between centers and have varied over time since the pandemic was declared. Nevertheless, beyond the differences in the immunosuppression changes after the COVID-19 diagnosis previously pointed out, other possible differences in COVID-19 treatment between groups were not captured, which is a significant potential confounder that could have impacted differences in mortality. To reduce these limitations on the final results, the center was included as a random effect, and the time since the index case was included as a covariate in the Cox regression analyses.

Of note, our study was carried out before the COVID-19 immunization for KTRs in Brazil. Although the real-life evidence is demonstrating no or modest reduction in the risk of death for transplanted patients after vaccination,[35] the present results may not be similar for vaccinated patients. Despite these limitations, as far as we know, this is the first study to explore the association between the baseline immunosuppressive regimens in COVID-19–related outcomes in KTRs in a large, multicenter cohort.

In conclusion, in this large, multicenter registry cohort analysis, the risk of COVID-19–associated death among KTRs receiving Cni is increased in patients receiving MPA and decreased in patients receiving mTORi, compared with those receiving AZA.

ACKNOWLEDGMENTS

The authors would like to thank the Associação Brasileira de Transplantes de Órgãos (ABTO) for the support and the Gerência de Ensino e Pesquisa (GEP)/Complexo Hospitalar da Universidade Federal do Ceará (CH-UFC).

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