

# Association Between Maintenance Immunosuppressive Regimens and COVID-19 Mortality in Kidney Transplant Recipients

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**Background.** Solid organ transplant recipients are at high risk for fatal forms of coronavirus disease 2019 (COVID-19). We conducted a cohort study among kidney transplant (KT) recipients from the French Solid Organ Transplant COVID-19 Registry to investigate the association between maintenance immunosuppressive drugs and 60-d mortality. **Methods.** Data from all KT recipients with COVID-19 included in the French Solid Organ Transplant COVID-19 Registry between February 28, 2020, and December 30, 2020, were retrieved. We evaluated associations between immunosuppressive drugs and death within 60 d using logistic regression, with all baseline characteristics considered to influence outcome or immunosuppressive regimen. The Benjamini-Hochberg correction was used for controlling false positive rate; 40 multiple imputations were performed. Adjusted *P* value <0.05 was considered statistically significant. **Results.** There were 1451 KT recipients included. Median age was 58 y, and 66.4% were men. Most frequent comorbidities were hypertension (81.9%), diabetes (34.5%), and cardiovascular disease (29.5%). Median time since transplant was 71 mo. Maintenance immunosuppression regimens included calcineurin inhibitors (1295, 89.2%), antimetabolites (1205, 83%), corticosteroids (1094, 75.4%), mammalian target of rapamycin inhibitors (144, 9.9%), and belatacept (58, 4.0%). Among 1451 transplant recipients, 201 (13.9%) died within 60 d. Older age and higher baseline serum creatinine were associated with mortality (odds ratios, 1.09 [1.07-1.11] and 1.01 [1.005-1.009], *P* < 0.001). Corticosteroid-free regimens were associated with a significantly lower risk of death (odds ratio, 0.48 [0.31-0.76]; *P* = 0.011). **Conclusions.** Corticosteroid-free regimens were associated with a lower risk of death in KT recipients with COVID-19. Long-term exposure to corticosteroids impairs immune functions and may predispose solid organ transplant recipients to severe forms of COVID-19.

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## INTRODUCTION

Since December 2019, the coronavirus disease 2019 (COVID-19) pandemic has had a large and unprecedented impact on societies and healthcare systems. Severe forms of the disease are characterized by respiratory failure and systemic complications, with a death toll of >6 million people. Solid organ transplant recipients receive immunosuppressive drugs, increasing their risk for fatal forms of COVID-19.<sup>1-4</sup> These patients are also less likely to mount effective immune responses to vaccination.<sup>5</sup> Since curative treatments are not readily available, all strategies aiming to mitigate the impact of COVID-19 on solid organ transplant recipients are worth considering. Yet, the impact of the different maintenance immunosuppressive regimens on COVID-19 mortality remains poorly known, and there is still no specific evidence to guide how best to adjust maintenance immunosuppression in solid organ transplant recipients.<sup>6,7</sup> We conducted a cohort study among kidney transplant (KT) recipients from the French Solid Organ Transplant COVID-19 Registry to investigate the association between maintenance immunosuppressive drugs and 60-d mortality in KT patients with COVID-19.

## MATERIALS AND METHODS

Data from all KT recipients with COVID-19 included in the French Solid Organ Transplant COVID-19 Registry between February 28 and December 30, 2020, were retrieved. Inclusion criteria were age >18 y at diagnosis of COVID-19 and the presence of a functioning kidney graft. Among the 1567 KT recipients included in the Registry during this period, 116 were not included because data on maintenance immunosuppressive therapy were missing. Clinical and laboratory variables were extracted from medical records.

Descriptive statistics were expressed as median (interquartile range [IQR]). We evaluated the associations between immunosuppressive drugs and death within 60 d of first symptoms using logistic regression. Baseline characteristics of patients considered to influence the outcome or the immunosuppressive regimen, which can constitute a source of confounding, were included in the multivariate analysis: immunosuppressive drugs, blood group, donor type (deceased or living), time from transplantation to diagnosis of COVID-19, sex, number of previous transplantations, induction therapy, baseline serum creatinine, cardiac disease, respiratory disease, diabetes, cancer, smoking, hypertension, and body mass index. To account for multiple testing, the Benjamini-Hochberg correction was used to help controlling the false positive rate. We performed 40 multiple imputations for missing data, using the package mice in the R software (R Core Team, 2020). An adjusted *P* value <0.05 was considered statistically significant.

A validation analysis, based on a penalized logistic regression, was conducted to corroborate the findings of the primary analysis. This analysis was performed on the same 40 multiple imputed data sets as the primary analysis but additionally on 500 bootstraps per multiple imputation. The bootstrap is a resampling method that enables assessment of the accuracy of an estimator by random sampling with replacement from an original dataset. It

allows to compute a variable inclusion probability (VIP), which weights the importance of each variable to predict the outcome (death, <60 d). The significance threshold for VIP is >80%. The penalized logistic regression considered the same variables as the primary multivariate analysis. A supplementary penalized logistic regression was also performed to analyze the impact of the immunosuppressive protocols.

The French Solid Organ Transplant COVID-19 Registry was approved by the Institutional Review Board of the Strasbourg University (approval number 02.26) and registered at clinicaltrials.gov (NCT04360707). All patients were duly informed about their inclusion in the registry.

## RESULTS

There were 1451 KT recipients with COVID-19 included in the study (Table 1). The median age of patients was 58 (IQR, 48–67) y, and 963 (66.4%) were men. The

**TABLE 1.**  
Baseline characteristics of kidney transplant recipients with COVID-19 (n = 1451)

Variable	Median (IQR) or n (%)
Age, y	58 (48–67)
Gender, male	963 (66.4)
Blood group	
A	624 (43.0)
B	163 (11.2)
AB	77 (5.3)
O	560 (38.6)
Comorbidities	
Hypertension	1188 (81.9)
Diabetes	501 (34.5)
Cardiovascular disease	428 (29.5)
Cancer	197 (13.6)
Smoking	193 (13.3)
Respiratory disease	162 (11.2)
BMI, kg/m <sup>2</sup>	26 (23–29)
≥2 transplantations	164 (11.3)
Donor type	
Deceased donor	1254 (86.4)
Living donor	185 (12.7)
Time from transplantation to COVID-19, mo	71 (29–144)
Baseline serum creatinine, μmol/L	131 (102–173)
Induction therapy	
Anti-CD25	611 (42.1)
Thymoglobulins	740 (51.0)
No induction	56 (3.9)
Maintenance immunosuppression	
Calcineurin inhibitors <sup>a</sup>	1295 (89.2)
Antimetabolites <sup>b</sup>	1205 (83.0)
Corticosteroids	1094 (75.4)
mTOR inhibitors	144 (9.9)
Belatacept	58 (4.0)

Data are expressed as median (IQR) or count (%), as appropriate.

<sup>a</sup>Tacrolimus or ciclosporine.

<sup>b</sup>Mycophenolate mofetil, mycophenolate acid, or azathioprine.

BMI, body mass index; COVID-19, coronavirus disease 2019; IQR, interquartile range; mTOR, mammalian target of rapamycin.

most frequent comorbidities were hypertension (n = 1188, 81.9%), diabetes (n = 501, 34.5%), and cardiovascular disease (n = 428, 29.5%). The median time since transplant was 71 (IQR, 29–144) mo.

Maintenance immunosuppression included calcineurin inhibitors (CNIs; n = 1295, 89.2%), antimetabolites (n = 1205, 83%), corticosteroids (n = 1094, 75.4%), mammalian target of rapamycin inhibitors (n = 144, 9.9%), and belatacept (n = 58, 4.0%). The most common regimens were combination of CNI, antimetabolites, and steroids (n = 718, 49.5%); combination of CNI and antimetabolites (n = 284, 19.6%); and combination of CNI and steroids (n = 104, 7.2%).

Among 1451 patients, 201 (13.9%) died within 60 d of first symptoms. In the primary multivariate analysis, older age (odds ratio [OR], 1.09 [1.07-1.11];  $P < 0.001$ ) and baseline serum creatinine (OR, 1.01 [1.005-1.009] for each 1  $\mu\text{mol/L}$  increase in serum creatinine;  $P < 0.001$ ) were significantly associated with 60-d mortality. The median age of deceased patients was 69 (IQR, 61–75) y, as compared with 56 (IQR, 46–65) y in patients who survived. Median baseline serum creatinine was 160 (IQR, 120–209)  $\mu\text{mol/L}$  in patients who died and 130 (IQR, 100–164)  $\mu\text{mol/L}$  in patients who survived. As for maintenance immunosuppression, corticosteroid-free regimens were associated with a significantly lower risk of death (OR, 0.48 [0.31-0.76];  $P = 0.011$ ). All other variables yielded nonsignificant adjusted  $P$  values in the logistic regression (Table 2).

In the validation analysis (penalized logistic regression), long-term treatment with corticosteroids was the only one to be associated with a higher risk of death (OR, 1.008 [1.00-1.44]; VIP = 83.6%; Table S1, SDC, <http://links.lww.com/TP/C487>), confirming the results of the primary analysis. Consistently, combination of CNI and antimetabolites without corticosteroids was the only regimen associated with a lower OR for death (OR, 0.625 [0.28-0.92]; VIP = 99.4%; Table S2, SDC, <http://links.lww.com/TP/C487>).

## DISCUSSION

In this evaluation of the association between immunosuppressive regimens and COVID-19 mortality in KT recipients, corticosteroid-free regimens were associated with a significantly lower risk of death. This finding in a large cohort of 1445 KT recipients with COVID-19 is in accordance with independent studies performed with a lower number of patients.<sup>8,9</sup>

Although a short course of high-dose corticosteroids is beneficial in severely ill COVID-19 patients with respiratory failure,<sup>10</sup> prolonged maintenance corticosteroid therapy exposes to chronic metabolic and immune disorders that may predispose solid organ transplant patients to severe forms of COVID-19. The timing, dose, and duration of the exposure to corticosteroids may be determinant. Indeed, high-dose pulse corticosteroids and low-dose chronic corticotherapy have different immunological effects. For instance, corticosteroids administered at high dose interfere on leukocyte aggregation and phagocytic function,<sup>11,12</sup> rapidly deplete most circulating T cells, and inhibit interleukin-2 signaling, which is not the case with low-dose steroids.<sup>13-15</sup> For these reasons, high-dose corticosteroids might rapidly mitigate the inflammatory storm

or lung inflammation and are, therefore, clearly beneficial in patients with severe COVID-19 pneumonia. As for low-dose corticosteroids, they profoundly alter innate and adaptive immune function through a range of direct effects on gene transcription and posttranslational events. Most of these effects are known to be dependent on the cumulative dose of corticosteroids, especially regarding the infectious risk.<sup>16</sup> Long-term preexisting corticosteroid exposure may, therefore, impair the establishment of an efficient immune response at the initial stages of the infection. This may underpin the increased COVID-19 mortality

**TABLE 2.**

**Logistic regression of risk factors for 60-d mortality in kidney transplant recipients with COVID-19 (n = 1451)**

	OR	95% CI	Adjusted $P$
Age, y	1.089	1.07-1.11	<0.001 <sup>a</sup>
Gender			
Female	Reference		
Male	0.636	0.44-0.92	0.06
Blood group			
A	Reference		
B	1.905	1.11-3.27	0.06
AB	1.082	0.48-2.42	0.875
O	1.044	0.72-1.52	0.875
Comorbidities			
Hypertension	1.051	0.57-1.94	0.875
Diabetes	1.524	1.07-2.17	0.06
Cardiovascular disease	1.078	0.75-1.55	0.868
Cancer	1.708	1.10-2.65	0.06
Smoking	1.178	0.72-1.91	0.754
Respiratory disease	0.745	0.45-1.23	0.466
BMI, kg/m <sup>2</sup>	1.04	1.01-1.08	0.063
≥2 transplantations	1.171	0.68-2.01	0.754
Living donor	0.738	0.37-1.48	0.628
Time from transplantation to COVID-19, mo	1.000	0.10-1.00	0.874
Baseline serum creatinine, $\mu\text{mol/L}$	1.006 <sup>b</sup>	1.005-1.009 <sup>b</sup>	<0.001 <sup>a</sup>
Induction therapy			
Anti-CD25	Reference		
Thymoglobulins	0.959	0.67-1.38	0.875
No induction	0.305	0.09-1.06	0.149
Maintenance immunosuppression			
Calcineurin inhibitors <sup>c</sup> : yes	Reference		
Calcineurin inhibitors: no	1.792	0.90-3.55	0.208
Antimetabolites <sup>d</sup> : yes	Reference		
Antimetabolites: no	0.773	0.48-1.24	0.497
Corticosteroids: yes	Reference		
Corticosteroids: no	0.483	0.31-0.76	0.011 <sup>a</sup>
mTOR inhibitors: yes	Reference		
mTOR inhibitors: no	0.824	0.44-1.55	0.754
Belatacept: yes	Reference		
Belatacept: no	1.89	0.68-5.24	0.441

ORs, 95% CIs, and multiple corrected (false discovery rate) adjusted  $P$  values from the logistic regression are shown.

<sup>a</sup>Statistically significant.

<sup>b</sup>For each 1  $\mu\text{mol/L}$  increase in serum creatinine.

<sup>c</sup>Tacrolimus or ciclosporine.

<sup>d</sup>Mycophenolate mofetil, mycophenolate acid, or azathioprine.

BMI, body mass index; CD, Cluster of Differentiation; COVID-19, coronavirus disease 2019; mTOR, mammalian target of rapamycin; OR, odds ratio.

observed in patients long-term treated with corticosteroids. Consistently, chronic corticosteroid exposition has also been associated with increased COVID-19 severity in an array of other conditions such as inflammatory bowel and rheumatic diseases, as well as myasthenia gravis.<sup>17-19</sup> Corticosteroid-free KT recipients were also recently shown to respond better to mRNA COVID-19 vaccines.<sup>5</sup> Yet, a relevant bias is still possible, and our findings warrant further confirmation. We may not have considered all potential confounding factors (eg, primary renal disease) despite all the variables included in the analysis. Besides, we did not include in the analysis the specific treatments given for COVID-19. We reasoned that this analysis would have been biased by the fact that most of these treatments were administered to the most severe patients at higher risk of death, especially during the first months of the pandemic.

Tapering or withdrawal of corticosteroids is increasingly attempted to minimize metabolic disorders and decrease overall immunosuppression. Corticosteroid-free maintenance immunosuppression might provide noninferior outcomes in long-term patient and graft survival in KT recipients,<sup>20-22</sup> as recently confirmed.<sup>23</sup> At the time of the COVID-19 pandemic, long-term safety and reduced COVID-19 mortality rate may support corticosteroid-free regimen in KT recipients with low-to-intermediate immune risk. However, corticosteroid withdrawal must be balanced against the risk of rejection and can only be envisaged by the clinician in charge of the patient on a case-by-case basis.

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