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BRIEF COMMUNICATION

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Is COVID-19 infection more severe in kidney transplant recipients?

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There are no studies which have compared the risk of severe COVID-19 and related mortality between transplant recipients and nontransplant patients. We enrolled two groups of patients hospitalized for COVID-19, that is, kidney transplant recipients (KTR) from the French Registry of Solid Organ Transplant (n = 306) and a single-center cohort of nontransplant patients (n = 795). An analysis was performed among subgroups matched for age and risk factors for severe COVID-19 or mortality. Severe COVID-19 was defined as admission (or transfer) to an intensive care unit, need for mechanical ventilation, or death. Transplant recipients were younger and had more comorbidities compared to nontransplant patients. They presented with higher creatinine levels and developed more episodes of acute kidney injury. After matching, the 30-day cumulative incidence of severe COVID-19 did not differ between KTR and nontransplant patients; however, 30-day COVID-19-related mortality was significantly higher in KTR (17.9% vs 11.4%, respectively, p = .038). Age >60 years, cardiovascular disease, dyspnea, fever, lymphopenia, and C-reactive protein (CRP) were associated with severe COVID-19 in univariate analysis, whereas transplant status and serum creatinine levels were not. Age >60 years, hypertension, cardiovascular disease, diabetes, CRP >60 mg/L, lymphopenia, kidney transplant status (HR = 1.55), and creatinine level >115 µmol/L (HR = 2.32) were associated with COVID-19-related mortality in univariate analysis. In multivariable analysis, cardiovascular disease, dyspnea, and fever were associated with severe disease, whereas age >60 years, cardiovascular disease, dyspnea, fever, and creatinine level>115 µmol/L retained their independent associations with mortality. KTR had a higher COVID-19-related mortality compared to nontransplant hospitalized patients.

KEYWORDS
cardiovascular disease, clinical research / practice, glomerular filtration rate (GFR), immunosuppressive regimens, infection and infectious agents - viral, infectious disease, kidney failure / injury, kidney transplantation / nephrology

1 | INTRODUCTION

Prior experience with respiratory viruses in patients who had undergone solid organ transplantation revealed how recipients have greater susceptibility, more rapid progression to pneumonia, greater disease severity, and prolonged viral shedding compared with nontransplant hosts. In light of past coronavirus outbreaks,[1,2] COVID-19 poses a significant threat for immunocompromised patients, and transplant physicians are particularly concerned about the impact of this new infection on this frail population. Single-center studies have reported a high mortality rate in kidney transplant recipients (KTR) with COVID-19.[3-5] There is also evidence that at least part of COVID-19's severity is linked to the "cytokine storm," which is a disproportionate hyperinflammatory reaction occurring in infected patients.[6] In this scenario, immunosuppressive drugs may be clinically useful in reducing this dysfunctional immune response by attenuating the positive feedback loop typical of the cytokine release syndrome (CRS). Nonetheless, the question as to whether KTR would actually exhibit a higher risk of severe COVID-19 or—alternatively—immunosuppression would protect them from CRS and critical forms of the disease remains unanswered.

Chronic kidney disease and acute kidney injury (AKI) have been reported to affect the prognosis of patients hospitalized for COVID-19.[7] Notably, KTR are in an immunosuppressed state with concurrent chronic kidney disease and are particularly susceptible to AKI. Starting from these premises, this research was undertaken to determine how these factors may influence the clinical outcomes of KTR with COVID-19. We also compared the prognosis of COVID-19 in KTR and nontransplant patients by using data from a French nationwide registry.

2 | PATIENTS AND METHODS

A cohort of KTR hospitalized for COVID-19 was identified from a multicenter nationwide French Registry—termed French SOT COVID—between March 1 and April 30, 2020. Inclusion criteria were age >18 years at the diagnosis of COVID-19 and presence of a functioning graft. The control group consisted of nontransplant adult patients with confirmed COVID-19 who were hospitalized at the Strasbourg University Hospital between March 1 and March 31, 2020. Cases with a history of immunosuppression (previous transplantation; patients on high-dose steroids, immunosuppressive drugs, or biological therapies in the month preceding hospitalization; those with primary immune deficiency; and those with previous splenectomy) were excluded from the control group. The diagnostic criteria for COVID-19 were as follows: (1) severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection determined by reverse transcriptase-polymerase chain reaction (RT-PCR) testing of nasopharyngeal swab specimens, or (2) presence of typical respiratory symptoms associated with evocative pulmonary lesions on low-dose chest computed tomography (CT) when RT-PCR yielded negative results. AKI was defined according to the Kidney Disease Improving Global Outcomes guidelines. Severe COVID-19 was defined as admission (or transfer) to an intensive care unit (ICU), need for mechanical ventilation, or death. All other patients were considered as nonsevere cases. Ethical approval for the creation of the French SOT COVID Registry was obtained from the Institutional Review Board of the Strasbourg University (approval number 02.26). The study was registered at clinicaltrials.gov (NCT04360707). While the requirement for informed consent was waived, all patients were informed about their inclusion in the registry. The study protocol for nontransplant patients was approved by the Human Investigation Review Committee of the Strasbourg University Hospital (approval number CE-2020–51). Patients who declined to participate were deemed ineligible.

2.1 | Statistical analysis

Discrete variables are presented as counts and percentages, whereas continuous data are summarized as medians and interquartile ranges (IQRs) upon verification of their skewed distribution. The composite endpoint of severe COVID-19 was considered as a time-dependent variable since the onset of the symptoms. Cumulative event curves (for severe COVID-19 or COVID-19-related mortality) of transplant recipients and nontransplant patients were plotted with the Kaplan–Meier method and compared using the log-rank test. Cox proportional hazards univariable and multivariable models were constructed using a backward-conditional selection procedure to identify predictors of the study endpoints. The optimal model was selected according to the highest concordance (Harrel's C statistic) value. Results are expressed as hazard ratios (HRs) with their 95% confidence intervals (CIs). Matching was performed by selection of nearest neighbor best control matches for each individual in the KTR group.[8] Patients were matched in a 1:1 ratio using the logit of the estimated propensity of being in the transplant group as the distance metric. Age, BMI, cardiovascular and respiratory diseases, cancer, and diabetes were included as covariates in the propensity score model because these variables are the main risk factors for COVID-19.[9-11] A caliper (0.3) was set for age only. There were 33 transplant recipients who could not be matched to a nontransplant patient. Tabular data for matched cohorts are reported as standardized mean differences with their 95% CIs. All analyses were undertaken in the R environment (R Foundation for Statistical Computing, Vienna, Austria). A value of $p < .05$ (two-tailed) was considered statistically significant.

3 | RESULTS

A total of 306 KTR were included in the SOT COVID Registry at the time of this analysis. The median recipient age was 62 years (IQR: 52–69 years) and 67.6% were men. The median time between transplantation and COVID-19 diagnosis was 74.6 months (IQR: 27.8–140.6 months), and only 12% of all KTR were in the first posttransplant year at the time of COVID-19 diagnosis. Immunosuppressive drugs used at baseline and management of immunosuppression at the time of COVID-19 diagnosis are summarized in Table S1. The control cohort consisted of 795 nontransplant patients with COVID-19 (median age: 69 years, IQR: 57–79 years; 58.6% men). The characteristics of the two study groups are reported in Table S2. KTR were younger, more commonly male, and had lower body mass index (BMI) but had more comorbidities (hypertension, cardiovascular diseases, respiratory diseases, and diabetes). They less frequently exhibited dyspnea during admission for COVID-19, but more commonly had fever and diarrhea than nontransplant patients. Of note, the median time from symptom onset to admission was shorter among KTR than nontransplant patients (5 vs 7 days, respectively, $p = .006$). KTR displayed a less severe inflammatory syndrome, a more profound lymphopenia, and a higher creatinine level at admission (176 µmol/L vs 75 µmol/L, respectively, $p < .001$). Infection management was slightly different, with antibiotics and azithromycin more frequently used in nontransplant patients, in contrast to more antifungal drugs (4.6% vs 2.1%, respectively, $p = .028$), fewer specific antivirals (lopinavir/ritonavir 5.2% vs 21.8%, respectively, $p < .01$), and more frequent tocilizumab (5.6% vs 1%, respectively, $p < .001$) in KTR. Moreover, KTR were less frequently in need of vasopressor support but were significantly more likely to develop AKI (46.1% vs

TABLE 1 Clinical characteristics, management, and outcomes of matched nontransplant patients and kidney transplant recipients hospitalized for COVID-19

	Nontransplant	Transplant		
	N = 273	*N = 273*	SMD [95% CI]	*N*
Baseline characteristics				
Median age [IQR], years	63.0 [48.0–74.0]	62.0 [53.0–69.0]	0.042 [−0.126;0.210]	546
Age >60 years, n (%)	147 (53.8%)	159 (58.2%)	0.089 [−0.079;0.256]	546
Men, n (%)	173 (63.4%)	181 (66.3%)	0.061 [−0.106;0.229]	546
Median BMI [IQR], kg/m^2	27.0 [23.0–30.0]	26.0 [24.0–30.0]	0.024 [−0.144;0.192]	546
BMI >25 kg/m^2, n (%)	181 (66.3%)	177 (64.8%)	0.031 [−0.137;0.199]	546
Hypertension, n (%)	136 (49.8%)	232 (91.3%)	1.024 [0.842;1.205]	527
RAS blockers, n (%)	94 (34.4%)	121 (48.8%)	0.294 [0.122;0.467]	521
Cardiovascular disease, n (%)	106 (38.8%)	106 (38.8%)	0.000 [−0.168;0.168]	546
Respiratory disease, n (%)	45 (16.5%)	38 (13.9%)	0.071 [−0.096;0.239]	546
Diabetes, n (%)	98 (35.9%)	101 (37.0%)	0.023 [−0.145;0.191]	546
Cancer, n (%)	26 (9.5%)	34 (12.5%)	0.094 [−0.074;0.262]	546
Smoking, n (%)	12 (4.4%)	28 (12.7%)	0.301 [0.123;0.480]	493
Clinical presentation				
Anosmia, n (%)	24 (11.5%)	34 (14.1%)	0.077 [−0.109;0.262]	449
Cough, n (%)	158 (57.9%)	162 (66.1%)	0.171 [−0.002;0.343]	518
Dyspnea, n (%)	174 (63.7%)	123 (45.1%)	0.382 [0.213;0.551]	546
Fever, n (%)	201 (73.6%)	199 (80.6%)	0.166 [−0.007;0.338]	520
Headache, n (%)	47 (17.2%)	41 (18.3%)	0.028 [−0.148;0.205]	497
Diarrhea, n (%)	63 (23.1%)	93 (36.3%)	0.293 [0.122;0.465]	529
Time from diagnosis to admission [IQR], days	7.0 [3.0–9.0]	5.0 [3.0–8.0]	0.088 [−0.086;0.262]	511
Laboratory data				
Median CRP [IQR], mg/L	80 [33–148]	62 [27–118]	0.143 [−0.044;0.330]	451
Median lymphocyte count [IQR], G/L	0.88 [0.65–1.29]	0.70 [0.41–0.96]	0.382 [0.193;0.571]	450
Median platelet count [IQR], G/L	200 [159–268]	180 [146–238]	0.173 [−0.014;0.360]	453
Thrombocytopenia <150 G/L, n (%)	57 (22%)	53 (27%)	0.129 [−0.058;0.315]	453
Median creatinine [IQR], µmol/L	76 [59–99]	176 [132–259]	0.945 [0.759;1.131]	495
Drug treatment				
Azithromycin, n (%)	123 (45.1%)	66 (24.2%)	0.450 [0.280;0.620]	546
Other antibiotics, n (%)	204 (74.7%)	179 (65.6%)	0.201 [0.033;0.369]	546
Antifungal drugs, n (%)	7 (2.6%)	12 (4.4%)	0.100 [−0.068;0.268]	546
Remdesivir, n (%)	0 (0.0%)	2 (0.7%)	0.121 [−0.046;0.289]	546
Lopinavir/Ritonavir, n (%)	71 (26.0%)	15 (5.5%)	0.587 [0.416;0.758]	546
Oseltamivir, n (%)	2 (0.7%)	6 (2.2%)	0.122 [−0.046;0.290]	546
Hydroxychloroquine, n (%)	55 (20.1%)	63 (23.1%)	0.071 [−0.097;0.239]	546
Tocilizumab, n (%)	3 (1.1%)	15 (5.5%)	0.248 [0.080;0.416]	546
Outcomes				
Bacterial coinfection, n (%)	169 (61.9%)	54 (19.8%)	0.948 [0.772;1.135]	546
Viral coinfection, n (%)	1 (0.4%)	9 (3.3%)	0.220 [0.052;0.388]	546
Fungal coinfection, n (%)	2 (0.7%)	11 (4.0%)	0.218 [0.029;0.386]	546
Oxygen therapy, n (%)	156 (71.2%)	170 (73.9%)	0.060 [−0.125;0.245]	449
Mechanical ventilation, n (%)	96 (35.2%)	78 (28.6%)	0.142 [−0.026;0.310]	546
Vasopressor support, n (%)	69 (25.3%)	36 (13.2%)	0.310 [0.142;0.479]	546

(Continues)

TABLE 1 (Continued)

	Nontransplant	Transplant		
	N = 273	*N = 273*	SMD [95% CI]	*N*
Acute kidney injury, n (%)	36 (13.2%)	125 (45.8%)	0.766 [0.592;0.939]	546
Renal replacement therapy, n (%)	27 (9.9%)	36 (13.2%)	0.103 [−0.065;0.271]	546

Data are expressed as medians (IQRs) or counts (percentages), as appropriate. Patients were matched (1:1 ratio) for age, BMI, cardiovascular and respiratory diseases, cancer, and diabetes.

Abbreviations: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; ICU, intensive care unit; IQR, interquartile range; RAS, renin-angiotensin system; SMD, standardized mean difference.

11.2%, respectively, $p < .001$) that would require dialysis (12.7% vs 8.1%, respectively, $p = .023$). The 30-day cumulative incidence of severe COVID-19 and death were similar in the two groups (43.8% vs 41.2%, $p = .21$, and 17% versus 16.6%, $p = .46$, in nontransplant patients and KTR, respectively; Figure S1A,B).

Owing to the significant differences in age and comorbidities, a further analysis was performed on matched KTR ($n = 273$) and nontransplant patients ($n = 273$). The median follow-up time from admission was 64 days (IQR: 55–71 days) for the entire matched cohort. Specifically, it was 58 days (IQR: 48–67 days) and 67 days (IQR: 62–73 days) for transplant recipients and nontransplant patients, respectively. The characteristics and outcomes of the matched groups are shown in Table 1. The univariable analysis showed that the 30-day cumulative incidence of severe disease was similar in both groups (Figure 1A; 42.2% versus 42.1% in KTR and nontransplant patients, respectively; $p = .6$), whereas the 30-day mortality was significantly higher among KTR (Figure 1B; 17.9% versus 11.4%, respectively; $p = .038$). Risk factors for severe COVID-19 were age >60 years, cardiovascular disease, dyspnea, fever, lymphopenia, and C-reactive protein >60 mg/L (Table 2). Furthermore, age >60 years, hypertension, cardiovascular disease, diabetes, lymphopenia, being a KTR (HR = 1.55, 1.02–2.35), and having a creatinine level >115 µmol/L (HR = 2.32, 1.45–3.70) were associated with mortality (Table 3). In multivariable analysis, cardiovascular disease, dyspnea, and fever were independent risk factors for severe disease. Age >60 years, cardiovascular disease, having dyspnea and fever at admission, and a serum creatinine >115 µmol/L were also independently associated with mortality, whereas being a KTR was not (Table 4). Because the two matched groups were not well balanced in terms of hypertension, we constructed a different model in which this variable was included for matching. However, the results of multivariable analysis were entirely consistent with those reported in the model that did not include hypertension as a matching variable (data not shown).

4 | DISCUSSION

The present study compared for the first time hospitalized KTR with COVID-19 to a cohort of hospitalized nontransplant patients in order to determine if they would have different outcomes and a higher mortality rate. First, we demonstrated that the entire cohort of KTR hospitalized for COVID-19 exhibited significant differences compared to the nontransplant cohort. Accordingly, KTR were younger (by 7 years) and had a higher burden of comorbidities. As expected, nontransplant patients had a better renal function at admission. This could reflect either the presence of a preexisting

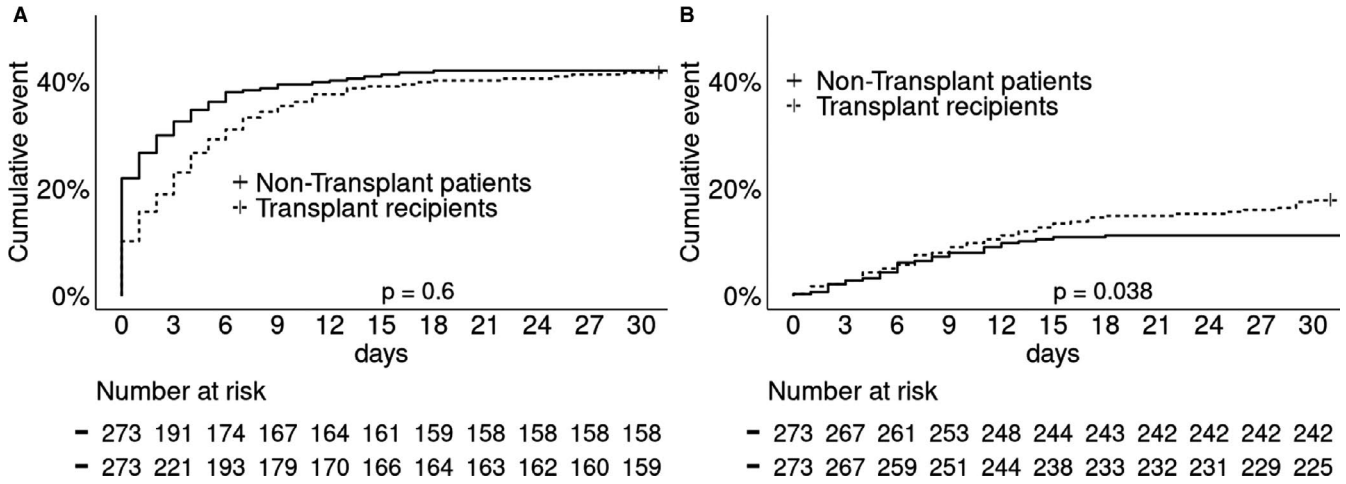

FIGURE 1 Thirty-day cumulative incidence of the composite endpoint (ICU admission or death) and death only in the nontransplant patients (solid line) and kidney transplant recipients (dashed line) matched cohorts. (A) Composite endpoint (nontransplant patients: 42.1%, kidney transplant recipients: 42.2%). (B) Death only (nontransplant patients: 11.4%, kidney transplant recipients: 17.9%)

TABLE 2 Risk factors for severe COVID-19 (ICU admission or mechanical ventilation or death) in univariable analysis in matched transplant and nontransplant cohorts (*n* = 546)

	No event	Event			
	N = 314	*N = 232*	HR	p.ratio	*N*
Baseline characteristics					
Renal transplantation - n (%)	157 (50.0%)	116 (50.0%)	0.91 [0.71;1.18]	0.498	546
Median age [IQR] - yr	60.0 [48.0–70.0]	65.0 [55.8–73.0]	1.01 [1.01;1.02]	0.002	546
Age >60 yr - n (%)	159 (50.6%)	147 (63.4%)	1.46 [1.12;1.91]	0.005	546
Male - no.(%)	194 (61.8%)	160 (69.0%)	1.30 [0.99;1.72]	0.063	546
BMI >25 kg/m2 - n (%)	200 (63.7%)	158 (68.1%)	1.20 [0.91;1.59]	0.187	546
Hypertension - n (%)	207 (68.5%)	161 (71.6%)	1.05 [0.78;1.40]	0.763	527
RAS blockers - n (%)	126 (42.0%)	89 (40.3%)	0.92 [0.70;1.20]	0.534	521
Cardiovasc. disease - n (%)	109 (34.7%)	103 (44.4%)	1.35 [1.05;1.76]	0.022	546
Respiratory disease - n (%)	47 (15.0%)	36 (15.5%)	1.04 [0.73;1.49]	0.819	546
Diabetes - n (%)	102 (32.5%)	97 (41.8%)	1.29 [1.00;1.68]	0.055	546
Cancer - n (%)	37 (11.8%)	23 (9.91%)	0.86 [0.56;1.32]	0.489	546
Smoking - n (%)	25 (8.80%)	15 (7.18%)	0.79 [0.46;1.33]	0.370	493
Admission characteristics					
Anosmia - n (%)	40 (15.2%)	18 (9.68%)	0.66 [0.40;1.07]	0.090	449
Cough - n (%)	196 (66.2%)	124 (55.9%)	0.74 [0.57;0.96]	0.025	518
Dyspnea - n (%)	152 (48.4%)	145 (62.5%)	1.71 [1.31;2.23]	<0.001	546
Fever - n (%)	216 (72.2%)	184 (83.3%)	1.61 [1.13;2.29]	0.009	520
Headache - no.(%)	57 (20.1%)	31 (14.6%)	0.73 [0.50;1.07]	0.109	497
Diarrhea - n (%)	90 (29.4%)	66 (29.6%)	1.00 [0.75;1.33]	0.995	529
Time from diag. to admission [IQR] - d	6.00 [3.00–9.00]	6.00 [3.00–8.00]	0.99 [0.96;1.02]	0.473	511
Biological data					
CRP >60 mg/l - n (%)	119 (45.6%)	135 (71.1%)	2.54 [1.86;3.48]	<0.001	451
Median lymphocyte count [IQR] - G/l	0.85 [0.58–1.21]	0.75 [0.50–1.03]	0.74 [0.57;0.98]	0.035	450
Median platelet count [IQR] - G/l	189 [148–257]	197 [153–257]	1.00 [1.00;1.00]	0.548	453
Thrombocytopenia <150 G/l - no.(%)	65 (25.3%)	45 (23.0%)	0.89 [0.64;1.24]	0.502	453
Median SCr [IQR] - µmol/l	102 [66.7–176]	127 [77.0–204]	1.00 [1.00;1.00]	0.373	495
SCr >115 µmol/l	129 (46.7%)	118 (53.9%)	1.15 [0.88;1.50]	0.292	495

Note. Patients were matched (1:1 ratio) for age, BMI, cardiovascular and respiratory diseases, cancer, and diabetes. Data are expressed as medians (IQRs) or counts (percentages), as appropriate.

Abbreviations: BMI, body mass index; cardiovasc, cardiovascular; CRP, C-reactive protein; diag, diagnosis; HR, hazard ratio; IQR, interquartile range; RAS, renin-angiotensin system; SCr, serum creatinine.

chronic kidney disease or an AKI in KTR—who were frequently admitted with diarrhea and high fever. Moreover, subsequent AKI and renal replacement therapy occurred more frequently among KTR than in nontransplant patients (46.1% and 11.2%, respectively) during hospitalization. AKI was observed in 5.1% of patients hospitalized with COVID-19 in Cheng et al's report,[7] and 4.5% of patients in the meta-analysis published by Yang et al.[12] The etiology of AKI during COVID-19 is multifactorial. In addition to SARS-CoV-2's direct attack of tubular cells via ACE2 receptors, other factors that may contribute to kidney injury include hypoxia, CRS, and a hypercoagulable state.[13] The susceptibility of KTR to dehydration, nephrotoxic drugs, and hemodynamic instability can also explain the high frequency of renal dysfunction in this cohort.

Given the differences between the transplant and nontransplant cohorts' baseline characteristics, we performed a matched analysis after adjusting for known risk factors of severe COVID-19 and COVID-19-related death[9-11] (i.e., age, BMI, cardiovascular and respiratory diseases, cancer, and diabetes) to minimize the effects of potential confounders. Our results validate the findings from previous studies in nontransplant patients with respect to known risk factors for severe COVID-19 and COVID-19-related death.[14,15] However, being a KTR was not associated with a more frequent need for ICU admission in our study. This could be explained by the shorter time from symptom onset to hospitalization (5 versus 7 days in KTR and nontransplant patients, respectively) and the lower incidence of pulmonary involvement at admission

TABLE 3 Risk factors for death in univariable analysis in the matched transplant and nontransplant cohorts (*n* = 546)

	No event	Event			
	N = 454	*N = 92*	HR	p.ratio	N
Baseline characteristics					
Renal transplantation - n (%)	218 (48.0%)	55 (59.8%)	1.55 [1.02;2.35]	0.039	546
Median age [IQR] - yr	60.0 [50.0–69.0]	71.0 [62.0–79.2]	1.05 [1.04;1.07]	<0.001	546
Age >60 yr - n (%)	232 (51.1%)	74 (80.4%)	3.61 [2.16;6.05]	<0.001	546
Male - n (%)	295 (65.0%)	59 (64.1%)	0.97 [0.63;1.49]	0.891	546
BMI >25 kg/m2 - n (%)	298 (65.6%)	60 (65.2%)	1.00 [0.65;1.53]	0.994	546
Hypertension - n (%)	298 (67.9%)	70 (79.5%)	1.76 [1.05;2.95]	0.033	527
RAS blockers - n (%)	177 (40.6%)	38 (44.7%)	1.16 [0.76;1.78]	0.492	521
Cardiovasc disease - no.(%)	160 (35.2%)	52 (56.5%)	2.23 [1.47;3.36]	<0.001	546
Resp. disease - n (%)	70 (15.4%)	13 (14.1%)	0.91 [0.51;1.64]	0.760	546
Diabetes - n (%)	154 (33.9%)	45 (48.9%)	1.75 [1.16;2.64]	0.007	546
Cancer - n (%)	51 (11.2%)	9 (9.78%)	0.86 [0.43;1.71]	0.668	546
Smoking - n (%)	32 (7.75%)	8 (10.0%)	1.27 [0.61;2.64]	0.519	493
Admission characteristics					
Anosmia - no.(%)	55 (14.2%)	3 (4.84%)	0.33 [0.10;1.05]	0.060	449
Cough - no.(%)	274 (63.3%)	46 (54.1%)	0.71 [0.46;1.09]	0.118	518
Dyspnea - n (%)	240 (52.9%)	57 (62.0%)	1.45 [0.95;2.20]	0.086	546
Fever - no.(%)	330 (75.9%)	70 (82.4%)	1.47 [0.84;2.56]	0.179	520
Headache - n (%)	76 (18.2%)	12 (15.0%)	0.82 [0.44;1.51]	0.524	497
Diarrhea - no.(%)	135 (30.5%)	21 (24.4%)	0.76 [0.46;1.24]	0.275	529
Time from diag. to admission [IQR] - d	6.00 [3.00–9.00]	4.00 [2.00–7.00]	0.94 [0.89;0.99]	0.018	511
Biological data					
CRP >60 mg/l - n (%)	207 (54.0%)	47 (69.1%)	1.84 [1.10;3.08]	0.020	451
Median lymphocyte count [IQR] - G/l	0.80 [0.57–1.18]	0.71 [0.45–0.96]	0.43 [0.24;0.77]	0.005	450
Median platelet count [IQR] - G/l	190 [150–253]	201 [153–259]	1.00 [1.00;1.00]	0.526	453
Thrombopenia <150 G/l - n (%)	93 (24.7%)	17 (22.4%)	0.87 [0.51;1.49]	0.604	453
Median SCr [IQR] - µmol/l	102 [69.7–179]	151 [100–219]	1.00 [1.00;1.00]	0.029	495
SCr >115 µmol/l	192 (46.4%)	55 (67.9%)	2.32 [1.45;3.70]	<0.001	495

Patients were matched (1:1 ratio) for age, BMI, cardiovascular and respiratory diseases, cancer, and diabetes.

Abbreviations: BMI, body mass index; cardiovasc, cardiovascular; CRP, C-reactive protein; diag, diagnosis; HR, hazard ratio; IQR, interquartile range; RAS, renin-angiotensin system; SCr, serum creatinine.

Data are expressed as medians (IQRs) or counts (percentages), as appropriate.

(dyspnea: 45.1 versus 63.7% in KTR and nontransplant patients, respectively).

However, the comparison of matched cohorts also showed that KTR had a twofold higher risk of COVID-19-related death compared to nontransplant patients after adjustment for age, BMI, and major comorbidities. While previous studies have shown that transplantation is a risk factor for mortality, a direct matched comparison between transplanted and nontransplant patients had never been performed. Data from a very large cohort of 17 million patients indicated that organ transplant recipients had an adjusted 3.55-fold higher risk of death, whereas those with glomerular filtration rates below 30 mL/min had a 2.5-fold increased risk.[16] In Cheng et al's cohort,[7] the incidence of in-hospital death in patients with increased baseline serum creatinine was 33.7%, which was higher than in those with normal creatinine levels (13.2%). Notably, this difference persisted after adjusting for age and comorbidities. In prior studies focusing on respiratory viruses (H1 N1, SARS, and MERS-CoV),[17,18] kidney injury was also associated with an increased risk of death. It remains uncertain whether the higher mortality rate observed in KTR is caused by immunosuppression and/or the increased rate of renal dysfunction. Multivariable analysis revealed that being a KTR was not independently associated with mortality, whereas a serum creatinine >115 µmol/L was retained in the model as an independent risk factor for death. These results indicate a prominent role for renal failure as a driver of COVID-19-related mortality.

Our findings need to be interpreted in the context of some limitations. First, one may argue that the comparability between a multicenter French nationwide transplant cohort and a single-center

TABLE 4 Multivariable analysis of risk factors for severe disease[a] and mortality in matched transplant and nontransplant cohorts (n = 546)

Severe disease	HR	p	Mortality	HR	p
Cardiovasc disease	1.35 [1.03;1.76]	.028	Cardiovasc disease	1.54 [0.96;2.46]	.071
Cough	0.61 [0.46;0.80]	<.001	Cough	0.58 [0.36;0.92]	.022
Dyspnea	1.90 [1.43;2.53]	.004	Dyspnea	1.74 [1.08;2.78]	.022
Fever	1.70 [1.19;1.76]	.004	Fever	1.81 [1.00;3.28]	.050
			SCr >115 µmol/L	2.40 [1.48;3.87]	<.001
			Age >60 years	3.47 [1.86; 6.47]	<.001

Concordance for the severe disease model: 0.63; concordance for the mortality model: 0.73. Patients were matched (1:1 ratio) for age, BMI, cardiovascular and respiratory diseases, cancer, and diabetes.

Missing data: - Severe model: 34 observations. - Death model: 64 observations.

Abbreviations: cardiovasc, cardiovascular; HR, hazard ratio; SCr, serum creatinine.

[a]Severe disease defined as requirement for ICU admission or mechanical ventilation, or death.

control group is low. Nevertheless, the single-center control group was large and representative of a different range of settings (i.e., medical, surgical, and ICU departments). Second, we are aware that KTR and control patients were managed differently—which can represent a potential source of confounding when their clinical outcomes are analyzed. While baseline lymphocyte count and creatinine concentrations were available for KTR, the majority of nontransplant patients had a negative clinical history before the onset of COVID-19. Therefore, we were unable to provide data on these parameters in nontransplant patients. Finally, all of the study patients were hospitalized. Thus, the question as to whether our findings are generalizable to an outpatient setting remains answered. These caveats notwithstanding, this study is the largest to date to comprehensively compare the clinical features and outcomes of COVID-19 in KTR with respect to nontransplant patients.

In summary, our study shows that, after adjustment for potential confounders, KTR with COVID-19 had a higher mortality rate than nontransplant patients, despite a similar occurrence of severe disease. While preexistent chronic kidney disease or AKI might have a greater prognostic impact than the immunosuppression state, further research is needed to shed more light on this issue.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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APPENDIX

FRENCH SOT COVID REGISTRY

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