Absence of Mortality Differences Between the First and Second COVID-19 Waves in Kidney Transplant Recipients

Bastien Berger¹, Marc Hazzan², Nassim Kamar³, Hélène Francois⁴, Marie Matignon⁵, Clarisse Greze⁶, Philippe Gatault⁷, Luc Frimat⁸, Pierre F. Westeel⁹, Valentin Goutaudier¹⁰, Renaud Sanoudl¹¹, Charlotte Colosio¹², Antoine Sicard¹³, Dominique Bertrand¹⁴, Christiane Mousson¹⁵, Jamal Bamoulid¹⁶, Antoine Thierry¹⁷, Dany Anglicheau¹⁸, Lionel Couzi¹⁹, Jonathan M. Chemouny²⁰, Agnes Duveau²¹, Valerie Moai²², Yannick Le Meur²³, Gilles Blanchon²⁴, Jérôme Tourret²⁵, Paolo Malvezzi²⁶, Christophe Maria²⁷, Jean-Philippe Rerolle²⁸, Nicolas Bouvier²⁹, Sophie Caillard³⁰,³¹, Olivier Thaunat¹,³²,³³ and on behalf of the French Solid Organ Transplant (SOT) COVID Registry³⁴

¹Department of Transplantation, Nephrology and Clinical Immunology, Edouard Herriot Hospital, Hospices civils de Lyon, Lyon, France; ²Department of Nephrology and Transplantation, University of Lille, Lille, France; ³Department of Nephrology and Transplantation, University of Toulouse, Toulouse, France; ⁴Department of Nephrology and Renal Transplantation, Assistance Publique-Hôpitaux de Paris, Hôpital Tenon, Paris, France; ⁵Department of Nephrology and Renal Transplantation, Assistance Publique-Hôpitaux de Paris, Institut Francilien de Recherche en Néphrologie et Transplantation IFRNT, Groupe Hospitalier Henri-Mondor/Albert-Chenevier, Université Paris-Est-Créteil, Département Hospitalo-Universitaire, Virus-Immunité-Cancer, Institut Mondor de Recherche Biomédicale, Equipe 21, INSERM U 955, Créteil, France; ⁶Department of Nephrology and Transplantation, Hôpital Bichat, Paris, France; ⁷Department of Nephrology and Transplantation, University of Tours, Tours, France; ⁸Department of Nephrology, University of Lorraine, CHRU-Nancy, Vandoeuvre, France, INSERM CIC-EC CIE6, Nancy, France; ⁹Department of Nephrology and Transplantation, University of Amiens, Amiens, France; ¹⁰Department of Nephrology and Transplantation, University of Montpellier, Montpellier, France; ¹¹Nephrology and Renal Transplantation Department, Hôpital Foch, Paris, France; ¹²Department of Nephrology and Transplantation, University of Reims, Reims, France; ¹³Service de Néphrologie-Dialyse-Transplantation, Hôpital Pasteur 2, CHU de Nice, Unité de Recherche Clinique Côte d’Azur, Université Côte d’Azur, Nice, France; ¹⁴Department of Nephrology and Transplantation, University of Rouen, Rouen, France; ¹⁵Department of Nephrology and Transplantation, University of Dijon, Dijon, France; ¹⁶Department of Nephrology, University of Besançon, Besançon, France; ¹⁷Department of Nephrology and Transplantation, University of Poitiers, Poitiers, France; ¹⁸Service de Néphrologie et Transplantation Adultes, Hôpital Universitaire Necker- APHP Centre-Université de Paris INEM INSERM U 1151 - CNRS UMR 8253, Paris, France; ¹⁹Service de Néphrologie-Transplantation-Dialyse-Aphérèse, Hôpital Pellegrin, CHU de Bordeaux Pellegrin, Unité Mixte de Recherche “ImmunoConcEpT” 5164 - Université de Bordeaux, Bordeaux, France; ²⁰University of Rennes, CHU Rennes, Inserm, EHESP, Ires (Institut de Recherche en Santé, Environnement et Travail) - UMR_S 1085, CIC-P 1414, Rennes, France; ²¹Department of Nephrology and Transplantation, University of Angers, Angers, France; ²²Centre de Néphrologie et Transplantation Renéa, Aix Marseille Université, Hôpitaux Universitaires de Marseille, Hôpital Conception, Marseille, France; ²³Department of Nephrology and Transplantation, CHU de Brest, UMR1227, Lymphocytes B et Auto-immunité, Université de Brest, Inserm, Labex IGO, Brest, France; ²⁴Department of Nephrology and Transplantation, Centre Hospitalier Universitaire de Nantes, Nantes, France; ²⁵Nephrology and Renal Transplantation Department, Assistance Publique-Hôpitaux de Paris, Hôpital de la Pitié Salpêtrière, Paris, France; ²⁶Department of Nephrology, University of Grenoble, Grenoble, France; ²⁷Department of Nephrology and Transplantation, University of St Etienne, St Etienne, France; ²⁸Department of Nephrology and Transplantation, University of Limoges, Limoges, France; ²⁹Department of Nephrology and Transplantation, University of Caen, Caen, France; ³⁰Department of Nephrology and Transplantation, Strasbourg University Hospital, Strasbourg, France; ³¹INSERM, IRM UMR-S 1109, University of Strasbourg, Strasbourg, France; ³²CIRI, INSERM U1111, University Claude Bernard Lyon 1, Lyon, France; and ³³Cirle Bernard University (Lyon 1), Villeurbanne, France

Introduction: SARS-CoV-2 pandemic evolved in 2 consecutive waves during 2020. Improvements in the management of COVID-19 led to a reduction in mortality rates among hospitalized patients during the second wave. Whether this progress benefited kidney transplant recipients (KTRs), a population particularly vulnerable to severe COVID-19, remained unclear.

Methods: In France, 957 KTRs were hospitalized for COVID-19 in 2020 and their data were prospectively collected into the French Solid Organ Transplant (SOT) COVID registry. The presentation, management, and outcomes of the 359 KTRs diagnosed during the first wave were compared to those of the 598 of the second wave.

Correspondence: Olivier Thaunat, Service de Transplantation, Néphrologie et Immunologie Clinique, Hôpital Édouard Herriot, 5 Place d’Arsonval, 69003 Lyon, France. E-mail: olivier.thaunat@chu-lyon.fr

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Results: Baseline comorbidities were similar between KTRs of the 2 waves. Maintenance immunosuppression was reduced in most patients but withdrawal of antimetabolites (73.7% vs. 58.4%, \( P < 0.001 \)) or calcineurin inhibitor (32.1% vs. 16.8%, \( P < 0.001 \)) was less frequent during the second wave. Hydroxychloroquine and azithromycin that were commonly used during the first wave (21.7% and 30.9%, respectively) but were almost abandoned during the second wave. In contrast, the use of high dose corticosteroids doubled (19.5% vs. 41.6%, \( P < 0.001 \)). Despite these changing trends in COVID-19 management, 60-day mortality was not statistically different between the 2 waves (25.3% vs. 23.9%; Log Rank, \( P = 0.48 \)) and COVID-19 hospitalization period was not associated with death due to COVID-19 in multivariate analysis (Hazard ratio 0.89, 95% confidence interval 0.67–1.17, \( P = 0.4 \)).

Conclusion: We conclude that changing of therapeutic trends during 2020 did not reduce COVID-19 related mortality among KTRs. Our data indirectly support the importance of vaccination and neutralizing monoclonal anti-SARS-CoV-2 antibodies to protect KTRs from severe COVID-19.

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After the initial outbreak in China in late 2019, COVID-19 spread globally. As of October 14, 2021, the pandemic had affected more than 238 million people causing more than 4.8 million deaths worldwide.

Like in the rest of the world, the viral pandemic evolved during 2020 in 2 consecutive waves in France. The first wave hit France during spring, only 3 months after SARS-CoV-2 discovery, in a context of limited knowledge about COVID-19, absence of proven specific treatment, and shortage of essential equipment such as face masks and diagnostic tests. The government imposed a national lockdown from March 17, 2020 to May 10, 2020, which successfully reduced the spread of the virus and led to the resolution of the first wave. Nevertheless, in the absence of available vaccine, SARS-CoV-2 resurged following the easing of social and physical distancing rules during the summer. As a result, a second pandemic wave started during fall 2020. In contrast to the first wave, enhanced testing capacities allowed diagnosis of asymptomatic cases during this second wave. In addition, intensivists had better experience of the stereotypical course of severe COVID-19, including the prolonged mechanical ventilation and Intensive Care Unit (ICU) stay, the increased risk of thrombotic events, and the high rates of acute kidney injury. More importantly, the RECOVERY trial had been published, providing evidence that dexamethasone reduces mortality among hospitalized patients who require oxygen therapy by 20%. These changes in medical care resulted in a 10% reduction of mortality rates among French hospitalized patients during the second wave compared to the first one.

Whether KTRs, a population that is particularly vulnerable to COVID-19, benefited from the progress made in COVID-19 management during 2020, remained unclear. Aiming at addressing this question, we retrospectively analyzed the prospectively collected data of the French SOT COVID registry and compared the course, management, and outcomes of COVID-19 diagnosed in 957 hospitalized French KTRs during the first wave versus the second wave.

METHODS

Data Collection
Cases of COVID-19 diagnosed in KTRs, were prospectively identified by the clinicians at all the 32 French University Hospitals, the only authorized structures for organ transplantation in France. Identified cases were reported on an ongoing basis to the French SOT COVID registry.

This prospective registry was approved by the Institutional Review Board of Strasbourg University (approval number 02.26) and registered at clinicaltrials.gov (NCT04360707). Of note, all patients were informed about their inclusion in the registry but the need for informed consent was waived.

KTRs hospitalized for COVID-19 in France between March 1 and December 31, 2020 were identified from the French SOT COVID registry.

The decision of hospitalization in case of COVID-19 diagnosis in a KTR was made by the physician in charge of the patient, based on the following criteria that remained similar during the 2 pandemic waves: severe symptoms (fever, dyspnea, and diarrhea), and/or high burden of co morbidities (overweight, age >60 years, and cardiovascular diseases).

Study Design and Patients
Inclusion criteria were age >18 years at the diagnosis of COVID-19 and presence of a functioning kidney graft.

The diagnostic criteria for COVID-19 was based on the following: (i) a positive reverse transcription polymerase chain reaction for SARS-CoV-2 in
nasopharyngeal swab or (ii) the presence of typical respiratory symptoms accompanied by evocative pulmonary lesions on low-dose chest computed tomography when reverse transcription polymerase chain reaction yielded negative results. KTRs admitted to hospital for other reasons, who developed pauci-symptomatic COVID-19 during hospitalization were excluded from the study.

Cases were considered to have occurred during the first wave if they were diagnosed between March 1 and July 31, 2020; and during second wave if they were diagnosed between August 1 and December 31, 2020. We used the time cutoff of December 31, 2020 for the end of the second wave to have an equal length of time compared to the first wave and to avoid the effect of the vaccination in order to increase baseline comparability.

Cardiovascular diseases included heart failure, coronary vascular disease, and dysrhythmia. Respiratory disease included chronic respiratory failure, asthma, and chronic obstructive pulmonary disease.

Chest computed tomography is considered one of the main tools for assessing SARS-CoV-2 infection severity, enabling stratification of patients into risk categories and estimation of their prognosis.18 Chest computed tomography scan severity was based on the extent of pulmonary involvement and was defined as follows: “mild” for <25%, “moderate” for 25% to 50%, and “severe” for >50% pulmonary involvement.

Statistical Analysis

Categorial variables are reported as counts and percentages. Continuous variables are presented as medians and interquartile ranges. Differences between groups were assessed with the chi-square test or two-sided Fisher’s exact test for categorical variables and with t-test or Wilcoxon’s rank-sum test for continuous variables. Survival curves were represented using the Kaplan-Meier method and compared with the log-rank test. The primary outcome is 60-day mortality. Secondary outcomes include the following: admission to the ICU, 60-day mortality in ICU, initiation of renal replacement therapy, use of mechanical ventilation, use of vasopressor support, occurrence of bacterial pulmonary superinfection, or thrombo-embolic event.

The multiple imputations method19 was used to handle missing data on relevant covariates. Five imputed data sets were generated and analyses were performed on each of them. Then, the results were combined using the Rubin rules20 to obtain average values. To assess risk factors for mortality, Cox proportional hazard univariable and multivariable models were built. All the variables with a univariable threshold \( P < 0.1 \) were selected as covariates for the initial multivariable model. The covariates in the final multivariable model were selected using a backward conditional procedure with a threshold \( P < 0.05 \). Results are expressed as hazard ratios with their 95% confidence intervals. All analyses were conducted in the R environment (R Foundation for Statistical Computing, Vienna, Austria) version 4.1.221 using the “survival” and “mice” packages. All tests were 2-sided, and \( P < 0.05 \) was considered statistically significant.

RESULTS

Baseline Patient Characteristics

Shortage in diagnosis assays during the first pandemic wave resulted in the fact that only symptomatic patients were tested to confirm clinically or radiologically suspected COVID-19.22,23 As the result of enhanced availability of these assays later in the year 2020, asymptomatic COVID-19 were identified during the second wave.22 Furthermore, from January 2021 onward anti-SARS-CoV-2 vaccines became available, reducing the risk of severe COVID-19 and contributing to the resolution of the second pandemic wave. Because the criteria for hospitalization of KTRs with symptomatic COVID-19 evolved only slightly over time and given the fact that our aim was to compare the 2 pandemic waves, the present study focused on the 957 cases (\( n = 359 \) [37.5%] from the first wave and \( n = 598 \) [62.5%] from the second wave) of COVID-19 diagnosed in KTRs that require hospitalization and occurred before January 1, 2021.

The characteristics of enrolled patients, which were prospectively collected in the French SOT COVID registry, are presented in Table 1. Briefly, a little less than 10% of the cohort received a graft from a living donor. The median recipient age was 63.0 (52.0–70.0) years and males represented 68.1% of the cohort. Most patients (537 of 864, 62.1%) were overweight and the median body mass index of the cohort was 26.0 [23.0–29.4] kg/m². The most common comorbidity was hypertension (798 of 918, 86.9%), followed by diabetes (371 of 914, 40.6%) and cardiovascular diseases (352 of 957, 36.8%). The median baseline estimated glomerular filtration rate was 41.0 [30.0–54.0] ml/min per 1.73 m². Regarding therapeutic immunosuppression, the vast majority of patients received an induction therapy, either with anti-interleukin-2 (385 of 931, 41.4%) or with antithymocyte globulin (508 of 931, 54.6%). At diagnosis of COVID-19, maintenance regimen of most patients consisted of a combination of calcineurin inhibitor (807 of 957, 84%), either tacrolimus 65.3% or cyclosporine 19%), an antimetabolite (722 of 957, 75.4% on mycophenolic acid) and corticosteroids (726 of 957, 75.9%). Only 4.0% of the cohort were on belatacept.
The patients of the 2 pandemic waves were largely similar except for diabetes, the prevalence of which was slightly lower in patients of the second wave (37.3% vs. 45.7% respectively; \( P = 0.014 \)). Difference in immunosuppression regimen were also minor with only slightly fewer patients on corticosteroids (72.7% vs. 81.1%, \( P = 0.005 \)) and mechanistic target of rapamycin inhibitors (8.9% vs. 13.1%, \( P = 0.050 \)) in the second pandemic wave. Although we do not have definitive explanation for these differences, it is tempting to speculate that they are due to changes in maintenance regimen made after the first pandemic wave to protect KTRs in case of infection with SARS-CoV-2. Due to their well-known pulmonary toxicity and proinflammatory effects, mechanistic target of rapamycin inhibitors were indeed suspected to have negative impacts on COVID-19 course. With regard to corticosteroids, some reports suggested that prolonged maintenance corticosteroids therapy may predispose patients, including KTRs, to severe forms of COVID-19.

Table 1. Baseline characteristics of kidney transplant patients at admission for COVID-19

| Variables | All cohort \((N = 957)\) | Missing data \((n = 359)\) | first wave \((n = 598)\) | second wave \((n = 598)\) | \( P \) value |
|-----------|--------------------------|---------------------------|-------------------------|-------------------------|----------------|
| Age (yr)  | 63.0 [52.0–70.0] | 0 (0.0%) | 63.0 [54.0–70.0] | 62.0 [51.2–70.0] | 0.298 |
| Male      | 652 (68.1%) | 0 (0.0%) | 243 (67.7%) | 409 (68.4%) | 0.876 |
| BMI (kg/m\(^2\)) | 26.0 [23.0–29.4] | 93 (9.7%) | 26.0 [23.0–29.0] | 26.0 [23.2–29.6] | 0.564 |
| Blood group | 30 (3.1%) | 0 (0.0%) | 144 (40.4%) | 251 (44.0%) | 0.472 |
| A         | 395 (42.6%) | 0 (0.0%) | 144 (40.4%) | 251 (44.0%) | 0.472 |
| AB        | 59 (6.4%) | 0 (0.0%) | 21 (5.9%) | 38 (6.7%) | 0.014 |
| B         | 107 (11.5%) | 0 (0.0%) | 39 (11.0%) | 68 (11.9%) | 0.014 |
| O         | 366 (39.5%) | 0 (0.0%) | 152 (42.7%) | 214 (37.5%) | 0.014 |
| Retransplantation | 104 (11.5%) | 50 (5.2%) | 45 (12.6%) | 59 (10.7%) | 0.462 |
| Multorgan Tx\(^*\) | 38 (4.0%) | 0 (0.0%) | 20 (5.6%) | 18 (3.0%) | 0.462 |
| Living donor | 90 (9.5%) | 0 (0.0%) | 27 (7.5%) | 63 (10.6%) | 0.125 |
| Delay Tx-COVID (mo) | 67.6 [28.2–134.2] | 0 (0.0%) | 71.1 [31.0–144.5] | 65.6 [27.3–129.9] | 0.215 |
| Hypertension | 798 (86.9%) | 39 (4.1%) | 320 (89.4%) | 478 (85.4%) | 0.050 |
| CV disease | 352 (38.8%) | 49 (5.1%) | 148 (41.2%) | 204 (37.2%) | 0.246 |
| Respiratory disease | 122 (13.4%) | 35 (4.1%) | 43 (12.0%) | 79 (14.3%) | 0.366 |
| Diabetes | 371 (40.6%) | 0 (0.0%) | 164 (45.7%) | 207 (37.3%) | 0.014 |
| Cancer | 144 (15.8%) | 0 (0.0%) | 63 (17.5%) | 81 (14.7%) | 0.290 |
| Smoking | 126 (15.0%) | 0 (0.0%) | 40 (12.1%) | 86 (16.8%) | 0.079 |
| Statin | 307 (46.2%) | 292 (30.5%) | 154 (49.7%) | 153 (43.1%) | 0.105 |
| RAS blockers | 371 (44.8%) | 0 (0.0%) | 155 (48.1%) | 216 (42.7%) | 0.143 |
| Baseline eGFR (ml/min/1.73m\(^2\)) | 41.0 [30.0–54.0] | 0 (0.0%) | 40.0 [29.0–55.0] | 42.0 [30.0–54.0] | 0.336 |
| Creatininemia at admission | 174 [129–256] | 0 (0.0%) | 176 [134–264] | 174 [127–250] | 0.644 |
| Acute Kidney Injury | 575 (66.9%) | 0 (0.0%) | 255 (72.6%) | 320 (62.9%) | 0.003 |
| Renal replacement therapy | 134 (14.0%) | 0 (0.0%) | 57 (15.9%) | 77 (12.9%) | 0.230 |
| Immunosuppression Induction | 26 (2.7%) | 0 (0.0%) | 28 (4.8%) | 10 (2.9%) | 0.140 |
| No induction | 38 (4.1%) | 10 (2.9%) | 28 (4.8%) | 6 (1.8%) | 0.079 |
| anti-IL2R | 385 (41.4%) | 137 (39.1%) | 248 (42.7%) | 77 (12.9%) | 0.230 |
| ATG | 508 (54.6%) | 203 (58.0%) | 305 (62.5%) | 77 (12.9%) | 0.230 |
| Maintenance | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0.234 |
| No CNI | 150 (15.7%) | 47 (13.1%) | 103 (17.2%) | 77 (12.9%) | 0.234 |
| Tacrolimus | 625 (65.3%) | 242 (67.4%) | 383 (64.0%) | 248 (42.7%) | 0.234 |
| Cyclosporine | 182 (19.0%) | 70 (19.5%) | 112 (18.7%) | 77 (12.9%) | 0.234 |
| Mycophenolate | 722 (75.4%) | 278 (77.4%) | 444 (74.2%) | 320 (62.9%) | 0.005 |
| Azathioprin | 32 (3.3%) | 12 (3.3%) | 20 (3.3%) | 8 (1.8%) | 0.050 |
| mTOR inhibitor | 100 (10.4%) | 47 (13.1%) | 53 (8.9%) | 28 (4.8%) | 0.050 |
| Steroids | 726 (75.9%) | 281 (81.1%) | 435 (72.7%) | 281 (47.1%) | 0.005 |
| Belatacept | 38 (4.0%) | 20 (5.6%) | 18 (3.3%) | 10 (1.8%) | 0.073 |

Anti-IL2R, anti-interleukin-2 receptor; ATG, antithymocyte globulin; BMI, body mass index; CNI, calcineurin inhibitor; CV, cardiovascular; eGFR, estimated glomerular filtration rate; IQR, interquartile range; mTOR, mechanistic target of rapamycin; RAS, renin-angiotensin-system; Tx, transplantation.

*Multorgan transplants includes 15 kidney/pancreas, 15 kidney/liver, 7 kidney/heart and 1 kidney/lung recipients.

Bold indicates \( P < 0.05 \).

The \( P \) values are for the comparisons of first wave 1 versus second wave.

Baseline eGFR is determined with the Modification of Diet in Renal Disease (MDRD) equation.
Clinical and Biological Presentation of COVID-19 at Admission

Almost all diagnoses of COVID-19 (919 of 957, 96%) were confirmed by reverse transcriptase polymerase chain reaction. SARS-CoV-2 infection occurred after a median of 67.6 [28.2–134.2] months after kidney transplantation. Of note, despite the fact that kidney transplantation activity in France was interrupted during the first wave but maintained during the second wave, there was no difference in the median delay from transplantation to COVID-19 diagnosis between the 2 pandemic waves (71.1 [31.0–144.5] vs. 65.6 [27.3–129.9] months, \( P = 0.215 \)).

Considering the whole cohort (Figure 1a), the most frequent symptom on admission was fever (585 of 957, 67.2%), followed by cough (494 of 957, 56.8%), dyspnea (466 of 957, 52.3%), and diarrhea (317 of 957, 36.2%). Median levels of C-reactive protein and procalcitonin were 67 (28–121) mg/l and 0.22 (0.12–0.70) ng/ml respectively. At admission, most (580 of 653, 89%) patients had low lymphocyte count (median lymphocyte count of the cohort 0.65 × 10^9 [0.40–1.00]/l) and median creatininemia was 174 (129–256) μmol/l.

KTRs from the second wave differed from those of the first in that they less frequently exhibited fever, cough, and myalgias, which could indicate earlier diagnosis during the second wave (Figure 1b). This hypothesis is coherent with the increased availability of diagnosis assays during the second half of 2020. Nevertheless, no significant differences in C-reactive protein and procalcitonin levels, nor in lymphocyte count were observed between the 2 pandemic waves (data not shown). Furthermore, chest computed tomography scan severity at presentation was also similar between the 2 waves with approximately 45%, 30%, and 25% of KTRs presented with mild, moderate and severe degree of involvement, respectively (Figure 1c; \( P = 0.921 \)).
Management of Immunosuppression and Antiviral Therapies

Maintenance immunosuppression was tapered in KTRs hospitalized for symptomatic COVID-19, particularly antimitabolites and mechanistic target of rapamycin inhibitors, which were discontinued in most patients during both pandemic waves (Figure 2a). Nevertheless, if modifications of maintenance immunosuppression did not differ in nature between the 2 waves, they were made in a smaller proportion of patients during the second wave, particularly regarding withdrawal of calcineurin inhibitor (32.1% vs. 16.6%,  \( P < 0.001 \)) and of antimitabolites (73.7% vs. 58.4%,  \( P < 0.001 \); Figure 2a), which is in line with a previous report from the US.\(^{28}\)

Contrasting with the global stability of immunosuppression management, anti-SARS-CoV-2 therapies differed in many respects between the 2 waves (Figure 2b). KTRs with COVID-19 from the second wave received empirical antibiotics less frequently compared to those of the first wave (75.8% vs. 49.2%,  \( P < 0.001 \)). Hydroxychloroquine and azithromycin, which were commonly used during the first wave were almost completely abandoned during the second wave (21.7% vs. 1.7% and 30.9% vs. 5.0%,  \( P < 0.001 \), respectively). Tocilizumab use declined between the first and second waves (7.5% vs. 2.2%,  \( P < 0.001 \)). Conversely, the use of high dose corticosteroids doubled (19.5% vs. 41.6%,  \( P < 0.001 \)). Of note, these changes of therapeutic trends for KTRs between the first and second pandemic waves in France were very similar to what was reported in the general population in Europe.\(^{29,30}\)

Risk Factors Associated With Death due to COVID-19 in KTRs

Univariate analysis conducted on the whole cohort identified the following: age, hypertension, preexisting cardiovascular disease, history of cancer, diabetes, dyspnea at admission, C-reactive protein >60 mg/l at...
admission, and baseline estimated glomerular filtration rate as significantly associated with mortality (data not shown). In contrast, diarrhea, anosmia, and headaches were associated with reduced risk of death.

In multivariate analysis, only age >50 years, history of cancer, dyspnea or C-reactive protein >60 mg/l at admission, and baseline estimated glomerular filtration rate <30 ml/min per 1.73 m² remained independently associated with a higher risk of death among KTRs hospitalized for COVID-19 (Figure 3), whereas anosmia at admission was associated with a better prognosis (Figure 3). Importantly, no association between the COVID-19 hospitalization period (during the first or second wave) and mortality was observed.

**Comparison of First Versus Second Wave Outcomes**

Though patients from the first and second pandemic waves had the same graft function at baseline and similar creatinine levels on admission, the proportion of the latter that developed acute kidney injury was lower during the second wave (72.6% in the first wave vs. 62.9% in the second wave; \( P = 0.003 \)). This possible beneficial effect on graft function of the changes in COVID-19 management between the 2 pandemic waves was however rather mild because the proportion of patients that required renal replacement therapy remained the similar during the 2 waves (15.9% vs. 12.9%; \( P = 0.230 \)).

The incidence of thromboembolic events (9.5% vs. 6.4%, \( P = 0.135 \)) and bacterial superinfection (27.0% vs. 30.7%, \( P = 0.304 \)) was similar between the 2 pandemic waves. A nonsignificant trend for lesser use of mechanical ventilation (26.5% vs. 22.1%, \( P = 0.152 \)) and vasopressor support (20.5% vs. 15.9%, \( P = 0.304 \)) was observed during the second wave but mortality at 60 days from admission (24.5%) was in the range of what was previously reported, with no significant difference between the first and second wave (Figure 4a; Log rank test, \( P = 0.48 \)).

A slight difference in dynamics between the 2 waves could however be observed on Kaplan-Meier curves (Figure 4a), with shorter duration between admission and death due to COVID-19 in KTRs of the first wave. When we assessed 14-day survival, we found a significant difference between the first and second wave (88.3% vs. 90.3%, \( P < 0.01 \)) that progressively reduced from 28-day follow-up (78.8% vs. 82.1%, \( P = 0.17 \)) and disappeared by the end of the 60-day follow-up period (75.7% vs. 77.5%, \( P = 0.48 \)). This difference is to be interpreted together with a faster and higher incidence of transfer of patients to the ICU during the first wave (Figure 4b), without difference on the mortality for patients transferred in ICU (Figure 4c). Altogether, these findings could indicate that patients of the first wave were diagnosed (and therefore hospitalized) later in the course of COVID-19, a hypothesis which is in line with the difference in clinical
presentation between the 2 waves reported above (Figure 1b) and consistent with the lack of available diagnosis tests during the first wave.

In contrast with the second wave that impacted the entire territory of France, the first pandemic wave had a heterogeneous geographic distribution\textsuperscript{11} that could have introduced a “learning-curve” bias. Physicians from the geographic areas impacted by the first wave could have accumulated knowledge and skills useful to better manage patients during the second wave. To test this hypothesis, we compared the survival of KTRs hospitalized for COVID-19 during the second wave in geographic areas impacted (in red on the map Figure 4d) versus areas preserved (in green on the map Figure 4d) during the first pandemic wave. The similarity in survival for patients of the second wave hospitalized in either of these 2 areas strongly argue against the theory of the learning curve bias (Figure 4e).

**DISCUSSION**

KTRs, who are characterized by a highly comorbid profile and receive therapeutic immunosuppression to prevent graft rejection, were identified very early as particularly vulnerable to COVID-19.\textsuperscript{15-17} An excess of
mortality, integrally explained by COVID-19, was indeed reported in this population during the first wave of the pandemic in France\(^\text{31}\) and several large multicenter KTR cohorts estimated short-term intrahospital mortality of about 20% to 32%.\(^\text{31,34,35}\) Among the risk factors identified in previous publications for death due to COVID-19 in KTRs are age, estimated glomerular filtration rate, and presence of comorbidities, including cardiovascular diseases, diabetes, and/or obesity.\(^\text{33,34,36,37}\) In addition, dyspnea and elevation of biochemical markers of inflammation at diagnosis of COVID-19 were also associated with less favorable survival figures.\(^\text{38–40}\)

Our study largely confirms these data. In addition, it provides original additional information regarding the stability of the risk of death due to COVID-19 in KTRs, despite the impressive accumulation of knowledge regarding the disease, which translated into better outcomes in the general population.\(^\text{13,14,41}\) Indeed, despite a more homogeneous COVID-19 management with wider prescription of dexamethasone and important decrease in the use of treatments deemed inefficient such as azithromycin,\(^\text{42}\) hydroxychloroquine,\(^\text{42,43}\) and lopinavir/ritonavir,\(^\text{44}\) survival of hospitalized KTRs during the second wave remained similar to that observed during the first wave.

Could it be that the fact that calcineurin inhibitor and antimetabolites that were less reduced during the second wave have offset the potential gains due to the changes in COVID-19 management? This simple explanation seems unlikely. The exact impact of maintenance immunosuppression during COVID-19 is unclear.\(^\text{45}\) On one hand, SOT recipients have been found to have delayed SARS-CoV-2 clearance\(^\text{46,47}\) but on the other hand, these drugs could be protective against the overproduction of proinflammatory cytokines during critical COVID-19.\(^\text{48,49}\)

The absence of net gain on mortality between the 2 pandemic waves for KTRs concurs with the conclusions of a recent meta-analysis, including 5559 KTRs with COVID-19 that reported a mean mortality rate of 23% (similar to what we observed) without significant difference between “early” (studies submitted before July 2020) and “late” (studies submitted from July 2020 onwards) phases of the pandemic.\(^\text{50}\) These findings conflict with a recent study showing a better prognosis in “late” (from June 20 to December 31, 2020) compared to “early” 2020 (from March 1 to June 19, 2020) among 973 SOT recipients hospitalized in USA for COVID-19.\(^\text{28}\) In their report, crude mortality by 28 days declined from 19.6% during the early period to 13.7% during the late period and after adjusting for differences in baseline comorbidities between both periods, the odds of death remained lower during the late period (adjusted odds ratio 0.67, 95% confidence interval 0.46–0.98, \(P = 0.04\)). Instead of the changing trends in management of COVID-19 patients, we believe that the observations made by Heldman et al.\(^\text{28}\) could be explained by the numerous differences in the baseline comorbid profiles of SOT recipients between the early and late period (SOT recipients in late period presented with less hypertension, diabetes, heart failure, coronary artery disease, and chronic lung disease) and/or by the short follow-up period of the study. Indeed, when we assessed 14-day mortality in our cohort, we found a significant difference between the first and second wave that progressively disappeared by the end of the 60-day follow-up period. Whether this effect is attributable to earlier diagnosis of COVID-19 in KTRs during the second wave is possible and supported by some clues discussed above remains to be formally demonstrated.

Among the strengths of our study are the relative high number of patients enrolled and the prospective collection of data. Our study however has some limitations. First, the identification of cases was based on individual clinicians, which carry theoretical risk of ascertainment bias. Nevertheless, we believe that this risk is low in the case of the present work because of the following: (i) all French University Hospitals participated to French SOT COVID registry, (ii) University Hospitals are the only authorized structures for organ transplantation in France, and (iii) the study period is 2020, the first year of the pandemic, when knowledge about COVID-19 in KTRs was embryonic, which pushed physicians diagnosing COVID-19 in a KTR outside a transplantation center to systematically seek advice from the experts. Among the other limitations is the fact that we compared 2 periods (first and second wave) but did not take into account COVID-19 ICU occupancy rates, a factor thought to impact mortality rates.\(^\text{13}\) Finally, our study was not designed to capture the impact of vaccines, which only became available early 2021.

Accumulating evidence suggests that KTRs have an impaired response to the “standard” 2 doses of mRNA vaccine,\(^\text{51–54}\) which leaves them at high risk of severe COVID-19.\(^\text{53,55}\) Despite intensified scheme of vaccination (with a third and even a fourth vaccine dose now recommended for weak responders), up to 20% of KTRs will not develop sufficient protection against COVID-19.\(^\text{54,56–58}\) In this regard, the development of neutralizing monoclonal anti-SARS-CoV-2 spike protein antibodies represents an interesting therapeutic option. The latter are already available in high-risk patients diagnosed with mild to moderate COVID-19 (postexposure therapy) and first reports about their use for prophylaxis (preexposure therapy) are promising.\(^\text{60}\)
In addition, KTRs should maintain individual measures such as social and physical distancing and wearing of face masks to minimize the risk of SARS-CoV-2 exposure.

In conclusion, changing of therapeutic trends during 2020 did not reduce COVID-19 related mortality among KTRs. Our data thus indirectly stress the importance of therapeutic progress made during 2021, including vaccination and neutralizing monoclonal anti-SARS-CoV-2 spike protein antibodies, to protect this vulnerable population from death due to COVID-19.

**APPENDIX**

List of French Solid Organ Transplant (SOT) COVID Registry

The French SOT COVID Registry Collaborators are as follows: Sophie Caillard, Bruno Moulin, Service de Néphrologie et Transplantation, Hôpitaux Universitaires de Strasbourg, Strasbourg; Samira Fafi-Kremer, Laboratoire de Virologie, Hôpitaux Universitaires de Strasbourg, Strasbourg; Marc Hazan, Service de Néphrologie, Hôpital Huriez, Lille; Dany Anglicheau, Service de Néphrologie et Transplantation Adultes, AP-HP, Hôpital Necker, Paris; Alexandre Hertig, Jérôme Tourret, Benoît Barrou, Service de Néphrologie, AP-HP, Hôpital La Pitié Salpêtrière, Paris; Emmanuel Morelon, Olivier Thaunat, Service de Néphrologie, Hôpital Edouard Herriot, Lyon; Lionel Couzi, Pierre Merville, Service de Néphrologie–Transplantation–Dialyse, Hôpital Pellegrin, Bordeaux; Valérie Moal, Tristan Legris, Service de Néphrologie et Transplantation, AP-HM, Hôpital de la Conception, Marseille; Pierre-François Westeel, Maité Jaureguy, Service de Néphrologie, CHU Amiens Picardie, Amiens; Luc Frimat, Service de Néphrologie, CHRU Nancy, Vandoeuvre; Didier Duclox, Jamal Bamoulid, Service de Néphrologie, Hôpital Jean-Minjoz, Besançon; Dominique Bertrand, Service de Néphrologie, CHU de Rouen, Rouen; Michel Tsimaratos, Florentine Garaix-Gilardo, Service de Pédiatrie Multidisciplinaire, Hôpital La Timone, Marseille; Jérôme Dumortier, Service d’Hépato-Gastroentérologie, Hôpital Edouard Herriot, Lyon; Sacha Musso, Antoine Roux, Centre Chirurgical Marie Lannelongue, Le Plessis Robinson; Laurent Sebbag, Service d’Insuffisance Cardiaque, Hôpital Louis Pradel, Bron; Yannick Le Meur, Service de Néphrologie, Hôpital de la Cavale Blanche, Brest; Gilles Blanchon, Christophe Masset, Service de Néphrologie–Transplantation, Hôtel Dieu, Nantes; Nassim Kamar, Service de Néphrologie et Transplantation, Hôpital Rangueil, Toulouse; Hélène Francois, Eric Rondeau, Service de Néphrologie, Dialyse et Transplantation, AP-HP, Hôpital Tenon, Paris; Nicolas Bouvier, Service de Néphrologie, Dialyse, Transplantation Rénale, CHU, Caen; Christiane Mousson, Service de Néphrologie, Dijon; Matthias Buchler, Philippe Gatault, Service de Néphrologie, Tours; Jean-François Augusto, Agnès Duveau, Service de Néphrologie, Dialyse, Transplantation, CHU Angers, Angers; Cécile Vigneau, Marie-Christine Morin, Jonathan Chemouy, Leonard Golbin, Service de Néphrologie, CHU de Rennes, Rennes; Philippe Grimbert, Marie Matignon, Antoine Durrbach, Service de Néphrologie, Hôpital Henri-Mondor, Créteil; Clarisse Greze, Service de Néphrologie, AP-HP, Hôpital Bichat Claude Bernard, Paris; Renaud Sranoudj, Service de Néphrologie, Hôpital Foch, Service de Néphrologie et Transplantation Hôpital du Kremlin Bicêtre, Le Kremlin Bicêtre; Charlotte Colosio, Betoul Schwartz, Service de Néphrologie, Hôpital Maisons Blanche, Reims; Paolo Malvezzi, Service de Néphrologie, Hémodialyse, Transplantation Rénale, Hôpital La Tronche, Grenoble; Christophe Mariat, Service de Néphrologie, CHU de Saint Etienne, Saint Etienne; Antoine Thierry, Service de Néphrologie, Hémodialyse et Transplantation Rénale, Hôpital Jean Bernard, Poitiers; Mogile Le Quinerc, Service de Néphrologie–Transplantation–Dialyse, CHU Lapeyronie, Montpellier; Antoine Sicard, Service de Néphrologie, Hôpital Pasteur, Nice; Jean Philippe Rerolle, Service de Néphrologie, CHU Dupuytren, Limoges; Anne-Élisabeth Heng, Cyril Garrouste, Service de Néphrologie, CHU Gabriel Montpied, Clermont-Ferrand; Henri Vacher Coponat, Service de Néphrologie, CHU de La Réunion, Saint Denis; Éric Epailly, Service de Cardiologie, Hôpitaux Universitaires de Strasbourg, Strasbourg; Olivier Brugiere, Service d’Hépato logie, Hôpital Foch, Suresnes; Sébastien Dharancy, Service d’Hépato logie, Hôpital Huriez, Lille; Éphrem Salame, Service de Chirurgie Hépatique, Hôpital Universitaire de Tours, Tours; Faouzi Saliba, Service d’Hépatologie, Centre hépato-biliaire Paul Brousse, Villejuif, France.

**DISCLOSURE**

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**SUPPLEMENTARY MATERIAL**

Supplementary File (PDF)

**STROBE Statement.**

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