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

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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.

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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 antimetabolite (73.7% vs. 58.4%, $P < 0.001$) or calcineurin inhibitor (32.1% vs. 16.6%, $P < 0.001$) 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.[1] As of October 14, 2021, the pandemic had affected more than 238 million people causing more than 4.8 million deaths worldwide.[2]

Like in the rest of the world,[3,4] 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,[5] 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.[6,7] 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.[8] 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,[9] the increased risk of thrombotic events,[10] and the high rates of acute kidney injury.[11] More importantly, the RECOVERY trial[12] 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.[13,14]

Whether KTRs, a population that is particularly vulnerable to COVID-19,[15-17] 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 comorbidities (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 paucisymptomatic 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 2-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 method[19] 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 rules[20] 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 4.1.2[21] 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/m^2. The most common comorbidity was hypertension (798 of 918, 86.9%), followed by diabetes (371 of 914, 40.6%) and cardiovascular diseases (352 of 908, 38.8%). The median baseline estimated glomerular filtration rate was 41.0 [30.0–54.0] ml/min per 1.73 m^2. 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.

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

Variables median [IQR] or n (%)	All cohort (*N* = 957)	Missing data	first wave (*n* = 359)	second wave (*n* = 598)	*P* value
Clinical characteristics					
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%)			0.472
A	395 (42.6%)		144 (40.4%)	251 (44.0%)	
AB	59 (6.4%)		21 (5.9%)	38 (6.7%)	
B	107 (11.5%)		39 (11.0%)	68 (11.9%)	
O	366 (39.5%)		152 (42.7%)	214 (37.5%)	
Retransplantion	104 (11.5%)	50 (5.2%)	45 (12.6%)	59 (10.7%)	0.462
Multiorgan Tx[a]	38 (4.0%)	0 (0.0%)	20 (5.6%)	18 (3.0%)	0.145
Living donor	90 (9.5%)	13 (1.3%)	27 (7.5%)	63 (10.8%)	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%)	0.096
CV disease	352 (38.8%)	49 (5.1%)	148 (41.2%)	204 (37.2%)	0.246
Respiratory disease	122 (13.4%)	45 (4.7%)	43 (12.0%)	79 (14.3%)	0.368
Diabetes	371 (40.6%)	43 (4.5%)	164 (45.7%)	207 (37.3%)	**0.014**
Cancer	144 (15.8%)	47 (4.9%)	63 (17.5%)	81 (14.7%)	0.290
Smoking	126 (15.0%)	115 (12.0%)	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%)	129 (13.5%)	155 (48.1%)	216 (42.7%)	0.143
Baseline eGFR (ml/min/1.73m^2)	41.0 [30.0–54.0]	36 (3.8%)	40.0 [29.0–55.0]	42.0 [30.0–54.0]	0.336
Creatininemia at admission	174 [129–256]	191 (19.9%)	176 [134–264]	174 [127–250]	0.644
Acute Kidney Injury	575 (66.9%)	97 (10.1%)	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%)			0.140
No induction	38 (4.1%)		10 (2.9%)	28 (4.8%)	
anti-IL2R	385 (41.4%)		137 (39.1%)	248 (42.7%)	
ATG	508 (54.6%)		203 (58.0%)	305 (52.5%)	
Maintenance					
CNI		0 (0.0%)			0.234
No CNI	150 (15.7%)		47 (13.1%)	103 (17.2%)	
Tacrolimus	625 (65.3%)		242 (67.4%)	383 (64.0%)	
Cyclosporine	182 (19.0%)		70 (19.5%)	112 (18.7%)	
Mycophenolate	722 (75.4%)	0 (0.0%)	278 (77.4%)	444 (74.2%)	0.302
Azathioprin	32 (3.3%)	0 (0.0%)	12 (3.3%)	20 (3.3%)	1.000
mTOR inhibitor	100 (10.4%)	0 (0.0%)	47 (13.1%)	53 (8.9%)	0.050
Steroids	726 (75.9%)	0 (0.0%)	291 (81.1%)	435 (72.7%)	**0.005**
Belatacept	38 (4.0%)	0 (0.0%)	20 (5.6%)	18 (3.0%)	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.
[a]Multiorgan 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.

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[24] and proinflammatory effects,[25] 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,[26] including KTRs[27] to severe forms of COVID-19.

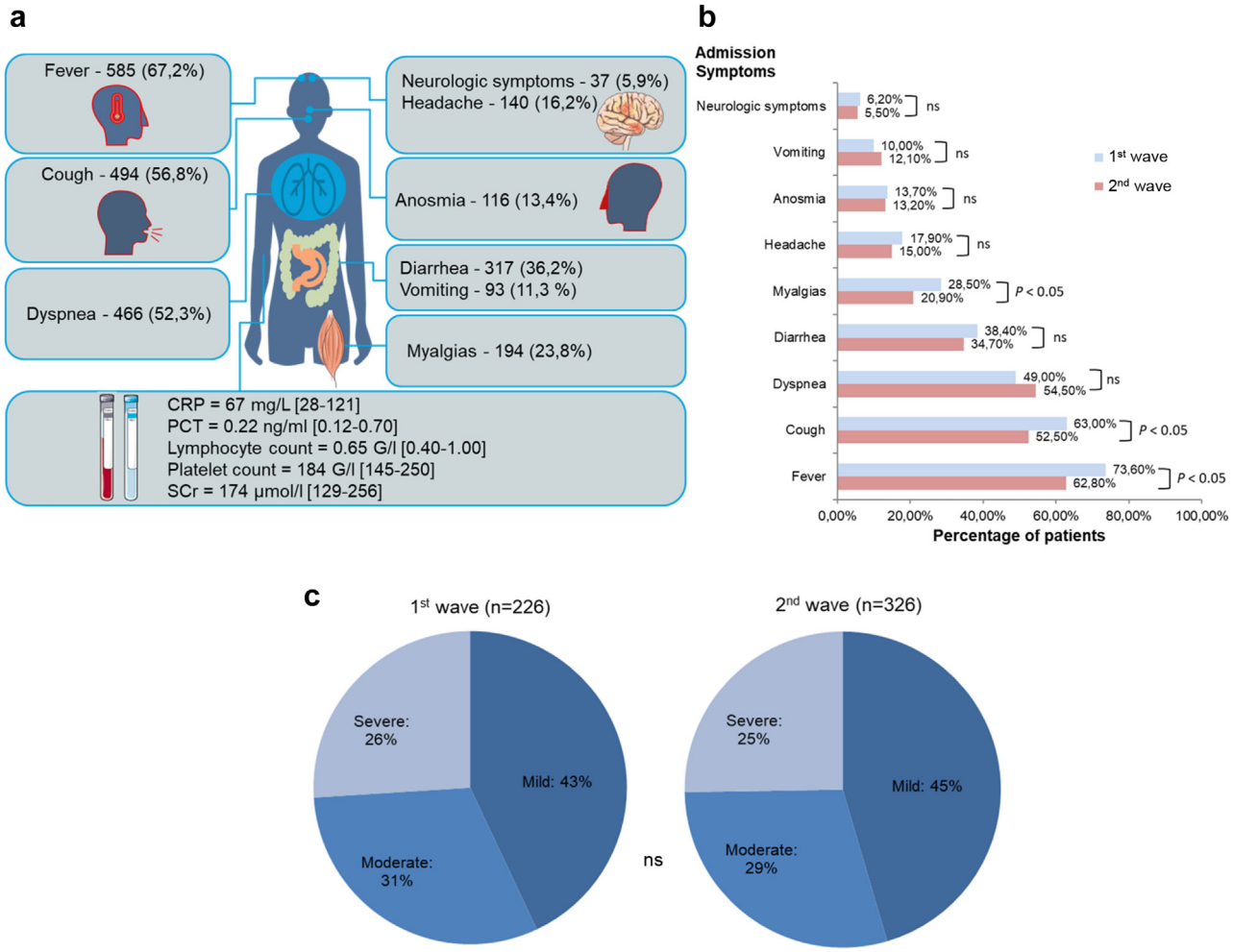

Figure 1. Clinical and biological presentation of COVID-19 at admission. *(a)* Summary of the main clinical and biological characteristics of the entire cohort ($N = 957$ KTRs), Median [IQR] or n (%), at hospital admission for COVID-19. b. Comparison of characteristics at hospital admission for COVID-19 of patients from the first versus second pandemic wave. c. Comparison of chest computed tomography scan severity between the first and second pandemic waves. c^2 test; $P > 0.05$, ns. CRP, C-reactive protein; PCT, procalcitonin; SCr, serum creatinine.

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; $P = 0.921$).

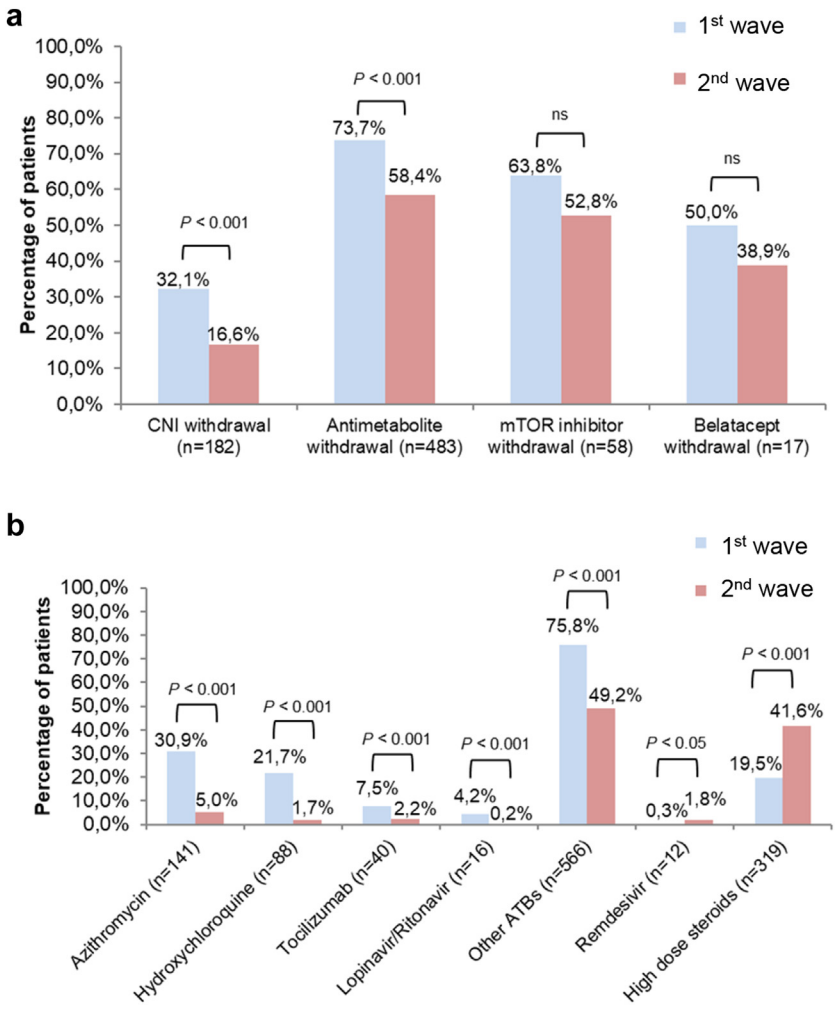

Figure 2. Changing of therapeutic trends between the first and second COVID-19 pandemic waves. Comparison of (a) the management of immunosuppression and (b) the use of COVID-19 specific treatments between the first (blue) versus second (red) pandemic waves. c^2 test; $P > 0.05$, ns. ATB, antibiotics; CNI, calcineurin inhibitor; mTor, mechanistic target of rapamycin.

Management of Immunosuppression and Antiviral Therapies

Maintenance immunosuppression was tapered in KTRs hospitalized for symptomatic COVID-19, particularly antimetabolites 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 antimetabolites (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

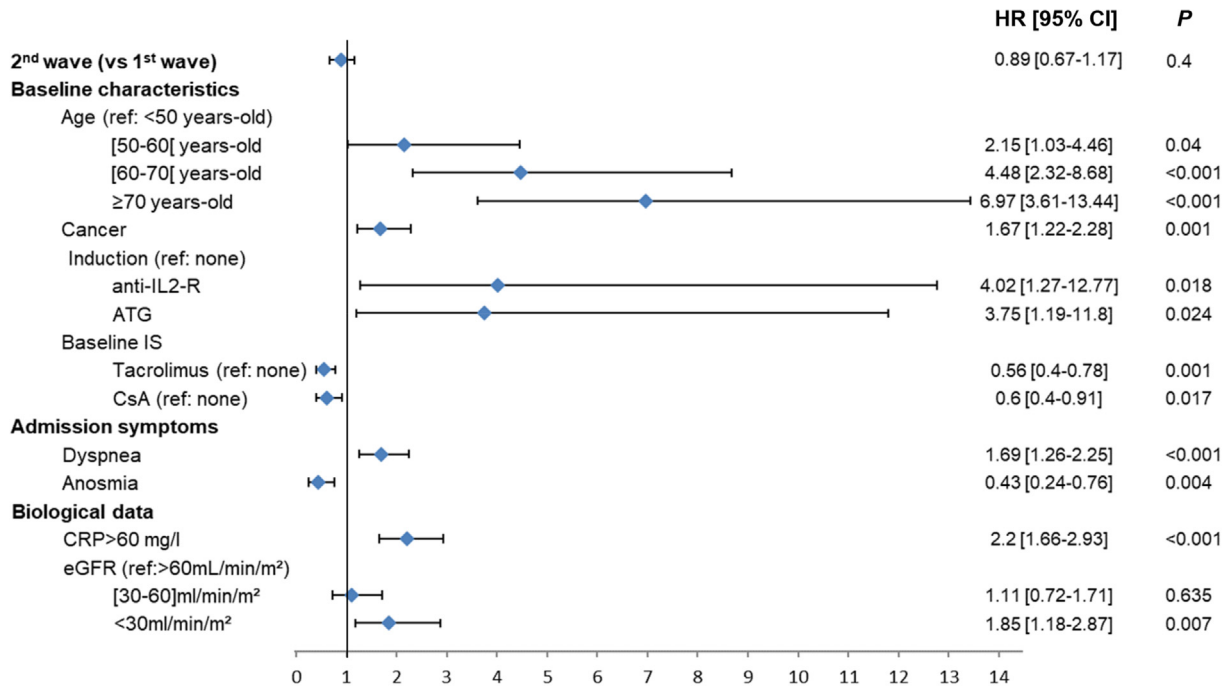

Figure 3. Variables associated with the risk of death due to COVID-19 in KTRs. This forest plot shows the variable independently associated with the risk of death in multivariate analysis for the 957 KTRs diagnosed with COVID-19 during the first or the second pandemic waves. ATG, antithymocyte globulin; CI, confidence interval; CRP, C-reactive protein; CsA, cyclosporin A; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

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 <30ml/min per 1.73 m^2 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,[31,32] 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

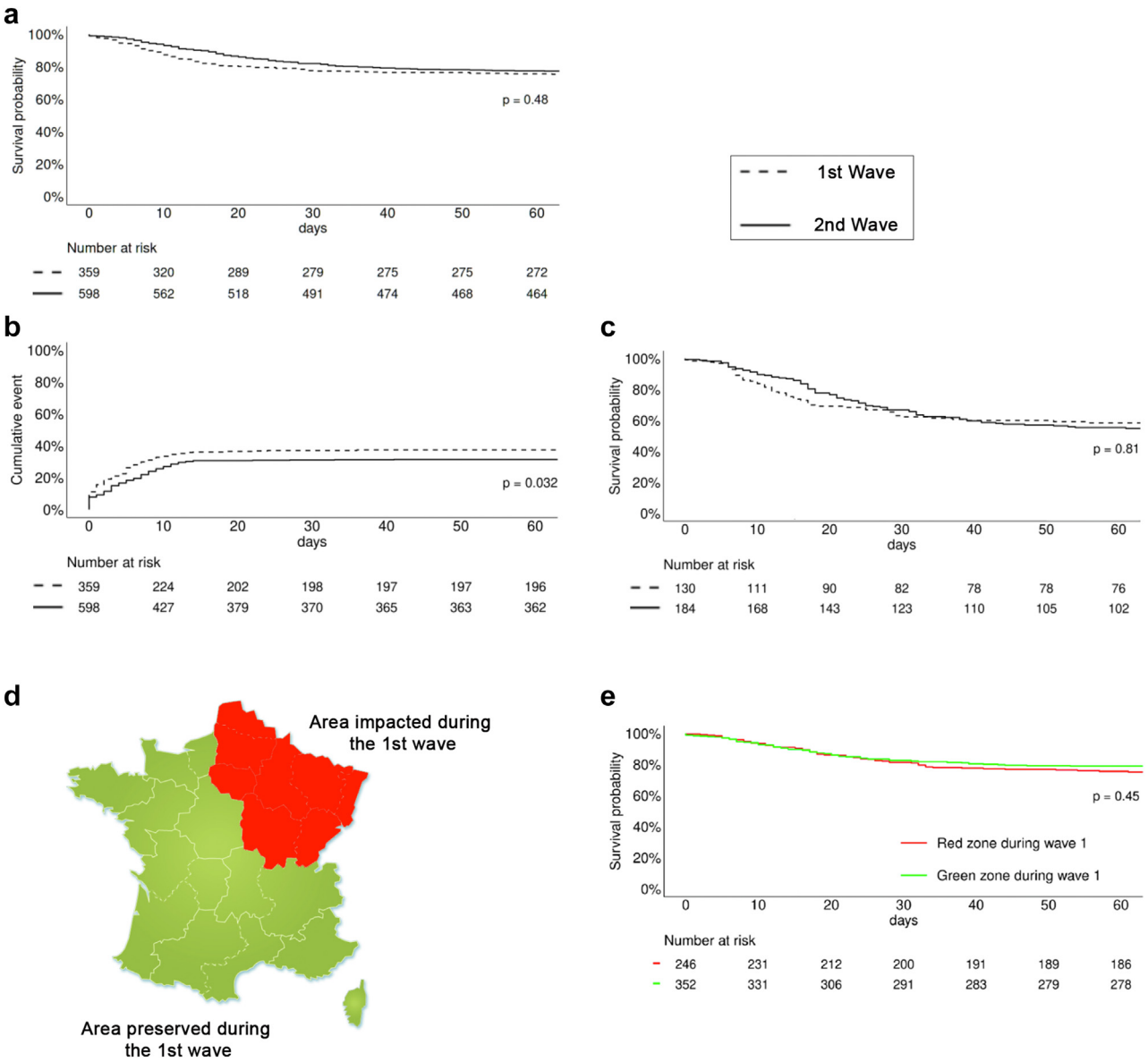

Figure 4. Comparison of COVID-19 outcomes between the first and second waves. (a) In-hospital survival of KTRS diagnosed with COVID-19 during the first and second wave. (b) Cumulative incidence of Intensive Care Unit admission of KTRS diagnosed with COVID-19 during the first and second wave. (c) Survival of KTRS diagnosed with COVID-19 transferred in ICU. (d) Map of the geographic distribution of the cases of COVID-19 in France during the first wave. Area in which the incidence of COVID-19 was the highest are in red. (e) In-hospital survival of KTRs diagnosed with COVID-19 during the second wave according to their geographic location (in the red or green area defined in panel d). Comparison were made using the Log Rank test.

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[33] 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.[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[33] and several large multicenter KTR cohorts estimated short-term intra-hospital mortality of about 20% to 32%.[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.[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.[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.[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,[42] hydroxychloroquine,[42,43] and lopinavir/ritonavir,[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.[45] On one hand, SOT recipients have been found to have delayed SARS-CoV-2 clearance[46,47] but on the other hand, these drugs could be protective against the overproduction of proinflammatory cytokines during critical COVID-19.[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.[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.[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.*[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.[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,[51-54] which leaves them at high risk of severe COVID-19.[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.[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[59] (post-exposition therapy) and first reports about their use for prophylaxis (preexposition therapy) are promising.[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 Hazzan, Service de Néphrologie, Hôpital Huriez, Lille; Dany Anglicheau, Service de Néphrologie et Transplantation Adultes, AP-HP, Hôpital Necker, Paris; Alexandre Hertig, Jérôme Tourret, Benoit Barrou, Service de Néphrologie, AP-HP, Hôpital La Pitié Salpétrière, 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, Maïté Jaureguy, Service de Néphrologie, CHU Amiens Picardie, Amiens; Luc Frimat, Service de Néphrologie, CHRU Nancy, Vandoeuvre; Didier Ducloux, 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 Mussot, 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 Blancho, 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 Chemouny, 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 Snanoudj, Service de Néphrologie, Hôpital Foch, Service de Néphrologie et Transplantation Hôpital du Kremlin Bicêtre, Le Kremlin Bicêtre; Charlotte Colosio, Betoul Schvartz, Service de Néphrologie, Hôpital Maison 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; Moglie Le Quintrec, 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'Hépatologie, Hôpital Foch, Suresnes; Sébastien Dharancy, Service d'Hépatologie, 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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