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An initial report from the French SOT COVID Registry suggests high mortality due to COVID-19 in recipients of kidney transplants

see commentary on page 1404

Sophie Caillard[1,2], Dany Anglicheau[3,4], Marie Matignon[5,6], Antoine Durrbach[5,6], Clarisse Greze[7], Luc Frimat[8,9], Olivier Thaunat[10,11], Tristan Legris[12], Valerie Moal[12], Pierre Francois Westeel[13], Nassim Kamar[14], Philippe Gatault[15], Renaud Snanoudj[16], Antoine Sicard[17,18], Dominique Bertrand[19], Charlotte Colosio[20], Lionel Couzi[21,22], Jonathan M. Chemouny[23], Christophe Masset[24], Gilles Blancho[24], Jamal Bamoulid[25], Agnes Duveau[26], Nicolas Bouvier[27], Nathalie Chavarot[3,4], Philippe Grimbert[5,6], Bruno Moulin[1,2], Yannick Le Meur[28,29] and Marc Hazzan[30]; on behalf of the French SOT COVID Registry[31]

[1]Department of Nephrology and Transplantation, Strasbourg University Hospital, Strasbourg, France; [2]INSERM, IRM UMR-S 1109, University of Strasbourg, Strasbourg, France; [3]Department of Nephrology and Transplantation, Necker University Hospital – APHP, Paris, France; [4]INEM INSERM U 1151- CNRS UMR 8253, Paris University, Paris, France; [5]Department of Nephrology and Renal Transplantation, Henri-Mondor/Albert-Chenevier Hospital, AP-HP, Créteil, France; [6]IFRNT, INSERM U 955, University of Paris-Est-Créteil, Créteil, France; [7]Department of Nephrology and Transplantation, Bichat hospital, Paris, France; [8]Department of Nephrology and Transplantation, CHRU-Nancy, Vandoeuvre, France; [9]INSERM CIC-EC CIE6, University of Lorraine, Nancy, France; [10]Department of Transplantation, Nephrology and Clinical Immunology, Edouard Herriot Hospital, Hospices civils de Lyon, Lyon, France; [11]CIRI, INSERM U1111, University Claude Bernard Lyon 1, Lyon, France; [12]Department of Nephrology and Transplantation, Marseille University Hospital, Conception hospital, Aix Marseille University, Marseille, France; [13]Department of Nephrology and Transplantation, University of Amiens, Amiens, France; [14]Department of Nephrology and Transplantation, University of Toulouse, Toulouse, France; [15]Department of Nephrology and Transplantation, University of Tours, Tours, France; [16]Department of Nephrology and Transplantation, Bicêtre Hospital, Le Kremlin-Bicêtre, France; [17]Department of Nephrology Dialysis and Transplantation, Pasteur 2 Hospital, Nice University Hospital, Nice, France; [18]Unité de Recherche Clinique Côte d'Azur (UR2CA), University of Côte d'Azur, Nice, France; [19]Department of Nephrology and Transplantation, University of Rouen, Rouen, France; [20]Department of Nephrology and Transplantation, University of Reims, Reims, France; [21]Department of Nephrology Dialysis, Transplantation and Apheresis, Bordeaux Pellegrin University Hospital, Bordeaux, France; [22]Research Unit ImmunoConcEpT CNRS 5164, University of Bordeaux, Bordeaux, France; [23]Inserm UMR_S 1085, EHESP, University of Rennes, Rennes, France; [24]Department of Nephrology and Transplantation, Nantes University Hospital, Nantes, France; [25]Department of Nephrology and Transplantation, University of Besançon, Besançon, France; [26]Department of Nephrology and Transplantation, University of Angers, Angers, France; [27]Department of Nephrology and Transplantation, University of Caen, Caen, France; [28]Department of Nephrology and Transplantation, Brest University Hospital, Brest, France; [29]Inserm UMR1227, University of Brest, Labex IGO, Brest, France; and [30]Department of Nephrology and Transplantation, University of Lille, Lille, France

Notwithstanding the ongoing coronavirus disease-2019 (Covid-19) pandemic, information on its clinical presentation and prognosis in recipients of a kidney transplant remain scanty. The aim of this registry-based observational study was to explore characteristics and clinical outcomes of recipients of kidney transplants included in the French nationwide Registry of Solid Organ Transplant Recipients with Covid-19. Covid-19 was diagnosed in symptomatic patients who had a positive PCR assay for SARS-CoV-2 or having typical lung lesions on imaging. Clinical and laboratory characteristics, management of immunosuppression, treatment for Covid-19, and clinical outcomes (hospitalization, admission to intensive care unit, mechanical ventilation, or death) were recorded. Risk factors for severe disease or death were determined. Of the 279 patients, 243 were admitted to hospital and 36 were managed at home. The median age of hospitalized patients was 61.6 years; most had comorbidities (hypertension, 90.1%; overweight, 63.8%; diabetes, 41.3%; cardiovascular disease, 36.2%). Fever, cough, dyspnea, and diarrhea were

Editor's Note

This is one of several articles we think you will find of interest that are part of our special issue of *Kidney International* addressing the challenges of dialysis and transplantation during the COVID-19 pandemic. Please also find additional material in our commentaries and letters to the editor sections. We hope these insights will help you in the daily care of your own patients.

Correspondence: *Sophie Caillard, Department of Nephrology and Transplantation, Strasbourg University Hospital, 1 Place de l'Hopital, 67091 Strasbourg, Cedex, France. E-mail: Sophie.caillard@chru-strasbourg.fr*

[31]Members of the French SOT COVID Registry are listed in the Appendix.

Received 22 May 2020; revised 4 August 2020; accepted 13 August 2020; published online 24 August 2020

the most common symptoms on admission. Laboratory findings revealed mild inflammation frequently accompanied by lymphopenia. Immunosuppressive drugs were generally withdrawn (calcineurin inhibitors: 28.7%; antimetabolites: 70.8%). Treatment was mainly based on hydroxychloroquine (24.7%), antiviral drugs (7.8%), and tocilizumab (5.3%). Severe Covid-19 occurred in 106 patients (46%). Forty-three hospitalized patients died (30-day mortality 22.8%). Multivariable analysis identified overweight, fever, and dyspnea as independent risk factors for severe disease, whereas age over 60 years, cardiovascular disease, and dyspnea were independently associated with mortality. Thus, Covid-19 in recipients of kidney transplants portends a high mortality rate. Proper management of immunosuppression and tailored treatment of this population remain challenging.

Kidney International (2020) **98,** 1549–1558; https://doi.org/10.1016/j.kint.2020.08.005

KEYWORDS: COVID-19; immunosuppression; kidney transplantation; mortality; prognosis

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has created an ongoing global pandemic of major concern. Frail patients with comorbidities are at high risk of developing severe disease, as shown by initial reports from China[1,2] and other countries.[3,4] Although preexisting kidney disease is a predisposing factor for COVID-19 morbidity and mortality,[5] information on its clinical presentation and prognosis in kidney transplant (KT) recipients under immunosuppressive therapy remains scant. Published data are limited to case reports[6–9] and small single-center case series.[10–21]

On March 1, 2020, a French nationwide registry of patients with COVID-19 and a history of solid organ transplantation was established under the auspices of the French-Speaking Society of Transplantation. As of April 21, 2020, a total of 598 patients were included in the registry—of whom 426 were KT recipients, 61 heart transplant recipients, 72 liver transplant recipients, and 39 lung transplant recipients. Here, we describe the disease presentation, immunosuppression management, clinical outcomes, and independent prognostic variables in a large sample of 279 KT recipients with COVID-19.

RESULTS

Patient characteristics

Of the 279 KT recipients included in the registry, COVID-19 was diagnosed by reverse transcriptase–polymerase chain reaction in 93% of cases. The diagnosis in the remaining 7% of the study participants was based on clinical presentation and pulmonary computed tomography findings (7%). A total of 243 patients were admitted to the hospital, and 36 were managed at home following assessment by a transplant physician (Table 1). In brief, the latter group consisted of younger patients with a lower frequency of dyspnea, fever, and gastrointestinal manifestations. One patient received home treatment with hydroxychloroquine. Antimetabolites and mammalian target of rapamycin (mTOR) inhibitors were stopped in 13 patients (36%). The general characteristics of hospitalized patients are summarized in Table 1. The median age was 61.6 years (interquartile range: 50.8−69.0 years; range: 19−93 years), and two-thirds were men. Most of them were overweight (63.8%), and the most common comorbidities were hypertension (90.1%), cardiovascular disease (36.2%), diabetes (41.3%), and a history of respiratory disease (14.8%). SARS-CoV-2 infection was identified after a median of 74.1 months (interquartile range: 27.6−138.7 months; range: 1−1943 months) from KT. The median delay between the onset of symptoms and hospital admission was 5 days (interquartile range: 3−8 days, range: 0−34 days). The most frequent symptom on admission was fever (80%), followed by cough (63.6%), diarrhea (43.5%), dyspnea (40.3%), and anosmia (14.1%). Median levels of C-reactive protein and procalcitonin were 62 mg/L and 0.20 ng/mL, respectively (Table 2). The median lymphocyte count was 0.66 $\times$ 10^9/L, whereas thrombocytopenia was identified in 54 (29%) patients. Lung infiltrates on chest computed tomography images were detected in 87% of cases.

Management of immunosuppression

On admission, calcineurin inhibitors (CNIs), antimetabolites, and steroids were being taken by 83.1%, 79.8%, and 72.8% of patients, respectively. Of note, 29 (12%) and 15 (6.2%) patients were on mammalian target of rapamycin inhibitors and belatacept, respectively. During hospitalization (Table 2), antimetabolites, CNIs, and mammalian target of rapamycin inhibitors were withdrawn in 70.8% (136 of 192), 28.7% (58 of 202), and 62.1% (18 of 29) of patients, respectively. Moreover, belatacept administration was postponed in 7 of the 15 participants taking this drug. Of note, changes in immunosuppressive drugs other than those withdrawn were not recorded.

Treatment and clinical course

Most patients received nasal oxygen therapy (72.4%) and antibiotics other than azithromycin (63%). Hydroxychloroquine and azithromycin were given to 60 (24.7%) and 71 (29.2%) patients, respectively (Table 2). CNIs were stopped in 7 of the 11 patients treated with lopinavir/ritonavir. Tocilizumab was administered to 13 (5.3%) cases. Bacterial coinfections were identified in 57 (23.5%) participants. Mechanical ventilation was required for approximately 30% of cases. Acute kidney injury occurred in 43.6% of patients, with renal replacement therapy being necessary in 11.1% of cases. A total of 88 patients (36%) required intensive

Table 1 | Baseline characteristics of kidney transplant recipients with COVID-19 managed at home versus in-hospital

Variable	Home management (n = 36)	In-hospital management (n = 243)	*P*	n
Baseline characteristics				
Age, yr	55.6 [48.0–61.1]	61.6 [50.8–69.0]	0.002	279
Male	20 (55.6)	162 (66.7)	0.263	279
BMI, kg/m^2	25.0 [23.4–28.9]	26.1 [23.0–30.7]	0.608	270
BMI >25 kg/m^2	18 (51.4)	150 (63.8)	0.221	270
Blood group			0.691	275
A	18 (50.0)	105 (43.9)		
AB	1 (2.8)	12 (5.0)		
B	6 (16.7)	29 (12.1)		
O	11 (30.6)	93 (38.9)		
Transplanted organ			0.525	279
Kidney	35 (97.2)	233 (95.9)		
Kidney–heart	0 (0.0)	4 (1.6)		
Kidney–liver	1 (2.8)	2 (0.8)		
Kidney–pancreas	0 (0.0)	4 (1.6)		
Time from Tx to COVID-19 [IQR], mo	58.9 [25.0–118.9]	74.1 [27.6–138.7]	0.626	279
Time from Tx to COVID, stratified, mo no. (%):			0.827	279
<6	3 (8.3)	20 (8.2)		
6–11	1 (2.8)	15 (6.2)		
12–59	14 (38.9)	73 (30.0)		
60–119	9 (25.0)	60 (24.7)		
≥120	9 (25.0)	75 (30.9)		
Hypertension	24 (82.8)	201 (90.1)	0.213	252
RAS blockers	15 (55.6)	97 (44.5)	0.377	245
Cardiovascular disease	6 (20.0)	81 (36.2)	0.122	254
Respiratory disease	5 (16.7)	33 (14.8)	0.786	253
Diabetes	12 (40.0)	92 (41.3)	1.000	253
Cancer	4 (13.3)	35 (15.5)	1.000	256
Smoking	3 (13.0)	30 (15.5)	1.000	217
Baseline immunosuppression				
CNIs	28 (77.8)	202 (83.1)	0.581	279
Mycophenolate acid	29 (80.6)	183 (75.3)	0.632	279
Azathioprine	1 (2.8)	11 (4.5)	1.000	279
mTOR inhibitors	5 (13.9)	29 (11.9)	0.784	279
Steroids	25 (69.4)	177 (72.8)	0.822	279
Belatacept	1 (2.8)	15 (6.2)	0.703	279
Clinical presentation				
Cough	20 (55.6)	145 (63.6)	0.459	264
Rhinitis	6 (16.7)	20 (9.3)	0.231	251
Dyspnea	2 (5.6)	98 (40.3)	<0.001	279
Anosmia	10 (29.4)	29 (14.1)	0.046	240
Fever	15 (41.7)	180 (80.0)	<0.001	261
Headache	11 (30.6)	39 (17.5)	0.106	259
Diarrhea	9 (25.0)	97 (43.5)	0.056	259

BMI, body mass index; CNI, calcineurin inhibitor; COVID-19, coronavirus disease 2019; mTOR, mammalian target of rapamycin; RAS, renin–angiotensin system; Ref, reference; Tx, transplantation.
Data are expressed as median [interquartile range] or count (%), as appropriate, unless otherwise indicated.

care unit (ICU) care either on admission (n = 25) or during hospitalization (n = 63). In the latter subgroup, the median interval between hospitalization and transfer to the ICU was 4 days (range: 1−25 days). The 30-day mortality rate of hospitalized patients was 22.8% (Figure 1). Nine patients lost their graft during hospitalization, 4 of whom died. The composite endpoint of severe COVID-19 within 30 days of hospital admission was reached by 46% of the study patients (Figure 2a).

Risk factors for severe COVID-19

Table 3 compares the general characteristics of hospitalized patients who developed severe COVID-19 (n = 109) versus those who did not (n = 137). Patients aged >60 years who were overweight or had diabetes were significantly overrepresented in the former group. Fever and dyspnea on admission—but not cough—were associated with severe disease. However, the time elapsed between symptom onset and hospitalization was similar in the 2 groups (5 days). C-reactive protein levels >60 mg/L, procalcitonin concentrations >0.2 g/L, and a partial pressure of oxygen <95% on admission were significantly associated with severe COVID-19. No similar associations were observed with lymphocyte count, platelet count, or creatinine levels. Treatment modalities and management of immunosuppression (Table 4) were slightly different in the 2 study groups in relation to disease

Table 2 | Laboratory data, management of immunosuppression, treatment modalities, and outcomes of kidney transplant recipients hospitalized with COVID-19

Variable	Value	n
Laboratory data		
CRP, mg/l	62 [27–114]	186
Procalcitonin, ng/ml	0.20 [0.14–0.48]	90
Lymphocyte count, $\times 10^9$/l	0.66 [0.40–0.96]	184
Platelet count, $\times 10^9$/l	178 [145–238]	188
Thrombocytopenia $<150 \times 10^9$/l	54 (29)	188
SaO_2	96 (91–98)	176
Creatinine, μmol/l	176 [131–244]	200
Immunusuppression management		
CNI withdrawal	58 (28.7)	202
Antimetabolite withdrawal	136 (70.8)	192
mTOR inhibitor withdrawal	18 (62.1)	29
Belatacept withdrawal	7 (46.7)	15
COVID-19 treatment modalities		
Azithromycin	71 (29.2)	243
Other antibiotics	153 (63.0)	243
Antifungal drugs	6 (2.5)	243
Remdesivir	2 (0.8)	243
Lopinavir/ritonavir	11 (4.5)	243
Oseltamivir	6 (2.5)	243
Hydroxychloroquine	60 (24.7)	243
Tocilizumab	13 (5.3)	243
Outcome		
Bacterial coinfection	57 (23.5)	243
Viral coinfection	5 (2.1)	243
Fungal coinfection	6 (2.5)	243
Oxygen therapy	152 (72.4)	210
Mechanical ventilation	72 (29.6)	243
Vasopressor support	27 (11.1)	243
Acute kidney injury	106 (43.6)	243
Renal replacement therapy	27 (11.1)	243

CNI, calcineurin inhibitors; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; mTOR, mammalian target of rapamycin; SaO_2, arterial oxygen saturation. Data are expressed as median [interquartile range] or count (%), as appropriate, unless otherwise indicated. Laboratory tests were performed on admission.

presentation and the clinical evolution over time. These differences were especially evident with respect to CNI withdrawal (52% and 11% in patients with severe and nonsevere disease, respectively, $P < 0.001$). Kaplan–Meier plots of severe COVID-19–free survival according to different risk factors are provided in Figure 2b–i. Multivariable analysis identified overweight, fever, and dyspnea as independent risk factors for severe disease (Figure 3a).

Risk factors for mortality

Table 5 compares the general characteristics of hospitalized patients who died (n = 43) versus those who did not (n = 200). Patients aged >60 years, who had cardiovascular disease, were receiving immunosuppressive drugs different from CNIs, and who presented with dyspnea or a partial pressure of oxygen <95% on admission, were significantly overrepresented in the former group. Multivariable analysis identified age >60 years, cardiovascular disease, and dyspnea as independent risk factors for death in hospitalized patients (Figure 3b).

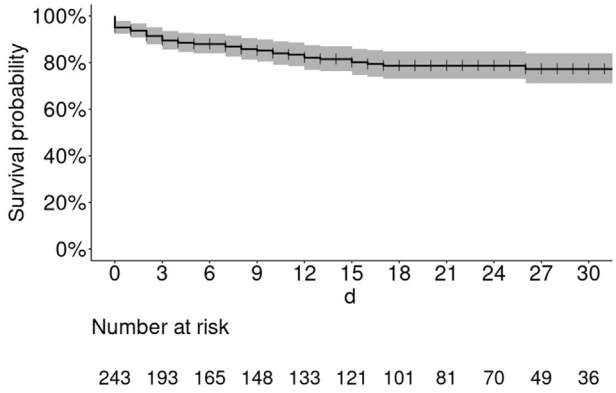

Figure 1 | Kaplan–Meier plot of survival in kidney transplant recipients who were hospitalized with coronavirus 2019. The 30-day mortality rate after admission was 22.8% (16.1%–28.9%).

Subgroup analyses conducted in patients who tested negative on reverse transcriptase-polymerase chain reaction (7%) yielded similar results both in terms of severe disease and mortality (data not shown). The median follow-up time was 22 days; a total of 66 patients were still in the ICU at the time the manuscript was written.

DISCUSSION

Despite the growing literature focusing on the clinical manifestations and prognosis of COVID-19, data on certain selected clinical populations that merit special consideration—including immunocompromised patients with a history of solid organ transplantation—remain scant. To address this knowledge gap, herein we report the general characteristics and the main risk factors for adverse outcomes—including severe disease and mortality—of a large nationwide French cohort consisting of 279 KT recipients with COVID-19.

First, we demonstrate that the clinical presentation of COVID-19 in KT recipients is similar to that reported in the general population—with fever and cough being the 2 more common symptoms. These findings are in line with those from initial large reports showing fever in 77%−94% and cough in 68%−79% of cases, respectively.[1–3] However, the occurrence of gastrointestinal symptoms (mainly diarrhea) was as high as 42% in our patients (i.e., significantly more frequent than that previously reported in general population studies conducted in both China [3%−5%][1,2] and the United States [24%]).[3] Patients with a history of solid organ transplantation are at high risk of gastrointestinal disorders—which may be exacerbated by immunosuppressive drugs. Importantly, anosmia was present in 14% of our patients, and in accordance with previous findings obtained in the general population,[22] tended to be associated with more favorable survival figures. We also demonstrate that some immunocompromised patients with COVID-19 were manageable at home with a favorable outcome, as described in an Italian cohort from Brescia.[23] This decision was made on a case basis and was chiefly implemented for young patients without

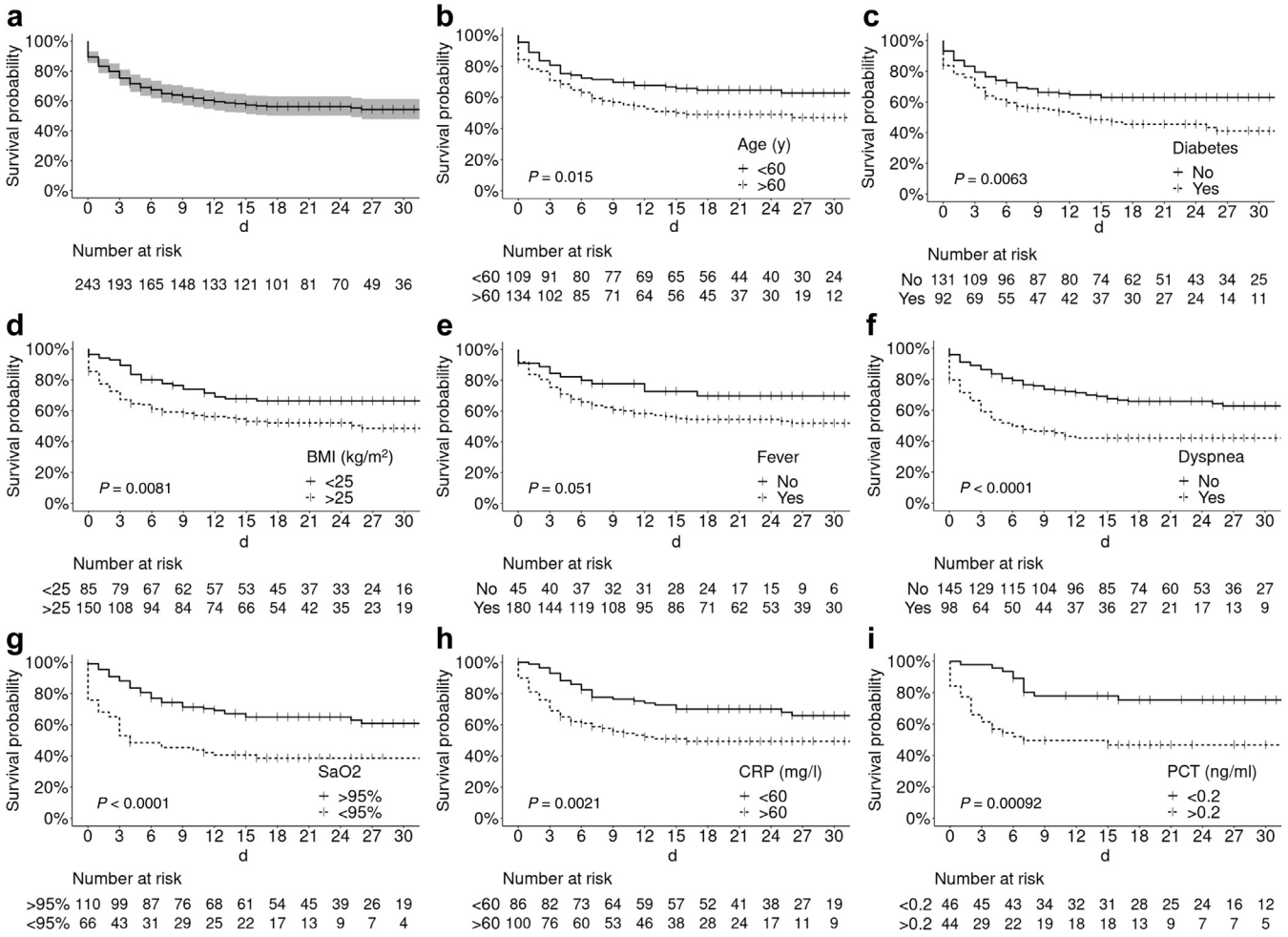

Figure 2 | Probability of reaching the composite endpoint of severe disease. (**a**) The 30-day severe disease–free survival in the entire study cohort was 54.2% (48%–61.4%). Kaplan–Meier plots stratified according to (**b**) age (<60 years vs. >60 years), (**c**) diabetes (yes vs. no), (**d**) body mass index (BMI; <25 kg/m^2 vs. >25 kg/m^2), (**e**) fever on admission (yes vs. no), (**f**) dyspnea on admission (yes vs. no), (**g**) arterial oxygen saturation (SaO_2) on admission (>95% vs. <95%), (**h**) C-reactive protein (CRP) level on admission (<60 mg/l vs. >60 mg/l), and (**i**) procalcitonin level on admission (<0.2 ng/ml vs. >0.2 ng/ml). PCT, procalcitonin.

dyspnea and high fever. This patient subgroup was offered daily teleconsultation surveillance until disease resolution, a strategy that has been successfully implemented in a recent report from the United States.[21] The laboratory findings of our patients on admission are also in line with previous studies. In general, there was evidence of mild inflammation—with lymphopenia being present in most patients, and thrombocytopenia in approximately one third. Notably, high procalcitonin levels were identified in 16% of our study participants—a markedly lower prevalence compared with that previously reported in KT recipients (42%).[13]

The initially reported mortality rate for COVID-19 in the general population of Wuhan, China, was 1.4%.[1] Higher mortality figures have been published for hospitalized patients in New York (10%),[3] and for Italian patients admitted to the ICU (26%).[4] Previous data obtained in small-sized series of transplanted patients indicated a death rate similar to that observed in our cohort.[24] Here, the 30-day mortality rate of our hospitalized KT recipients with COVID-19 was 22.8%, a value similar to that reported for Italian patients admitted to the ICU.[4] The high mortality rate observed in these patients may reflect the frailty of KT recipients and/or a high burden of comorbidities. Mechanical ventilation and ICU transfer were required in 36% of our patients—a slightly higher percentage than that reported for immunocompetent subjects (16%−33%).[2,3]

Male sex has been previously linked to severe COVID-19.[25] However, no significant association between male sex and severe disease or mortality was observed in our cohort—possibly because of the high burden of comorbidities. Conversely, overweight, fever, and dyspnea were independent risk factors for severe disease in our cohort. The association between overweight/obesity and severe COVID-19—which has been shown here for the first time in transplant recipients—is in accordance with previous data obtained in the general population.[3] In our study, age, cardiovascular disease, and dyspnea were independent risk factors for mortality. Age[2,25] and comorbidities have been reported to have an

Table 3 | Baseline characteristics of kidney transplant recipients with severe versus nonsevere COVID-19

Characteristics	Nonsevere (n =137)	Severe (n = 106)	HR [95% CI]	*P*	n
Baseline					
Age, yr	59.5 [48.7–67.8]	63.5 [54.7–69.6]	1.02 [1.00–1.04]	0.013	243
Age >60 yr	67 (48.9)	67 (63.2)	1.63 [1.10–2.43]	0.015	243
Male	90 (65.7)	72 (67.9)	1.07 [0.71–1.61]	0.740	243
BMI > 25 kg/m^2	78 (57.8)	72 (72.0)	1.80 [1.16–2.79]	0.008	235
Blood group					239
A	65 (48.5)	40 (38.1)	Ref	Ref	
AB	6 (4.48)	6 (5.71)	1.52 [0.64–3.59]	0.340	
B	16 (11.9)	13 (12.4)	1.27 [0.68–2.38]	0.449	
O	47 (35.1)	46 (43.8)	1.32 [0.86–2.02]	0.198	
Transplanted organ					243
Kidney	129 (94.2)	104 (98.1)	Ref	Ref	
Kidney–heart	2 (1.46)	2 (1.89)	1.36 [0.34–5.51]	0.668	
Kidney–liver	2 (1.46)	0 (0.00)	0.00 [–]	0.997	
Kidney–pancreas	4 (2.92)	0 (0.00)	0.00 [–]	0.996	
Time from Tx to COVID-19, mo	73.4 [30.9–151]	77.8 [25.4–131]	1.00 [1.00–1.00]	0.660	243
Tx within 1 yr	19 (13.9)	16 (15.1)	0.97 [0.57–1.65]	0.912	243
Hypertension	112 (89.6)	89 (90.8)	1.14 [0.57–2.25]	0.717	223
RAS blockers	58 (47.2)	39 (41.1)	0.83 [0.55–1.25]	0.377	218
Cardiovascular disease	41 (32.5)	40 (40.8)	1.32 [0.88–1.98]	0.176	224
Respiratory disease	19 (15.2)	14 (14.3)	0.96 [0.54–1.69]	0.885	223
Diabetes	42 (33.6)	50 (51.0)	1.73 [1.16–2.57]	0.007	223
Cancer	17 (13.4)	18 (18.2)	1.33 [0.80–2.21]	0.276	226
Smoking	16 (14.8)	14 (16.3)	0.99 [0.56–1.76]	0.977	194
CNIs	115 (83.9)	87 (82.1)	0.96 [0.58–1.58]	0.868	243
Mycophenolate acid	102 (74.5)	81 (76.4)	1.08 [0.69–1.69]	0.743	243
Azathioprine	5 (3.65)	6 (5.66)	1.32 [0.58–3.01]	0.509	243
mTOR inhibitors	15 (10.9)	14 (13.2)	1.08 [0.62–1.90]	0.785	243
Steroids	96 (70.1)	81 (76.4)	1.24 [0.79–1.94]	0.347	243
Belatacept	8 (5.84)	7 (6.60)	1.08 [0.50–2.33]	0.844	243
On admission					
Cough	81 (62.3)	64 (65.3)	1.20 [0.79–1.82]	0.390	228
Rhinitis	12 (9.76)	8 (8.70)	0.82 [0.40–1.69]	0.592	215
Dyspnea	42 (30.7)	56 (52.8)	2.28 [1.55–3.34]	<0.001	243
Anosmia	19 (16.1)	10 (11.4)	0.71 [0.37–1.38]	0.315	206
Fever	98 (75.4)	82 (86.3)	1.77 [0.99–3.19]	0.055	225
Headache	25 (19.5)	14 (14.7)	0.75 [0.43–1.32]	0.322	223
Diarrhea	59 (46.1)	38 (40.0)	0.86 [0.57–1.30]	0.486	223
Time from symptom onset to admission, d	5.00 [3.00–9.00]	5.00 [3.00–7.00]	1.00 [0.96–1.04]	0.873	219
C-reactive protein >60 mg/l	51 (46.4)	49 (64.5)	2.07 [1.29–3.31]	0.003	186
Procalcitonin > 0.2 ng/ml	21 (37.5)	23 (67.6)	3.19 [1.55–6.57]	0.002	90
Lymphocyte count, $\times 10^9$/l	0.70 [0.40–0.95]	0.60 [0.40–0.96]	1.10 [0.74–1.64]	0.627	184
Platelet count, $\times 10^9$/l	178 [146–229]	178 [145–247]	1.00 [1.00–1.00]	0.742	188
Thrombocytopenia < 150 × 10^9/l	31 (28.7)	23 (28.7)	0.98 [0.60–1.58]	0.923	188
SaO_2 < 95%	26 (26.8)	40 (50.6)	2.47 [1.59–3.84]	<0.001	176
Creatinine, µmol/l	173 [126–230]	182 [132–251]	1.00 [1.00–1.00]	0.378	200

BMI, body mass index; CNI, calcineurin inhibitor; COVID-19, coronavirus disease 2019; HR, hazard ratio; mTOR, mammalian target of rapamycin; RAS, renin–angiotensin system; Ref, reference; Tx, transplantation.
Data are expressed as median [interquartile range] or count (%), as appropriate, unless otherwise indicated.

adverse prognostic significance in previous general population studies. The lack of prognostic significance of hypertension in our sample may be explained by its high prevalence (90%). In accordance with previous studies,[2,3] severe inflammation on admission was found to have an adverse prognostic significance. Procalcitonin and C-reactive protein levels were higher in patients in the United States requiring mechanical ventilation,[3] whereas procalcitonin levels were an unfavorable predictor of mortality in Chinese patients.[2] However, in contrast to previous studies,[2,26] lymphopenia did not predict severe COVID-19 or mortality in our sample. A potential explanation may lie in the fact that lymphopenia occurs commonly in KT patients and thus might not be invariably linked to SARS-CoV-2 infection.

The debate on the management of immunosuppression in transplant recipients following SARS-CoV-2 infection remains unresolved.[27] Published case reports and small-size series of KT recipients diagnosed with COVID-19 have consistently documented a reduction in maintenance immunosuppression,[6–14] and this approach is currently being recommended by guidelines.[28] However, precise guidance on the management of CNIs, antimetabolites, and steroids is still

Table 4 | Treatment modalities and immunosuppression management in kidney transplant recipients hospitalized for COVID-19 according to the presence of severe versus non-severe disease

Therapy	Nonsevere n = 137	Severe n = 106	*P*	n
COVID-19 treatment				
Azithromycin	38 (27.7)	33 (31.1)	0.790	243
Other antibiotics	81 (59.1)	72 (67.9)	0.190	243
Antifungal drugs	1 (0.7)	5 (4.7)	0.060	243
Remdesivir	0 (0.0)	2 (1.9)	0.035	243
Lopinavir/ritonavir	2 (1.5)	9 (8.5)	0.002	243
Oseltamivir	3 (2.2)	3 (2.8)	0.708	243
Hydoxychloroquine	28 (20.4)	32 (30.2)	0.168	243
Tocilizumab	4 (2.9)	9 (8.5)	0.077	243
Immunosuppression management				
CNI withdrawal	13 (11.3)	45 (51.7)	<0.001	202
Antimetabolite withdrawal	73 (68.2)	63 (74.1)	0.376	192
mTOR inhibitor withdrawal	8 (53.3)	10 (71.4)	0.187	29
Belatacept withdrawal	4 (50.0)	3 (42.9)	0.549	15

COVID-19, coronavirus disease 2019; CNI, calcineurin inhibitor; mTOR, mammalian target of rapamycin.
Values are n (%), unless otherwise indicated.

lacking. In our registry, CNIs and antimetabolites were withdrawn in 28.7% and 70.8% of the study patients, respectively. Similar figures have been reported in United States case series.[11,13] These management strategies have been chiefly informed by alterations in T-cell responses induced by SARS-CoV-2. Although CNIs may exert an inhibitory effect against the replication of coronaviruses in vitro,[29,30] whether or not this effect can have clinical implications is arguable. In our study, patients who were free from CNIs on admission had a lower risk of mortality in univariable but not multivariable analysis (probably because of their older age; data not shown). No firm conclusions can therefore be drawn on the potential beneficial or detrimental effects of CNIs in KT recipients with COVID-19.

A minority of our patients received specific antiviral drugs. The lopinavir/ritonavir combination has strong pharmacological interactions with CNIs and mammalian target of rapamycin inhibitors, which have been related to the onset of acute renal failure in solid organ transplant recipients.[9,10,12] Only 25% of our patients received hydroxychloroquine. The lower usage of this drug compared with the usage level in other cohorts[10,13] may be explained by low-quality evidence on its effectiveness[31,32] and the potential risk of severe adverse events in KT recipients. The potential benefits of interleukin-6 inhibition merit comment. A hyperinflammatory state characterized by the release of massive amounts of cytokines (cytokine storm) has been reported in patients with severe or catastrophic forms of COVID-19.[33] Because interleukin-6 plays a central role in the cytokine storm, interleukin-6–targeting therapies have been proposed to tackle its occurrence.[34,35] Trials of tocilizumab have been already attempted in nontransplanted[36] and transplanted patients,[10–13] and this drug was given to 13 patients included in our registry. Of them, 11 had favorable outcomes despite severe COVID-19. Although no firm conclusions can be drawn because of the retrospective, nonrandomized nature of our study, our results are in line with those by Alberici *et al.*[10] who demonstrated a 50% reduction in the oxygen therapy requirement and a significant improvement in imaging features of pulmonary lesions upon tocilizumab administration.

Our findings need to be interpreted in the context of several limitations. First, we acknowledge that some baseline clinical, laboratory, and imaging data were missing. Similarly, information on the exact management of immunosuppression (i.e., dose reduction) and changes in laboratory parameters over time is lacking. Second, we

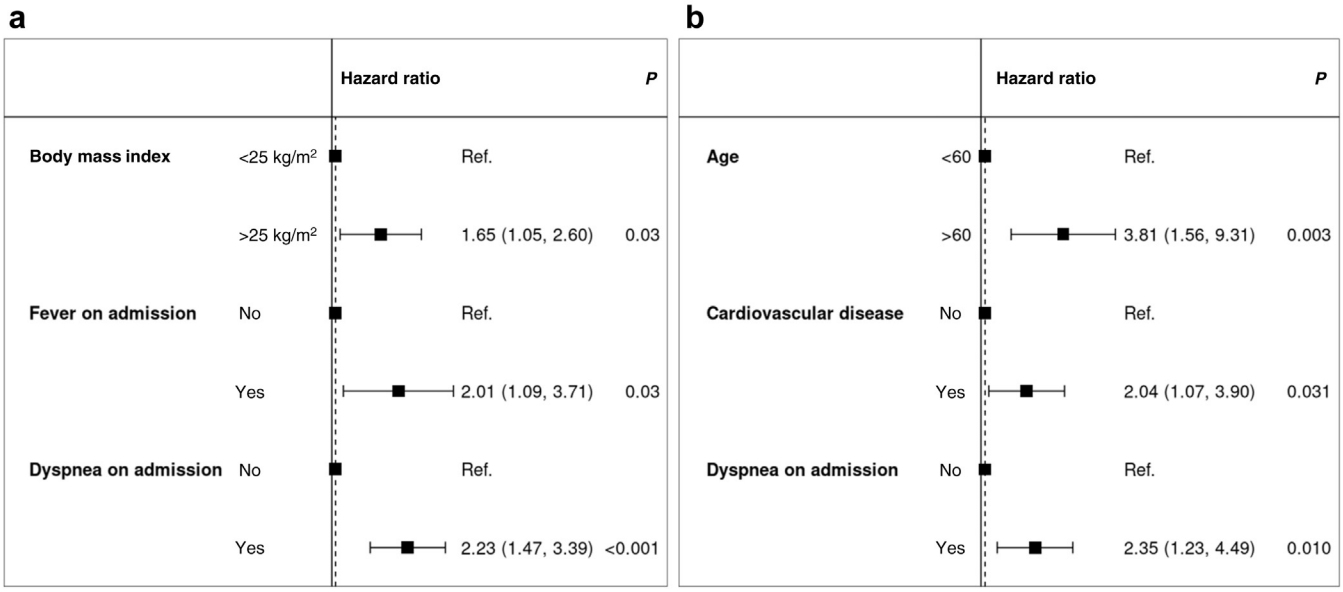

Figure 3 | Multivariable analysis of risk factors for (a) severe disease (intensive care unit admission/need for mechanical ventilation/mortality) and (b) mortality. Concordance for the severe disease model: 0.66; concordance for the mortality model: 0.76. Ref., reference.

Table 5 | Baseline characteristics of kidney transplant recipients with COVID-19 who died versus those who did not

Characteristics	Alive (n = 200)	Dead (n = 43)	HR [95% CI]	*P*	n
Baseline					
Age, yr	59.8 [49.8–67.5]	68.9 [61.7–75.1]	1.07 [1.04–1.10]	<0.001	243
Age >60 yr	99 (49.5)	35 (81.4)	3.98 [1.85–8.59]	<0.001	243
Male	137 (68.5)	25 (58.1)	0.68 [0.37–1.25]	0.215	243
BMI >25 kg/m^2	122 (61.9)	28 (73.7)	1.65 [0.80–3.39]	0.177	235
Blood group					239
A	89 (45.2)	16 (38.1)	Ref.	Ref.	
AB	11 (5.58)	1 (2.38)	0.58 [0.08–4.40]	0.601	
B	23 (11.7)	6 (14.3)	1.36 [0.53–3.48]	0.521	
O	74 (37.6)	19 (45.2)	1.42 [0.73–2.77]	0.299	
Transplanted organ					243
Kidney	190 (95.0)	43 (100)	Ref.	Ref.	
Kidney–heart	4 (2.00)	0 (0.00)	0.00 [0.00]	0.997	
Kidney–liver	2 (1.00)	0 (0.00)	0.00 [0.00]	0.998	
Kidney–pancreas	4 (2.00)	0 (0.00)	0.00 [0.00]	0.997	
Time from Tx to COVID-19, mo	72.5 [27.7–147]	83.7 [25.7–116]	1.00 [1.00–1.00]	0.933	243
Tx within 1 yr	29 (14.5)	6 (14.0)	0.95 [0.40–2.26]	0.914	243
Hypertension	165 (89.7)	36 (92.3)	1.39 [0.43–4.53]	0.580	223
RAS blockers	80 (44.4)	17 (44.7)	1.07 [0.56–2.03]	0.836	218
Cardiovascular disease	59 (31.9)	22 (56.4)	2.74 [1.45–5.17]	0.002	224
Respiratory disease	28 (15.2)	5 (12.8)	0.77 [0.30–1.96]	0.577	223
Diabetes	69 (37.5)	23 (59.0)	2.27 [1.20–4.29]	0.012	223
Cancer	28 (15.0)	7 (17.9)	1.17 [0.52–2.65]	0.708	226
Smoking	25 (15.5)	5 (15.2)	0.97 [0.38–2.52]	0.953	194
CNIs	172 (86.0)	30 (69.8)	0.46 [0.24–0.88]	0.019	243
Mycophenolate acid	152 (76.0)	31 (72.1)	0.83 [0.43–1.62]	0.586	243
Azathioprine	8 (4.00)	3 (6.98)	1.41 [0.43–4.55]	0.569	243
mTOR inhibitors	22 (11.0)	7 (16.3)	1.38 [0.61–3.10]	0.439	243
Steroids	147 (73.5)	30 (69.8)	0.81 [0.42–1.56]	0.533	243
Belatacept	12 (6.00)	3 (6.98)	1.15 [0.36–3.71]	0.817	243
On admission					
Cough	123 (64.4)	22 (59.5)	0.81 [0.42–1.56]	0.521	228
Rhinitis	16 (8.89)	4 (11.4)	1.24 [0.44–3.51]	0.687	215
Dyspnea	74 (37.0)	24 (55.8)	1.99 [1.09–3.63]	0.025	243
Anosmia	28 (16.0)	1 (3.23)	0.20 [0.03–1.45]	0.110	206
Fever	151 (79.9)	29 (80.6)	1.05 [0.46–2.41]	0.901	225
Headache	35 (18.6)	4 (11.4)	0.59 [0.21–1.68]	0.323	223
Diarrhea	84 (44.7)	13 (37.1)	0.75 [0.38–1.48]	0.401	223
Time from symptom onset to admission, d	6.00 [3.00–9.00]	4.00 [2.75–6.00]	0.94 [0.88–1.02]	0.138	219
CRP >60 mg/l	82 (51.9)	18 (64.3)	1.69 [0.78–3.66]	0.185	186
Procalcitonin > 0.2 ng/ml	34 (44.7)	10 (71.4)	2.79 [0.87–8.89]	0.083	90
Lymphocyte count, $\times 10^9$/l	0.70 [0.40–0.97]	0.60 [0.44–0.96]	0.80 [0.38–1.65]	0.538	184
Platelet count, $\times 10^9$/l	178 [144–232]	178 [155–257]	1.00 [1.00–1.00]	0.894	188
Thrombocytopenia <150 $\times 10^9$/L	48 (30.8)	6 (18.8)	0.54 [0.22–1.32]	0.176	188
SaO_2 <95%	47 (32.2)	19 (63.3)	3.39 [1.61–7.14]	0.001	176
Creatinine level, μmol/l	176 [131–249]	184 [131–230]	1.00 [1.00–1.00]	0.864	200

BMI, body mass index; CI, confidence interval; CNI, calcineurin inhibitor; COVID-19, coronavirus 2019; CRP, C-reactive protein; HR, hazard ratio; IQR, interquartile range; mTOR, mammalian target of rapamycin; RAS, renin-angiotensin system; Ref, reference; SaO_2, arterial oxygen saturation; Tx, transplantation.
Data are expressed as median [interquartile range] or count (%), as appropriate, unless otherwise indicated.

are aware that the follow-up time is limited, and 88 patients were still being hospitalized at the time of analysis. We cannot exclude the possibility that some of these cases will ultimately develop severe disease and eventually die. We also acknowledge that some patients with severe disease did not qualify for admission to the intensive care unit. Third, we are aware that representativeness can affect the generalizability of our registry data and that our findings need external validation. However, efforts to address potential sources of bias in our registry included the prospective data collection and the controlling for potential confounders in multivariable analysis. Notwithstanding the potential caveats, this study is by far the largest so far to provide a comprehensive description of KT recipients with COVID-19.

Conclusion

COVID-19 in KT recipients portends a high risk of mortality. Proper management of immunosuppression and tailored treatment of this fragile population remain challenging. Overweight, fever, and dyspnea were independent risk factors for severe COVID-19 in this patient group, whereas age >60 years, cardiovascular disease, and dyspnea were independently associated with mortality.

PATIENTS AND METHODS

Patients

Data from all French patients with COVID-19 and a history of KT included in a nationwide registry—termed French Solid Organ Transplant (SOT) COVID—between March 4 and April 21, 2020, were retrieved. Inclusion criteria were age >18 years at the diagnosis of COVID-19 and presence of a functioning kidney graft. Patients who received double solid organ transplantation (kidney with pancreas, liver, or heart transplantation) were deemed eligible. The diagnostic criteria for COVID-19 were as follows: (i) evidence of SARS-CoV-2 infection on reverse transcriptase–polymerase chain reaction testing performed on nasopharyngeal swab specimens; or (ii) presence of typical respiratory symptoms accompanied by evocative pulmonary lesions on low-dose chest computed tomography even when reverse transcriptase–polymerase chain reaction yielded negative results. Clinical and laboratory variables were extracted from medical records. In case of hospitalization, data on presentation and other clinical and biological variables (including ongoing immunosuppressive therapy) were collected on admission. Changes in immunosuppression during the course of hospitalization were thoroughly recorded. Patients were divided into 2 groups according to their need for hospitalization (admitted to hospital vs. managed at home). 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 nonsevere cases. Acute kidney injury was defined according to the Kidney Disease Improving Global Outcomes guidelines as an increase in serum creatinine of >50%. The creation of the French SOT COVID Registry was approved by the Institutional Review Board of Strasbourg University (approval number 02.26) and registered at clinicaltrials.gov (NCT04360707). The need for informed consent was waived. However, all patients were informed about their inclusion in the registry.

Statistical analysis

Categorical data are presented as counts and percentages. Continuous variables are expressed as medians and interquartile ranges upon verification of their skewed distribution with the Shapiro-Wilk test. Two time-dependent variables served as the outcome measures. The first was a composite endpoint of severe COVID-19 (including admission/transfer to an ICU, need for mechanical ventilation, or death), whereas the second was a hard endpoint consisting of death only. Survival curves were plotted with the Kaplan-Meier method and compared with the log-rank test. Cox proportional hazard univariable and multivariable models were constructed to identify predictors of the study endpoints. All variables showing an association with a $P < 0.1$ in univariable analysis were included as covariates in the multivariable model using a backward conditional selection procedure. The optimal model was selected according to the highest concordance value. 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), and 2-tailed P values <0.05 were considered statistically significant.

APPENDIX

French SOT COVID Registry

Sophie Caillard and 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, and Benoit Barrou, Service de Néphrologie, AP-HP, Hôpital La Pitié Salpétrière, Paris; Emmanuel Morelon and Olivier Thaunat, Service de Néphrologie, Hôpital Edouard Herriot, Lyon; Lionel Couzi and Pierre Merville, Service de Néphrologie–Transplantation–Dialyse, Hôpital Pellegrin, Bordeaux; Valérie Moal and Tristan Legris, Service de Néphrologie et Transplantation, AP-HM, Hôpital de la Conception, Marseille; Pierre-François Westeel and Maïté Jaureguy, Service de Néphrologie, CHU Amiens Picardie, Amiens; Luc Frimat, Service de Néphrologie, CHRU Nancy, Vandoeuvre; Didier Ducloux and Jamal Bamoulid, Service de Néphrologie, Hôpital Jean-Minjoz, Besancon; Dominique Bertrand, Service de Néphrologie, CHU de Rouen, Rouen; Michel Tsimaratos and Florentine Garaix-Gilardo, Service de Pédiatrie Multidisciplinaire, Hôpital La Timone, Marseille; Jérôme Dumortier, Service d'Hépato-Gastroentérologie, Hôpital Edouard Herriot, Lyon; Sacha Mussot and 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 and Christophe Masset, Service de Néphrologie–Transplantation, Hôtel Dieu, Nantes; Nassim Kamar, Service de Néphrologie et Transplantation, Hôpital Rangueil, Toulouse; Hélène Francois and 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 and Philippe Gatault, Service de Néphrologie, Tours; Jean-François Augusto and 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, and Antoine Durrbach, Service de Néphrologie, Hôpital Henri-Mondor, Creteil; 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 Bicetre; 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 and 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; and Faouzi Saliba, Service d'Hépatologie, Centre Hépato-Biliaire Paul Brousse, Villejuif

DISCLOSURE

All the authors declared no competing interests.

AUTHOR CONTRIBUTIONS

SC and MH had full access to all the data of the cohort study and take responsibility for the integrity of the data and the accuracy of the analyses. Conception and design were completed by SC, MH, and YL. Acquisition, analysis, and interpretation of data were conducted by SC, DA, MM, ADur, CG, LF, OT, TL, VM, PFW, NK, PGa, RS, AS, DB, CC, LC, JC, CM, GB, JB, ADuv, NB, NC, PGr, BM, YL, and MH. Drafting of the manuscript was completed by SC and MH. Statistical analysis was conducted by MH. Critical revision of the manuscript for important intellectual content was performed by SC, DA, MM, ADur, CG, LF, OT, TL, VM, PFW, NK, PGa, RS, AS, DB, CC, LC, JC, CM, GB, JB, ADuv, NB, NC, PGr, BM, YL, and MH.

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