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ORIGINAL ARTICLE

Covid-19 in liver transplant recipients: the French SOT COVID registry

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The French SOT COVID Registry was approved by the Institutional Review Board of the Strasbourg University (approval number 02.26) and registered at clinicaltrials.gov (NCT04360707).

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KEYWORDS
Covid-19;
Liver transplantation;
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Abstract
Background: Notwithstanding the ongoing coronavirus disease-2019 (Covid-19) pandemic, information on its clinical presentation and prognosis in organ transplant recipients remains limited. The aim of this registry-based observational study was to report the characteristics and clinical outcomes of liver transplant (LT) recipients included in the French nationwide Registry of Solid Organ Transplant Recipients with Covid-19.
Methods: COVID-19 was diagnosed in patients who had a positive PCR assay for SARS-CoV-2 or in presence of typical lung lesions on imaging or specific SARS-CoV-2 antibodies. 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.
Results: Of the 104 patients, 67 were admitted to hospital and 37 were managed at home (including all 13 children). Hospitalized patients had a median age of 65.2 years (IQR: 58.1 — 73.2 years) and two thirds were men. Most common comorbidities included overweight (67.3%), hypertension (61.2%), diabetes (50.7%), cardiovascular disease (20.9%) and respiratory disease (16.4%). SARS-CoV-2 infection was identified after a median of 92.8 months (IQR: 40.1 — 194.7 months) from LT. During hospitalization, antimetabolites, mTOR inhibitor, and CNIs were withdrawn in 41.9%, 30.0% and 12.5% of patients, respectively. The composite endpoint of severe Covid-19 within 30 days after diagnosis was reached by 33.0% of the adult patients. The 30-day mortality rate was 20.0%, and 28.1% for hospitalized patients. Multivariate analysis identified that age was independently associated with mortality.
Conclusion: In our large nationwide study, Covid-19 in LT recipients was associated with a high mortality rate.

Introduction

Coronavirus disease-2019 (Covid-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is an ongoing global pandemic of major concern. As of July 7, 2020, a total of 168,810 confirmed cases of Covid-19 occurred in France, of whom 29,933 died; Covid-19-related hospitalization totaled 105,048, of which 18,413 were intensive care unit (ICU) admissions. Patients with comorbidities are at high risk of developing severe disease. This includes solid organ transplant recipients [1], who are well known to be at increased risk for infectious complications, among which community-acquired respiratory viruses are unique due to the frequent exposure [2]. For instance, despite the availability of effective vaccines, severe influenza, requiring ICU-level care (11%) or mechanical ventilation (8%), can occur in solid organ transplant recipients, leading to 2%—4% mortality [3,4].

Available data on clinical presentation and prognosis in liver transplant (LT) recipients under immunosuppressive therapy remains limited [5—11]. On March 1, 2020, a French nationwide registry of patients with Covid-19 and history of solid organ transplantation has been established under the auspices of the *French Speaking Society of Transplantation*. As of July 7, 2020, a total of 696 patients were included in the registry, of whom 492 were kidney transplant (KT) recipients, 104 LT recipients, 61 heart transplant recipients, and 39 lung transplant recipients. Here, we describe the disease presentation, immunosuppression management, clinical outcomes, and prognostic factors in 104 LT recipients with Covid-19.

Patients and methods

Patients

Data from all French patients with Covid-19 and a history of LT included in a nationwide registry, termed French SOT COVID, between March 4 and July 1, 2020, were retrieved.

Patients who received double solid organ transplantation (liver with kidney, lung, or heart) were deemed eligible. The diagnostic criteria for Covid-19 were as follows: (1) evidence of SARS-CoV-2 infection on reverse transcriptase-polymerase chain reaction (RT-PCR) testing performed on nasopharyngeal swab specimens or (2) presence of typical respiratory symptoms accompanied by evocative pulmonary lesions on low-dose chest computed tomography (CT) and detection of specific antibodies against SARS-CoV-2 (in case of RT-PCR yielded negative results). Clinical and laboratory variables were extracted from medical records. In case of hospitalization, data on presentation and other clinical variables (including ongoing immunosuppressive therapy) were collected on admission. Changes in immunosuppression during the course of hospitalization were thoroughly recorded. Patients were divided into two groups according to their need for hospitalization (admitted to hospital *versus* managed at home). Severe COVID-19 was defined as admission (or transfer) to an intensive care unit (ICU), need for mechanical ventilation (MV), or death. All other patients were considered non-severe cases. The creation of the French SOT COVID Registry was approved by the Institutional Review Board of the 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 (IQRs) 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 MV, 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 univariate and multivariate models were constructed to identify predictors of the study endpoints. All variables showing an association with a $P < 0.1$ in univariate analysis were included as covariates in the multivariate model using a backward conditional selection procedure. The optimal model was selected according to the highest concordance value. Results are expressed as hazard ratios (HRs) with their 95% confidence intervals. All analyses were conducted in the R environment (R Foundation for Statistical Computing, Vienna, Austria), and two-tailed p values <0.05 were considered statistically significant.

Results

Patient characteristics

Study population consisted in 104 LT recipients: 91 adults and 13 children. The median follow-up time was 92 days, and none of the hospitalized patients were still in ICU at last follow-up. The first of our case was diagnosed on March the 1st and the last one on May the 5th.

Covid-19 was diagnosed by RT-PCR in 93.3% of cases. A total of 67 patients were admitted to hospital and 37 were managed at home, including all children (Table1). Main indications for adult LT were alcohol-related liver disease (40/91) and hepatitis C (18/91). In brief, adult patients managed at home consisted of younger patients, with lower BMI (and also a trend to lower rate of diabetes) and with a lower frequency of dyspnea, fever, and cough (Table 2). Immunosuppressive treatment was not modified for patients managed at home. Hospitalized patients had a median age of 65.2 years (IQR: 58.1 — 73.2 years) and two thirds were men. Most of them were overweight (67.3%) and the most common comorbidities included hypertension (61.2%), diabetes (50.7%), cardiovascular disease (20.9%) and history of respiratory disease (16.4%). Last available liver function tests before SARS-CoV-2 infection (median delay 5.6 months) were within normal ranges in the vast majority of cases (75/91). SARS-CoV-2 infection was identified after a median of 92.8 months (IQR: 40.1 — 194.7 months) from LT. The median delay between the onset of symptoms and hospital admission was 6 days (IQR: 3 — 9 days). The most frequent symptom was fever (70.1%), followed by cough (64.2%) and dyspnea (62.7%). At admission, available median levels of C-reactive protein (CRP) and procalcitonin were 70 mg/L and 0.26 ng/mL, respectively (Table 3). The median lymphocyte count was 0.70×10^9/L. Lung infiltrates on chest CT images were detected in all cases. Liver enzymes (defined as more than 2 upper normal or basal values during hospitalization) deteriorated in 11/67 hospitalized patients (16.4%).

Management of immunosuppression

On admission, calcineurin inhibitors (CNIs), antimetabolites, mTOR inhibitor and steroids were being taken by 92.2%, 64.2%, 14.9% and 22.4% of patients, respectively (Table 2). During hospitalization, antimetabolites, mTOR inhibitor, and CNIs were withdrawn in 41.9%, 30.0% and 12.5% of patients, respectively (Table 3). No liver biopsy was performed. No case of biopsy proven rejection or graft lost (excepting patients who died) occurred.

Treatment and outcome

Most patients received nasal oxygen therapy (59.7%). Antibiotics were given for preventive or curative purpose. From the 20 hospitalized patients with recognize superinfection (29.9%), it included 18 cases of pulmonary superinfection, and it included 17 cases of bacterial infections, 2 cases of fungal infection and one combined. Antibiotics other than azithromycin were given to 59.7% of the patients; hydroxychloroquine and azithromycin were given to 20.9% and 23.9% of the patients, respectively. Antiviral drugs and tocilizumab were administered to only 4 (6.0%) and 1 (1.5%) cases, respectively. MV was required for 25.4% of patients. Acute kidney injury occurred in 47.8% of patients, with renal replacement therapy being necessary in third of cases. Considering all adult patients, the composite endpoint of severe Covid-19 within 30 days of diagnosis was reached by 33.0% of the adult patients (Fig. 1A). The composite endpoint of severe Covid-19 within 30 days of hospital admission was reached by 44.8% of the patients (Fig. 1B). The 30-day mor-

Table 1 Characteristics of children LT recipients.

	Children recipients *N* = 13	N
Baseline characteristics		
Median age [IQR] - yr	13.0 [7.4—14.2]	13
Age > 65 yr - no.(%): N	13 (100.0%)	13
Male, n (%)	5 (38.5%)	13
Median BMI [IQR] - kg/m^2	19.4 [17.0—20.6]	11
Blood group, n (%):		13
A	4 (30.8%)	
AB	2 (15.4%)	
B	1 (7.7%)	
O	6 (46.2%)	
Transplanted organ, n (%):		13
Liver	12 (92.3%)	
Liver-Kidney	1 (7.7%)	
Retransplantation, n (%)	(0.0%)	13
Living donor, n (%)	3 (23.1%)	13
Time Tx to COVID [IQR] - mo	9.2 [5.4—86.8]	13
Tx within 1 yr - no.(%)	7 (53.8%)	13
Hypertension, n (%)	1 (7.7%)	13
Cardiovascular disease, n (%)	0 (0.0%)	13
Ischemic disease, n (%)	0 (.0%)	13
Respiratory disease, n (%)	(0.0%)	13
Diabetes, n (%)	3 (23.1%)	13
Cancer, n (%)	1 (7.7%)	13
Median baseline SCr [IQR] - μmol/l	46.0 [36.0—54.5]	11
RAS blockers, n (%)	1 (7.7%)	13
Statin, n (%)	(0.0%)	13
Baseline immunosuppression		
Induction, n (%):		13
No induction	3 (23.1%)	
anti-IL2R	10 (76.9%)	
CNI, n (%): Tacrolimus	13 (100.0%)	13
Mycophenolate, n (%)	6 (46.2%)	13
Azathioprin, n (%)	0 (0.0%)	13
mTOR inhibitor, n (%)	1 (7.7%)	13
Steroids, n (%)	4 (30.8%)	13
Clinical data		
Cough, n (%)	7 (53.8%)	13
Rhinitis, n (%)	3 (23.1%)	13
Dyspnea, n (%)	5 (38.5%)	13
Anosmia, n (%)	2 (15.4%)	13
Fever, n (%)	4 (30.8%)	13
Headache, n (%)	3 (23.1%)	13
Diarrhea, n (%)	2 (15.4%)	13
Vomiting, n (%)	2 (15.4%)	13
Myalgia, n (%)	2 (15.4%)	13
Neurological signs, n (%)	(0.0%)	13
Cutaneous lesions, n (%)	1 (7.7%)	13
Biological data		
Median CRP [IQR] - mg/l	15 [8—26]	6
Median procalcitonin [IQR] - ng/mL	10.37 [5.56—15.19]	2
Median lymphocyte count [IQR] - G/l	0.97 [0.90—1.44]	5
Median platelet count [IQR] - G/l	180 [179—182]	5
Median SaO2 [IQR] - %	99 [99—100]	5
Median admission SCr [IQR] - μmol/l	66 [56—78]	4

Table 2 Comparison of home-managed and In-hospital adult LT recipients.

	All cohort *N* = 91	Home *N* = 24	In-hospital *N* = 67	p	N
Baseline characteristics					
Median age [IQR] - yr	64.4 [54.9–71.3]	58.5 [46.3–65.0]	65.2 [58.1–73.2]	0.002	91
Age > 65 yr - n (%)	40 (44.0%)	6 (25.0%)	34 (50.7%)	0.052	91
Male, n (%)	64 (70.3%)	18 (75.0%)	46 (68.7%)	0.746	91
Median BMI [IQR] - kg/m^2	26.0 [23.2–29.7]	23.4 [20.5–27.5]	26.4 [23.8–31.0]	0.021	71
BMI > 25 kg/m^2 - n (%)	44 (62.0%)	9 (47.4%)	35 (67.3%)	0.209	71
Blood group, n (%):				0.155	63
A	26 (41.3%)	10 (55.6%)	16 (35.6%)		
AB	2 (3.2%)	1 (5.6%)	1 (2.2%)		
B	5 (7.9%)	2 (11.1%)	3 (6.7%)		
O	30 (47.6%)	5 (27.8%)	25 (55.6%)		
Transplanted organ, n (%):				0.316	91
Liver	78 (85.7%)	23 (95.8%)	55 (82.1%)		
Liver-Heart	1 (1.1%)	0 (0.0%)	1 (1.5%)		
Liver-Kidney	12 (13.2%)	1 (4.2%)	11 (16.4%)		
Retransplantation, n (%)	4 (5.2%)	2 (8.7%)	2 (3.7%)	0.578	77
Time Tx to COVID [IQR] - mo	84.9 [34.0–168.4]	57.0 [24.5–119.8]	92.8 [40.1–194.7]	0.084	90
Tx within 1 yr - n (%)	10 (11.1%)	3 (12.5%)	7 (10.6%)	0.723	90
Hypertension, n (%)	51 (56.0%)	10 (41.7%)	41 (61.2%)	0.157	91
Cardiovascular disease, n (%)	19 (20.9%)	5 (20.8%)	14 (20.9%)	1.000	91
Ischemic disease, n (%)	13 (14.3%)	3 (12.5%)	10 (14.9%)	1.000	91
Respiratory disease, n (%)	13 (14.3%)	2 (8.3%)	11 (16.4%)	0.501	91
Diabetes, n (%)	40 (44.0%)	6 (25.0%)	34 (50.7%)	0.052	91
Cancer, n (%)	19 (20.9%)	4 (16.7%)	15 (22.4%)	0.765	91
Median baseline SCr [IQR] - μmol/l	103.0 [80.0–135.0]	100.0 [76.0–123.5]	107.5 [85.5–141.5]	0.268	69
Baseline SCr > 115 μmol/l, n (%)	28 (40.6%)	6 (31.6%)	22 (44.0%)	0.507	69
Smoking, n (%)	13 (14.3%)	3 (12.5%)	10 (14.9%)	1.000	91
RAS blockers, n (%)	24 (26.4%)	3 (12.5%)	21 (31.3%)	0.127	91
Statin, n (%)	22 (24.2%)	3 (12.5%)	19 (28.4%)	0.201	91
Baseline immunosuppression					
CNI, n (%):				1.000	90
No CNI	14 (15.6%)	4 (16.7%)	10 (15.2%)		
Tacrolimus	70 (77.8%)	19 (79.2%)	51 (77.3%)		
Cyclosporine	6 (6.7%)	1 (4.2%)	5 (7.6%)		
Mycophenolate, n (%)	53 (58.2%)	13 (54.2%)	40 (59.7%)	0.818	91
Azathioprin, n (%)	3 (3.3%)	0 (0.0%)	3 (4.5%)	0.563	91
mTOR inhibitor, n (%)	14 (15.4%)	4 (16.7%)	10 (14.9%)	1.000	91
Steroids, n (%)	16 (17.6%)	1 (4.2%)	15 (22.4%)	0.060	91
Belatacept, n (%)	2 (2.2%)	0 (0.0%)	2 (3.0%)	1.000	91
Clinical symptoms					
Cough, n (%)	51 (56.0%)	8 (33.3%)	43 (64.2%)	0.018	91
Rhinitis, n (%)	13 (14.3%)	5 (20.8%)	8 (11.9%)	0.316	91
Dyspnea, n (%)	45 (49.5%)	3 (12.5%)	42 (62.7%)	<0.001	91
Anosmia, n (%)	9 (9.9%)	3 (12.5%)	6 (9.0%)	0.694	91
Fever, n (%)	55 (60.4%)	8 (33.3%)	47 (70.1%)	0.003	91
Headache, n (%)	20 (22.0%)	6 (25.0%)	14 (20.9%)	0.897	91
Diarrhea, n (%)	19 (20.9%)	2 (8.3%)	17 (25.4%)	0.142	91
Vomiting, n (%)	6 (6.6%)	2 (8.3%)	4 (6.0%)	0.652	91
Myalgia, n (%)	28 (30.8%)	6 (25.0%)	22 (32.8%)	0.648	91
Neurologic signs, n (%)	9 (9.9%)	1 (4.2%)	8 (11.9%)	0.436	91
Cutaneous lesions, n (%)	4 (4.4%)	0 (0.0%)	4 (6.0%)	0.570	91

Abbreviations: IQR, interquartile range; BMI, body mass index; Ref, reference; Txtransplantation; RAS, renin-angiotensin system; CNI, scalcineurin inhibitors; mTOR, mammalian target of rapamycin. Data are expressed as medians (IQRs) or counts (percentages), as appropriate.

Table 3 Biological data, treatments and outcome of In-hospital LT recipients.

	In-hospital recipients *N* = 67	N
Biological data		
Median CRP [IQR] - mg/l	70 [28—122]	46
Median procalcitonin [IQR] - ng/mL	0.26 [0.17—1.34]	23
Median lymphocyte count [IQR] - G/l	0.70 [0.55—1.08]	38
Median platelet count [IQR] - G/l	186 [126—299]	45
Median SaO2 [IQR] - %	96 [93—97]	57
Median admission SCr [IQR] - μmol/l	125 [97—185]	41
Lung CT scan, n (%):		44
Mild	19 (43%)	
Moderate	17 (39%)	
Severe	8 (18%)	
Immunosuppression management		
CNI withdrawal, n (%)	7 (12.5%)	56
Antimetabolite withdrawal, n (%)	18 (41.9%)	43
mTOR inhibitor withdrawal,n (%)	3 (30.0%)	10
Belatacept withdrawal, n (%): N	2 (100.0%)	2
Treatments		
Azithromycin, n (%)	16 (23.9%)	67
Other antibiotics, n (%)	40 (59.7%)	67
Remdesivir, n (%)	2 (3.0%)	67
Lopinavir/Ritonavir, n (%)	2 (3.0%)	67
Hydroxychloroquine, n (%)	14 (20.9%)	67
High steroids dose, n (%)	6 (9.0%)	67
Tocilizumab, n (%)	1 (1.5%)	67
Outcome		
Superinfection, n (%)	20 (29.9%)	67
Thromboembolic event, n (%)	9 (13.4%)	67
Mechanical ventilation, n (%)	17 (25.4%)	67
Vasopressor support, n (%)	10 (14.9%)	67
Acute Kidney Injury, n (%)	32 (47.8%)	67
Renal Replacement Therapy, n (%)	11 (16.4%)	67

Abbreviations: IQR, interquartile range; BMI, body mass index; Tx, transplantation; RAS, renin-angiotensin system; CNIs, calcineurin inhibitors; mTOR, mammalian target of rapamycin. Data are expressed as medians (IQRs) or counts (percentages), as appropriate.

tality rate of all adult patients was 20.0% (Fig. 1C). The 30-day mortality rate of hospitalized patients was 28.1% (Fig. 1D).

Risk factors for severe Covid-19

Table 4 compares the general characteristics of patients who developed severe Covid-19 (n = 33) *versus* those who did not (n = 58). Age, dyspnea, fever, CRP level, lymphocyte count, a partial pressure of oxygen <95% on admission, an acute kidney injury and a moderate/severe lung involvement were significantly associated with severe Covid-19. Considering only baseline characteristics and clinical symptoms, multivariate analysis identified dyspnea and fever as independent risk factors for severe disease (Table 5).

Risk factors for mortality

Table 6 compares the general characteristics of patients who died (n = 20) *versus* those who did not (n = 71). Univariate analysis disclosed that age, fever, neurologic signs, and baseline serum creatinine were significantly associated with death. Considering only baseline characteristics and clinical symptoms, multivariate analysis identified only age as independent risk factor for death (there was a tendency for baseline serum creatinine without reaching statistical significance, p = 0.071) (Table 5).

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 limited. Herein we report comprehensive data on from a large cohort consisting of 104 French LT recipients with Covid-19. Since the number of alive LT French recipients was 14,948 at the 1st of January 2020 (personal communication, Corinne Antoine, Agence de

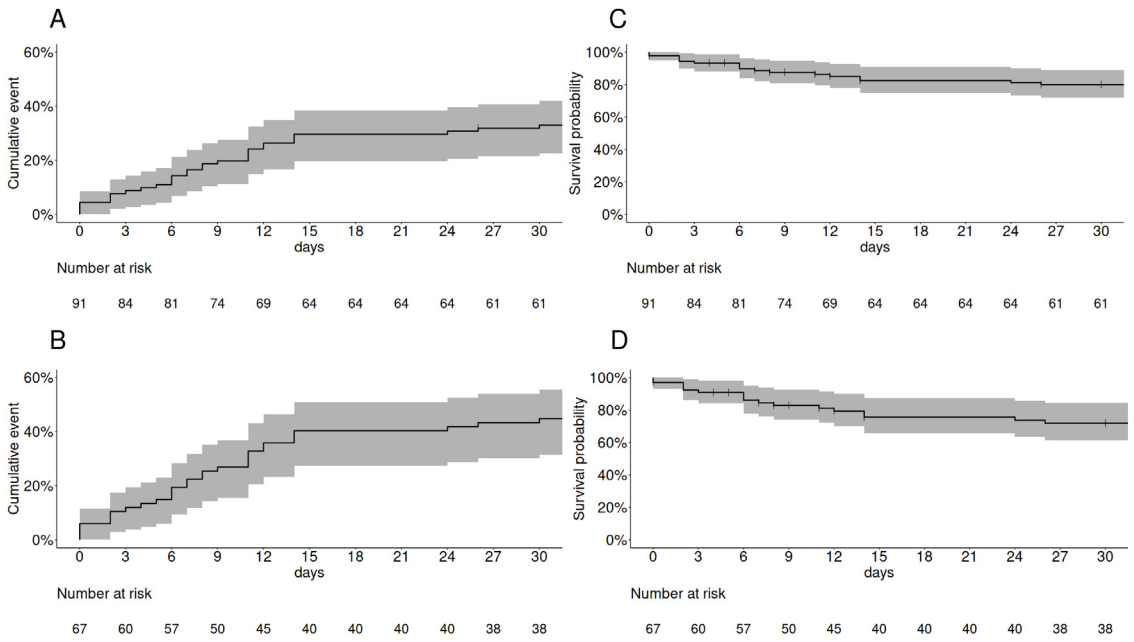

Figure 1 Outcome of 91 adult LT recipients with Covid-19.
A. Probability of reaching the composite endpoint of severe disease (ICU admission or mechanical ventilation or death) in LT adult recipients with Covid-19. The cumulative incidence for the composite endpoint at day-30 was 33.0% (22.6—42.0).
B. Probability of reaching the composite endpoint of severe disease (ICU admission or mechanical ventilation or death) in LT adult recipients who were hospitalized with Covid-19. The cumulative incidence for the composite endpoint at day-30 was 44.8% (31.5—55.5).
C. Kaplan—Meier plot of survival in adult LT recipients with Covid-19. The 30-day survival rate after diagnosis was 80.0% (71.8—89.0).
D. Kaplan—Meier plot of survival in adult LT recipients who were hospitalized with Covid-19. The 30-day survival rate after diagnosis was 71.9% (61.3—84.3).

la Biomédecine), the incidence of Covid-19 in LT recipients was 0.7%, but was probably underestimated.

First, and unsurprisingly, we observed that the clinical presentation of Covid-19 in LT recipients is similar to that reported in the general population, with fever and cough being the two 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 [12—14]. Interestingly, anosmia, which is highly suggestive but was not reported in initial series because it was not identified as a Covid-19-related symptom, was present in almost 10% of our patients. We also report here that some immunocompromised patients with Covid-19 were manageable at home. This decision was taken on a case-basis and was chiefly implemented for younger patients without dyspnea and high fever, which were significant predictors of severe disease in our population. This patient subgroup was offered teleconsultation or phone call surveillance until disease resolution. We hypothesize that some LT recipients who presented Covid-19 and stay at home were not identified by now, and therefore not included in our cohort. On the opposite, we are confident that almost all French LT recipients hospitalized were included in the present report.

The initially reported mortality rate for Covid-19 in the general population of Wuhan, China, was 1.4% [12]. Mortality dramatically increase for hospitalized patients (10%) [14] and moreover for patients admitted to ICU (26%). [15] Early data from small-sized series of transplanted patients reported one death out of 15 patients [16] five out of 25 [17], and ten out of 36 patients [18]. More recently, Pereira and coll. reported their initial experience with 90 solid organ transplant recipients (including 13 L T recipients) from two centers during the first 3 weeks of the outbreak in New York City. Sixteen patients died (18% overall, 24% of hospitalized, 52% of ICU) [5]. Focusing on LT recipients, Webb and coll. reported details of 39 L T recipients who developed COVID-19 worldwide, including nine (23%) who died from respiratory failure [11]. According to the European Liver Transplant registry, from the first 103 COVID-19 cases observed between March 1, and April 24, 2020, mainly from centers located in specific areas of Italy, Spain, and France (including some French patients reported here), after a median follow-up of 18 days, 16 patients (15.5%) had died [10]. When considering only patients requiring mechanical ventilation, the mortality rate increased to 44.4%. Becchetti and coll. reported data on a 57 L T recipients European cohort, 41 (71.9%) patients were hospitalized and 11 (19.3%) developed acute respiratory distress syndrome [19]. Estimated mortality rate was 12% (95%CI 5% to 24%), which increased to 17% (95%CI 7%—32%) among hospitalized patients. From the 38 L T recipients described by Lee and coll., seven died (18% overall, 29% hospitalized) [20]. Herein, the 30-day mortality rate of our hospitalized LT recipients with Covid-19 was 28.1%, but it must be pointed that our follow-up was longer. MV was required in 25.4% of our hospitalized patients, recalling what has been reported for immunocompetent subjects (16 — 33%) [13,14]. Rabiee and coll. conducted a multicenter comparative study in the

Table 4 Risk factors for ICU admission or mechanical ventilation or death (univariate).

	No event *N* = 58	Event *N* = 33	HR	p.ratio	N
Baseline characteristics					
Median age [IQR] - yr	62.0 [52.9—68.9]	65.8 [60.3—73.2]	1.04 [1.00;1.07]	0.029	91
Age > 65 yr - n (%)	22 (37.9%)	18 (54.5%)	1.66 [0.84;3.29]	0.148	91
Male, n (%)	39 (67.2%)	25 (75.8%)	1.45 [0.65;3.21]	0.364	91
Median BMI [IQR] - kg/m^2	25.0 [22.0—28.9]	27.0 [24.8—31.0]	1.04 [0.98;1.10]	0.220	71
BMI > 25 kg/m^2 - n (%)	23 (53.5%)	21 (75.0%)	2.07 [0.88;4.89]	0.096	71
Blood group, n (%):					63
A	18 (45.0%)	8 (34.8%)	Ref.	Ref.	
AB	2 (5.00%)	0 (0.00%)	0.00 [0.00;.]	0.997	
B	3 (7.50%)	2 (8.70%)	1.47 [0.31;6.90]	0.629	
O	17 (42.5%)	13 (56.5%)	1.42 [0.59;3.42]	0.437	
Time Tx to COVID [IQR] - mo	76.1 [26.6—163]	89.3 [48.0—183]	1.00 [1.00;1.01]	0.277	90
Tx within 1 yr - n (%)	6 (10.5%)	4 (12.1%)	1.24 [0.43;3.52]	0.692	90
Hypertension, n (%)	33 (56.9%)	18 (54.5%)	0.93 [0.47;1.84]	0.831	91
Cardiovascular disease, n (%)	13 (22.4%)	6 (18.2%)	0.82 [0.34;1.99]	0.660	91
Ischemic disease, n (%)	8 (13.8%)	5 (15.2%)	1.13 [0.44;2.93]	0.799	91
Respiratory disease, n (%)	7 (12.1%)	6 (18.2%)	1.26 [0.52;3.06]	0.606	91
Diabetes, n (%)	22 (37.9%)	18 (54.5%)	1.72 [0.87;3.42]	0.121	91
Cancer, n (%)	9 (15.5%)	10 (30.3%)	2.09 [0.99;4.40]	0.052	91
Median baseline SCr [IQR] - μmol/l	100 [80.0—128]	105 [88.5—140]	1.00 [1.00;1.01]	0.386	69
Baseline SCr >115 μmol/l, n (%)	19 (41.3%)	9 (39.1%)	0.93 [0.40;2.15]	0.864	69
Smoking, n (%)	7 (12.1%)	6 (18.2%)	1.62 [0.67;3.93]	0.284	91
RAS blockers, n (%)	16 (27.6%)	8 (24.2%)	0.82 [0.37;1.82]	0.626	91
Statin, n (%)	17 (29.3%)	5 (15.2%)	0.48 [0.19;1.25]	0.133	91
CNI, n (%)	50 (86.2%)	26 (81.2%)	0.74 [0.31;1.81]	0.515	90
Mycophenolate, n (%)	34 (58.6%)	19 (57.6%)	1.00 [0.50;1.99]	0.992	91
Azathioprin, n (%)	3 (5.17%)	0 (0.00%)	0.00 [0.00;.]	0.997	91
mTOR inhibitor, n (%)	8 (13.8%)	6 (18.2%)	1.23 [0.51;2.99]	0.643	91
Steroids, n (%)	9 (15.5%)	7 (21.2%)	1.46 [0.63;3.36]	0.378	91
Clinical symptoms					
Cough, n (%)	31 (53.4%)	20 (60.6%)	1.27 [0.63;2.56]	0.499	91
Rhinitis, n (%)	9 (15.5%)	4 (12.1%)	0.80 [0.28;2.29]	0.681	91
Dyspnea, n (%)	22 (37.9%)	23 (69.7%)	3.01 [1.43;6.33]	0.004	91
Anosmia, n (%)	7 (12.1%)	2 (6.06%)	0.52 [0.12;2.18]	0.371	91
Fever, n (%)	29 (50.0%)	26 (78.8%)	3.10 [1.34;7.15]	0.008	91
Headache, n (%)	11 (19.0%)	9 (27.3%)	1.39 [0.64;2.98]	0.404	91
Diarrhea, n (%)	14 (24.1%)	5 (15.2%)	0.60 [0.23;1.56]	0.299	91
Vomiting, n (%)	6 (10.3%)	0 (0.00%)	0.00 [0.00;.]	0.997	91
Myalgia, n (%)	17 (29.3%)	11 (33.3%)	1.15 [0.56;2.37]	0.707	91
Neurologic signs, n (%)	4 (6.90%)	5 (15.2%)	2.15 [0.83;5.59]	0.116	91
Cutaneous lesions, n (%)	1 (1.72%)	3 (9.09%)	2.85 [0.87;9.35]	0.085	91
Admission characteristics*					
CRP > 70 mg/l—n (%)	10 (31.2%)	13 (59.1%)	2.49 [1.06;5.85]	0.037	54
Procalcitonin >0.2 ng/mL - n (%)	8 (61.5%)	6 (54.5%)	0.94 [0.29;3.09]	0.924	24
Median lymphocyte count [IQR] - G/l	0.88 [0.72—1.16]	0.62 [0.46—0.85]	0.25 [0.07;0.89]	0.033	49
Thrombocytopenia <150 G/l—n (%)	13 (36.1%)	8 (40.0%)	1.18 [0.48;2.89]	0.718	56
SaO2 < 95% - n (%)	5 (15.2%)	14 (50.0%)	3.30 [1.57;6.96]	0.002	61
Admission SCr >115 μmol/l, n (%)	13 (37.1%)	13 (76.5%)	4.48 [1.46;13.8]	0.009	52
Lung CT scan, n (%):					48
mild	17 (65.4%)	6 (27.3%)	Ref.	Ref.	
moderate	7 (26.9%)	10 (45.5%)	3.29 [1.19;9.09]	0.021	
severe	2 (7.69%)	6 (27.3%)	5.16 [1.63;16.3]	0.005	

Abbreviations: IQR, interquartile range; CRP, C-reactive protein; SaO_2, arterial oxygen saturation; CNIs, calcineurin inhibitors; mTOR, mammalian target of rapamycin. Data are expressed as medians (IQRs) or counts (percentages), as appropriate.

* Available only for In-hospital patients.

Table 5 Risk factors for the composite endpoint (ICU admission or mechanical ventilation or death) and death only in multivariate analysis.

	Composite endpoint		Death only	
	HR [95%CI]	p	HR [95%CI]	p
Dyspnea	2.39 [1.11, 5.15]	0.026	–	–
Fever	2.40 [1.01, 5.69]	0.047	–	–
Baseline SCr (μmol/l)	–		2.75 [0.92, 8.26]	0.071
Age (years)	–		1.05 [1.01, 1.10]	0.024

SCr: Serum creatinine.
Concordance is 0.68 for the composite endpoint model, and 0.71 for the death only model.

US including 112 adult LT recipients with COVID-19 [21]. The mortality rate was 22.3%; 72.3% were hospitalized and 26.8% admitted to the ICU. Compared to age and gender matched non-transplant patients with chronic liver disease and COVID-19 (n = 375), the incidence of acute liver injury was lower in LT recipients but liver injury was significantly associated with mortality and ICU admission in LT recipients. Diabetes was also associated with mortality in LT recipients.

We aimed to identify risk factors for severe disease (composite endpoint including need for ICU, need for mechanical ventilation, or death) and death. Fever and dyspnea are probably clinical features of severe disease instead of risk factors. First of all, age had a significant impact on severity of the disease and mortality, as observed in general population [13]. Male gender has been previously linked to severe Covid-19 [22]; it was not in our cohort, but males represented the vast majority of our cases. Similarly, the association between overweight/obesity and severe Covid-19 was not demonstrated in our cohort, whereas it has been shown in the general population (BMI $\geq 30\,kg/m^2$) (14) but also in French kidney transplant recipients from our SOT COVID registry (BMI $\geq 25\,kg/m^2$) [23]. Biological markers of severe inflammation were available only for hospitalized patients and were associated with severe disease (univariate analysis). Previous studies reported that procalcitonin and CRP levels were higher in patients requiring MV and that procalcitonin levels were an unfavorable predictor of mortality [13,14]. Similarly, previous studies reported that lymphopenia could predict severe Covid-19 or mortality [13,24]. In the solid organ transplant cohort from Pereira and coll., advanced age, hypertension and active cancer were significantly associated (univariate analysis) with severe disease [5].

A majority of our patients received antibiotics including azithromycin, whereas a minority received specific antiviral drugs. The lopinavir/ritonavir combination has strong pharmacological interactions with CNIs and mTOR inhibitors which have been largely evaluated in HIV patients [25–27]. The low usage of hydroxychloroquine may be explained by low-quality evidence on its effectiveness. The debate on the management of immunosuppression in transplant recipients following SARS-CoV-2 infection remains unresolved. In our study, baseline immunosuppressive regimen had no impact on severity of Covid-19. Although not statistically significant, time since LT seems shorter for LT recipients remaining at home that those hospitalized, pointing towards lesser importance of level of immunosuppression (as compared to other major risk factors including age, but also past duration of immunosuppression). As previously reported in solid organ transplant recipients [5,16–19,21,28–31], a reduction in maintenance immunosuppression was made in a large part of our hospitalized patients: antimetabolites, mTOR inhibitor, and CNIs were withdrawn in 41.9%, 30.0% and 12.5% of patients, respectively. According to the French recommendations on management of immunosuppressive (and also most recommendations for organ transplant recipients) modification (*i.e.* reduction) of immunosuppression was driven by Covid-19 severity [32], leading to a major bias regarding global outcome. Precise guidance on the management of immunosuppressive drugs is still lacking, and no firm conclusions can therefore be drawn on the beneficial impact of such strategy by now.

Our findings need to be interpreted in the context of some limitations. We acknowledge that some baseline clinical, laboratory, or imaging data were missing and that probably some patients who were managed at home were not captured by now. Notwithstanding the potential caveats, length of follow-up makes it possible to avoid the risk of ignoring the pejorative evolutions of certain patients (none of the patient is still on ICU at last follow-up) and therefore this study is by far the largest so far to provide a comprehensive description of LT recipients with Covid-19. Finally, in our study, we were not able to compare LT recipients and non-transplant patients, which would have been of great interest to assess whether the different outcomes are different in the LT immunosuppressed population as opposed to the general population matched by age and presence of comorbidities. We plane to do so from our global cohort of solid organ transplant recipients, and also by comparing our LT patients to the ongoing French cohort including patients with chronic liver disease built by the French society of Hepatology (AFEF). Nevertheless, in the large study in UK general population, it has been reported that history of organ transplantation had a great pejorative prognostic value, together with other morbid conditions including chronic renal failure and chronic liver disease [1].

In conclusion, our results from a large nationwide cohort confirm that Covid-19 in LT recipients portends a high risk of mortality. Proper management of immunosuppression and tailored treatment of this fragile population remain challenging, and further data on large cohorts are necessary in order to improve our level of knowledge and generate robust recommendations.

Table 6 Risk factors for death (univariate).

	No event *N = 71*	Event *N = 20*	HR	p.ratio	N
Baseline characteristics					
Median age [IQR] - yr	62.2 [53.5—69.1]	70.4 [62.3—74.9]	1.05 [1.01;1.10]	0.017	91
Age > 65 yr - n (%)	28 (39.4%)	12 (60.0%)	2.01 [0.82;4.92]	0.126	91
Male, n (%)	50 (70.4%)	14 (70.0%)	1.02 [0.39;2.66]	0.966	91
Median BMI [IQR] - kg/m^2	25.9 [23.0—29.2]	26.0 [23.7—30.2]	1.01 [0.92;1.11]	0.769	71
BMI > 25 kg/m^2 - n (%)	35 (62.5%)	9 (60.0%)	0.91 [0.33;2.57]	0.866	71
Blood group, n (%):					63
A	23 (46.0%)	3 (23.1%)	Ref.	Ref.	
AB	2 (4.00%)	0 (0.00%)	0.00 [0.00;.]	0.998	
B	4 (8.00%)	1 (7.69%)	2.01 [0.21;19.3]	0.546	
O	21 (42.0%)	9 (69.2%)	2.90 [0.78;10.7]	0.110	
Time Tx to COVID [IQR] - mo	79.2 [27.6—162]	120 [57.6—210]	1.00 [1.00;1.01]	0.220	90
Tx within 1 yr - n (%)	8 (11.4%)	2 (10.0%)	0.92 [0.21;3.96]	0.910	90
Hypertension, n (%)	43 (60.6%)	8 (40.0%)	0.46 [0.19;1.13]	0.091	91
Cardiovascular disease, n (%)	13 (18.3%)	6 (30.0%)	1.74 [0.67;4.54]	0.255	91
Ischemic disease, n (%)	8 (11.3%)	5 (25.0%)	2.32 [0.84;6.40]	0.104	91
Respiratory disease, n (%)	8 (11.3%)	5 (25.0%)	2.17 [0.79;5.96]	0.134	91
Diabetes, n (%)	30 (42.3%)	10 (50.0%)	1.31 [0.54;3.14]	0.552	91
Cancer, n (%)	13 (18.3%)	6 (30.0%)	1.92 [0.74;4.99]	0.182	91
Median baseline SCr [IQR] - μmol/l	102 [80.0—124]	135 [87.0—157]	1.01 [1.00;1.01]	0.049	69
Baseline SCr > 115 μmol/l, n (%)	22 (37.9%)	6 (54.5%)	1.82 [0.56;5.96]	0.323	69
Smoking, n (%)	9 (12.7%)	4 (20.0%)	1.79 [0.60;5.36]	0.298	91
RAS blockers, n (%)	19 (26.8%)	5 (25.0%)	0.89 [0.32;2.45]	0.822	91
Statin, n (%)	18 (25.4%)	4 (20.0%)	0.79 [0.26;2.36]	0.669	91
CNI, n (%)	62 (87.3%)	14 (73.7%)	0.45 [0.16;1.25]	0.126	90
Mycophenolate, n (%)	44 (62.0%)	9 (45.0%)	0.58 [0.24;1.39]	0.222	91
Azathioprin, n (%)	3 (4.23%)	0 (0.00%)	0.00 [0.00;.]	0.998	91
mTOR inhibitor, n (%)	9 (12.7%)	5 (25.0%)	1.98 [0.72;5.44]	0.187	91
Steroids, n (%)	13 (18.3%)	3 (15.0%)	0.84 [0.25;2.87]	0.782	91
Clinical symptoms					
Cough, n (%)	39 (54.9%)	12 (60.0%)	1.16 [0.48;2.84]	0.741	91
Rhinitis, n (%)	10 (14.1%)	3 (15.0%)	1.11 [0.33;3.80]	0.863	91
Dyspnea, n (%)	32 (45.1%)	13 (65.0%)	2.05 [0.82;5.13]	0.127	91
Anosmia, n (%)	8 (11.3%)	1 (5.00%)	0.44 [0.06;3.30]	0.426	91
Fever, n (%)	39 (54.9%)	16 (80.0%)	3.02 [1.01;9.03]	0.048	91
Headache, n (%)	17 (23.9%)	3 (15.0%)	0.57 [0.17;1.95]	0.370	91
Diarrhea, n (%)	17 (23.9%)	2 (10.0%)	0.38 [0.09;1.62]	0.190	91
Vomiting, n (%)	6 (8.45%)	0 (0.00%)	0.00 [0.00;.]	0.998	91
Myalgia, n (%)	23 (32.4%)	5 (25.0%)	0.70 [0.26;1.94]	0.496	91
Neurologic signs, n (%)	5 (7.04%)	4 (20.0%)	3.08 [1.03;9.22]	0.045	91
Cutaneous lesions, n (%)	2 (2.82%)	2 (10.0%)	2.56 [0.59;11.1]	0.207	91
Admission characteristics[a]					
CRP > 70 mg/l—n (%)	19 (43.2%)	4 (40.0%)	0.85 [0.24;3.01]	0.801	54
Procalcitonin > 0.2 ng/mL - n (%)	12 (57.1%)	2 (66.7%)	1.54 [0.14;17.0]	0.724	24
Median lymphocyte count [IQR] - G/l	0.85 [0.59—1.10]	0.67 [0.56—0.90]	0.44 [0.09;2.14]	0.311	49
Thrombocytopenia < 150 G/l—n (%)	16 (34.8%)	5 (50.0%)	1.78 [0.52;6.16]	0.361	56
SaO2 < 95% - n (%)	12 (26.7%)	7 (43.8%)	2.00 [0.74;5.38]	0.169	61
Admission SCr > 115 μmol/l, n (%)	21 (46.7%)	5 (71.4%)	2.73 [0.53;14.1]	0.229	52
Lung CT scan, n (%):					48
Mild	17 (47.2%)	6 (50.0%)	Ref.	Ref.	
Moderate	12 (33.3%)	5 (41.7%)	1.20 [0.37;3.93]	0.764	
Severe	7 (19.4%)	1 (8.33%)	0.46 [0.06;3.85]	0.477	

Abbreviations: IQR, interquartile range; BMI, body mass index; Ref, reference; Tx, transplantation; RAS, renin-angiotensin system; CNIs, calcineurin inhibitors; mTOR, mammalian target of rapamycin. Data are expressed as medians (IQRs) or counts (percentages), as appropriate.

[a] Available only for In-hospital patients.

Authors' contributions

Jérôme Dumortier and Marc Hazzan had full access to all the data of the cohort study and takes responsibility for the integrity of the data and the accuracy of the analyses

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Conflict of interest

None of the authors have any conflict of interest disclosures to make.

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