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Protective Role of Tacrolimus, Deleterious Role of Age and Comorbidities in Liver Transplant Recipients With Covid-19: Results From the ELITA/ELTR Multi-center European Study

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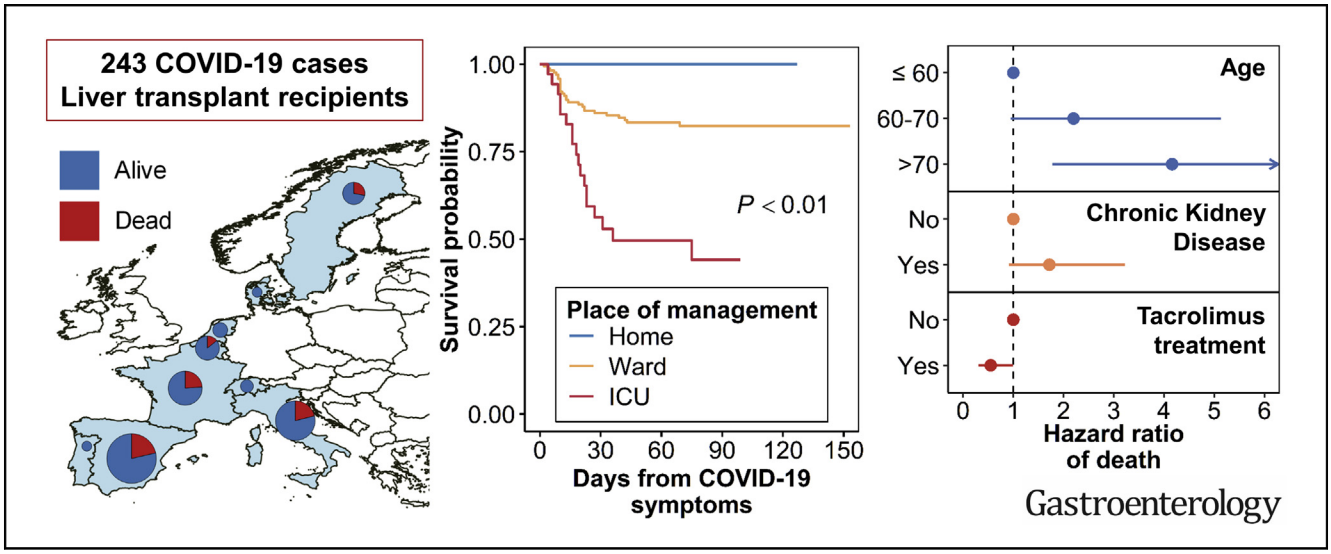

See editorial on page 1012.

BACKGROUND AND AIMS: Despite concerns that liver transplant (LT) recipients may be at increased risk of unfavorable outcomes from COVID-19 due the high prevalence of co-morbidities, immunosuppression and ageing, a detailed analysis of their effects in large studies is lacking. **METHODS:** Data from adult LT recipients with laboratory confirmed SARS-CoV2 infection were collected across Europe. All consecutive patients with symptoms were included in the analysis. **RESULTS:** Between March 1 and June 27, 2020, data from 243 adult symptomatic cases from 36 centers and 9 countries were collected. Thirty-nine (16%) were managed as outpatients while 204 (84%) required hospitalization including admission to the ICU (39 of 204, 19.1%). Forty-nine (20.2%) patients died after a median of 13.5 (10–23) days, respiratory failure was the major cause. After multivariable Cox regression analysis, age >70 (HR, 4.16; 95% CI, 1.78–9.73) had a negative effect and tacrolimus (TAC) use (HR, 0.55; 95% CI, 0.31–0.99) had a positive independent effect on survival. The role of co-morbidities was strongly influenced by the dominant effect of age where comorbidities increased with the increasing age of the recipients. In a second model excluding age, both diabetes (HR, 1.95; 95% CI, 1.06–3.58) and chronic kidney disease (HR, 1.97; 95% CI, 1.05–3.67) emerged as associated with death **CONCLUSIONS:** Twenty-five percent of patients requiring hospitalization for COVID-19 died, the risk being higher in patients older than 70 and with medical co-morbidities, such as impaired renal function and diabetes. Conversely, the use of TAC was associated with a better survival thus encouraging clinicians to keep TAC at the usual dose.

Keywords: COVID-19; Liver transplantation; Outcome; Tacrolimus.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Few studies have analyzed the impact of Cocid-19 in liver transplant recipients and the association of co-morbidities, immunosuppression and ageing on the mortality risk.

NEW FINDINGS

Age > 70 and tacrolimus use had respectively a negative and a positive independent effect on survival. The role of co-morbidities was strongly influenced by the dominant effect of age as the number of comorbidities increased with the increasing age of the recipients.

LIMITATIONS

Although we attempted to collect data on major co-variables there remains the possibility of missing confounders.

IMPACT

Thees findings should encourage clinicians to keep Tacrolimus at the usual dose as it may be beneficial when treating COVID-19.

The current coronavirus disease 2019 (COVID-19) pandemic has presented unforeseen challenges to health care systems worldwide, with several issues remaining unmet. To date, firm knowledge on disease evolution, risk factors, and optimal management in specific categories of patients is lacking. All transplant recipients are potentially vulnerable to severe acute respiratory syndrome coronavirus (CoV) 2 (SARS-CoV-2) infection, with immune suppression, aging, and metabolic or cardiovascular comorbidities likely being risk factors for symptomatic disease and its severe complications.[1] Liver transplant (LT) patients, in particular, represent one of the largest immunosuppressed cohorts in Europe, with 102,116 alive recipients being reported in the European Liver Transplant Registry (ELTR), 42,432 (41.6%) of whom are in their 60s and 12,669 in their 70s or older.[2]

At present, available data related to COVID-19 in LT patients are limited to a small number of case series,[3–5] to preliminary reports from 2 international registries,[6–8] and to a single international prospective cohort of 57 patients.[9] All authors agreed that greater case numbers were urgently required to accurately improve our understanding of individual risk in LT recipients. Thus, a large-scale collaborative study promoted by the European Liver Transplant Association (ELITA) and European Liver Transplant Registry (ELTR) was performed, the main aim being the search for risk factors associated with mortality during the COVID-19 pandemic and with a specific focus on comorbidities and immunosuppression.

Methods

Study Population

ELITA called for a COVID-19 study, which was circulated on March 30, 2020, among 149 LT centers affiliated to ELTR and located in 30 European countries. All centers that reported at least 1 case were provided with a database and instructions on how to record structured data. Data collection was managed by ELTR. Responses were received from 114 centers (76.5%), with 56 centers (38%) having observed COVID-19 in adult LT recipients between March 1 and May 19, 2020. The study included all patients with symptoms and with SARS-CoV-2 infection confirmed by a positive result on a reverse-transcriptase polymerase chain reaction (RT-PCR) assay of a specimen collected on a nasopharyngeal swab or on bronchoalveolar lavage.

Data Collection and Definitions

Demographic and clinical data, including clinical symptoms or signs at presentation, laboratory, and radiologic results during

Abbreviations used in this paper: **ALT, alanine aminotransferase; CI, confidence interval; CNI, calcineurin inhibitor; COVID-19, coronavirus disease 2019; CsA, cyclosporine A; ELITA, European Liver Transplantation Association; ELTR, European Liver Transplant Registry; ICU, intensive care unit; LT, liver transplant; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; TAC, tacrolimus.**

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COVID-19 management, as well as administered antiviral therapies and antithrombotic prophylaxis were retrospectively collected. All laboratory tests and radiologic assessments were performed at the discretion of the treating physician. Serum creatinine was converted to mg/dL for analysis. Information on baseline immunosuppression and on changes during COVID-19, namely reduction or discontinuation, was also obtained.

Obesity was defined as a given body mass index of >30 kg/m^2. Liver injury during COVID-19 was defined as alanine aminotransferase (ALT) level >30 IU/L for male patients and 19 IU/L for female patients in those with normal ALT levels at the last outpatient visit.[10] Hepatic flare was defined as ALT level $\geq$5 times the upper limit of normal. The time on study started at occurrence of COVID-19 symptoms.

All submitted files from each center were manually reviewed to assess for data quality, completeness, and inconsistencies. In addition, submitting clinicians were contacted and asked to provide corrections or data integration whenever needed.

Ethical and Regulatory Approval

Data were collected in accordance with General Data Protection Regulation, the European Union legislation, and the ELTR privacy policy.

Statistical Analysis

Analysis was led by the Research Centre on Public Health, University of Milan-Bicocca, Monza, Italy. A descriptive analysis of the cohort was performed on the overall population and after stratifying the population by site of management: at home, in general wards, or in intensive care units (ICUs). Categorical variables are summarized through percentages, and continuous variables through median, first quartile and third quartile. Categorical variables were compared using the χ^2 or Fisher's exact tests; continuous variables were compared using the Mann-Whitney *U* test or the Kruskal-Wallis test, when appropriate. All tests were 2-sided and used a significance level of 0.05.

The rates of missing data for each variable were reported. For each patient, the time between the date of COVID-19 symptoms and death or end of follow-up was computed, and the association between mortality and baseline patients' characteristics was evaluated through univariate Cox's proportional hazard models. All characteristic analyzed in the univariate model were included in a stepwise selection process that identified the best multivariate model. The same process was repeated after excluding age from potential predictors. Given the exploratory nature of the study and the limited sample size, a 0.1 significance level was established to retain predictors in the final multivariate models possibly favoring the tracing of borderline significant associations that could be the basis for further studies on wider samples. All statistical analyses were conducted using SAS 9.4 software (SAS Institute, Inc, Cary, NC) and R 4.0.0 software (R Core Team, Vienna, Austria). The map was drawn using QGIS 3.10 software (QGIS Development Team).

Results

Demographic and General Characteristics of Patients

The COVID-19 pandemic was not uniformly experienced in Europe, with large areas being spared. This explains why of the 111 centers responding to the ELITA/ELTR call, only 36 centers from 9 European countries observed at least 1 patient with RT-PCR–confirmed SARS-CoV-2 infection (Figures 1 and 2). Of the 29,981 alive patients in regular follow-up at the participating centers, 258 (0.9%) have been consecutively reported in the registry. Excluded from the study were 11 patients (4.3%) who were asymptomatic, in whom the RT-PCR test was performed according to surveillance protocols in case of contact with a SARS-CoV-2–positive individual. Four additional patients were excluded because they were aged <18 years. The remaining 243 symptomatic patients were considered for statistical analysis, with 39 patients (16%) receiving home care, and the remaining 204 requiring hospitalization (Figure 2). Of these, 167 patients (68.7%) were treated in a general ward and 37 in ICUs. Baseline patient characteristics are reported in Table 1. Thirty-two LT recipients with COVID-10 analyzed in this study were also included in the report from Becchetti et al.[9]

Comorbidities

A total of 111 patients (45.7%) had arterial hypertension, 94 (38.7%) had diabetes mellitus, 49 (20.2%) had chronic kidney disease with a creatinine >2 mg/dL, and 25 (10.3%) had chronic lung diseases. Concurrent comorbidities were frequent, with 107 patients (44%) having $\geq$2

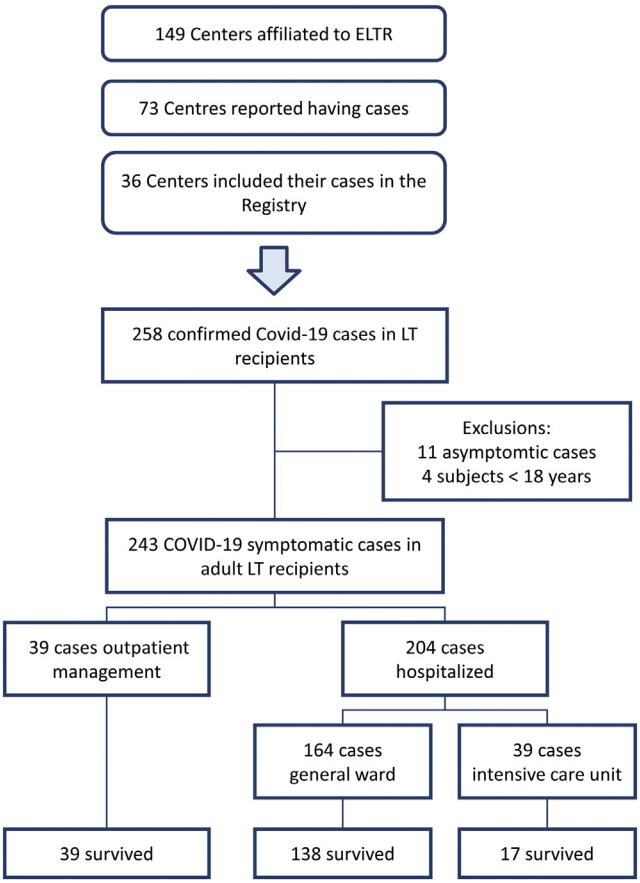

Figure 1. Flowchart shows the selection of the study population.

Country	All patients	Deaths
Belgium	21	3
Denmark	1	0
France	42	10
Italy	57	12
Portugal	1	0
Spain	89	19
Sweden	18	5
Switzerland	6	0
The Netherlands	8	0

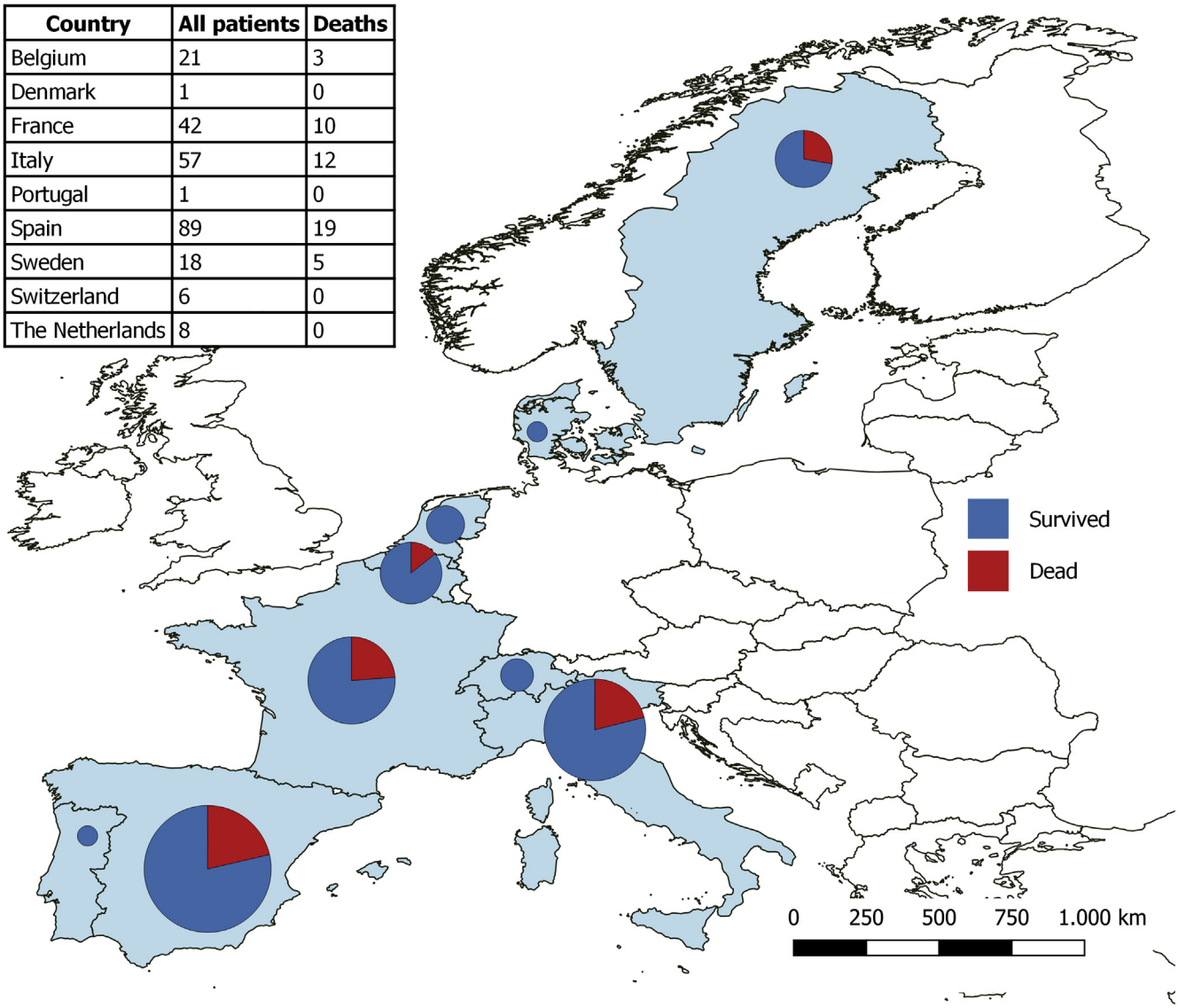

Figure 2. Patients with COVID-19 included in the study by country.

(Table 1). The prevalence of at least 2 comorbidities increased with age being observed in 25.3%, 53.4%, and 64.2% in recipients aged <60 years, 60 to 70 years, or >70 years, respectively.

Immunosuppressive Drugs and Other Drugs

Tacrolimus (TAC) and cyclosporine A (CsA) were considered as the main immunosuppressive drugs. Because some of the patients were off a calcineurin inhibitor (CNI), the proportion of patients receiving each immunosuppressive drug or combination of drugs was also obtained. At the time of analysis, 162 patients (66.7%) were on TAC, alone or in combination, 29 (11.9%) were on CsA alone or in combination, 119 (49.0%) were on mycophenolate mofetil (MMF) alone or in combination, and 37 (15.2%) were on mammalian target of rapamycin inhibitors alone or in combination (Table 1).

Clinical Presentation and Course of Liver Transplant Recipients With COVID-19

At the time of diagnosis, the most commonly self-reported symptoms included fever in 190 patients (78.2%), cough in 143 (58.8%), dyspnea in 82 (33.7%), muscle pain or asthenia in 90 (37.0%), anosmia or dysgeusia in 21 (8.6%), and diarrhea in 55 (22.6%). Radiologic findings on computed tomography scan or on chest radiography showed typical ground-glass opacities in 145 patients (59.7%) (Table 2). Overall, 137 patients (56.4%) required respiratory support during hospitalization, with 26 requiring noninvasive ventilation and 25 mechanical ventilation (Table 2). Specific anti–SARS-CoV-2 treatment was administered to 149 patients: 116 (47.7%) were treated with hydroxychloroquine alone or in combination, 41 (16.9%) with lopinavir-ritonavir, 34 (14.0%) with high doses of corticosteroids, and 15 (6.2%) with tocilizumab.

Table 1. Baseline Characteristics of the Study Population

Variables	Place of management				
	Home (n = 39)	Ward (n = 167)	ICU (n = 37)	Total (N = 243)	*P* value
Male sex	24 (61.54)	121 (72.46)	26 (70.27)	171 (70.37)	.4051
Age at symptoms, *y*[a,b]	54 (37.0–61.0)	64 (57.0–72.0)	64 (58.0–68.0)	63 (55.0–69.0)	<.0001
Age class at symptoms, *y*[a,b]					<.0001
≤50	16 (41.03)	20 (11.98)	3 (8.11)	39 (16.05)	
50–60	11 (28.21)	39 (23.35)	10 (27.03)	60 (24.69)	
60–70	9 (23.08)	59 (35.33)	20 (54.05)	88 (36.21)	
>70	1 (2.56)	48 (28.74)	4 (10.81)	53 (21.81)	
Location of patient at occurrence of symptoms[b]					.0119
Home	39 (100.00)	148 (88.62)	30 (81.08)	217 (89.30)	
Hospital	0 (0.00)	19 (11.38)	7 (18.92)	26 (10.70)	
Time between last LT and COVID-19 symptoms, *y*	6 (2.2–10.9)	9 (3.8–15.4)	5 (1.5–13.3)	8 (3.1–15.0)	.0295
Time between last LT and COVID-19 symptoms					.1005
<1 year	5 (12.82)	19 (11.38)	7 (18.92)	31 (12.76)	
1–5 years	12 (30.77)	32 (19.16)	11 (29.73)	55 (22.63)	
5–10 years	9 (23.08)	34 (20.36)	7 (18.92)	50 (20.58)	
≥10 years	10 (25.64)	81 (48.50)	10 (27.03)	101 (41.56)	
Missing	3 (7.69)	1 (0.60)	2 (5.41)	6 (2.47)	
Indication for LT					
Decompensated cirrhosis	21 (53.85)	96 (57.49)	24 (64.86)	141 (58.02)	.6034
Hepatocellular carcinoma	8 (20.51)	43 (25.75)	12 (32.43)	63 (25.93)	.4933
Other[b]	10 (25.64)	29 (17.37)	1 (2.70)	40 (16.46)	.0226
Etiology					
Alcohol[a]	3 (7.69)	49 (29.34)	8 (21.62)	60 (24.69)	.0149
After nonalcoholic steatohepatitis	2 (5.13)	10 (5.99)	6 (16.22)	18 (7.41)	.1262
Hepatitis B virus	5 (12.82)	34 (20.36)	4 (10.81)	43 (17.70)	.2492
Hepatitis C virus active or inactive	10 (25.64)	41 (24.55)	11 (29.73)	62 (25.51)	.8282
Other[a]	20 (51.28)	49 (29.34)	10 (27.03)	79 (32.51)	.0256
Missing	0 (0.00)	2 (1.20)	0 (0.00)	2 (0.82)	
Body mass index, kg/m^2	25.5 (22.0–28.9)	25.8 (23.4–29.4)	27.9 (24.5–29.9)	25.9 (23.4–29.4)	.1701
Missing	3 (7.69)	18 (10.78)	1 (2.70)	22 (9.05)	
Body mass index >30 kg/m^2	7 (17.95)	30 (17.96)	9 (24.32)	46 (18.93)	.7924
Comorbidities					
None[a,b]	19 (48.72)	35 (20.96)	3 (8.11)	57 (23.46)	<.0001
Diabetes[b]	8 (20.51)	67 (40.12)	19 (51.35)	94 (38.68)	.0176
Hypertension[b,c]	11 (28.21)	71 (42.51)	29 (78.38)	111 (45.68)	<.0001
Chronic lung disease	3 (7.69)	20 (11.98)	2 (5.41)	25 (10.29)	.5267
Chronic kidney disease[d]	4 (10.26)	37 (22.16)	8 (21.62)	49 (20.16)	.2419
Coronary artery disease	3 (7.69)	9 (5.39)	5 (13.51)	17 (7.00)	.2071
Other	4 (10.26)	34 (20.36)	5 (13.51)	43 (17.70)	.2541
Number of comorbidities[a,b]					.0002
0	19 (48.72)	35 (20.96)	3 (8.11)	57 (23.46)	
1	11 (28.21)	57 (34.13)	11 (29.73)	79 (32.51)	
≥2	9 (23.08)	75 (44.91)	23 (62.16)	107 (44.03)	
Drugs					
β-Blockers	6 (15.38)	34 (20.36)	10 (27.03)	50 (20.58)	.4515
ACE inhibitors or angiotensin II receptor antagonists[a,b]	1 (2.56)	47 (28.14)	11 (29.73)	59 (24.28)	.0025
Smoking					.3508
Missing	0 (0.00)	1 (0.60)	1 (2.70)	2 (0.82)	
No	35 (89.74)	151 (90.42)	30 (81.08)	216 (88.89)	
Yes	4 (10.26)	15 (8.98)	6 (16.22)	25 (10.29)	

Table 1. Continued

Variables	Place of management			Total (N = 243)	*P* value
	Home (n = 39)	Ward (n = 167)	ICU (n = 37)		
Type of immunosuppressant[e]					
TAC	32 (82.05)	106 (63.47)	24 (64.86)	162 (66.67)	.0831
MMF	15 (38.46)	80 (47.90)	24 (64.86)	119 (48.97)	.0627
Steroids	7 (17.95)	35 (20.96)	14 (37.84)	56 (23.05)	.0625
mTOR	5 (12.82)	27 (16.17)	5 (13.51)	37 (15.23)	.8296
CsA	1 (2.56)	23 (13.77)	5 (13.51)	29 (11.93)	.1188
Other	0 (0.00)	1 (0.60)	0 (0.00)	1 (0.41)	>.9999
Combinations of immunosuppressant					
CsA only	1 (2.56)	10 (5.99)	2 (5.41)	13 (5.35)	.8264
CsA, MMF	0 (0.00)	7 (4.19)	2 (5.41)	9 (3.70)	.3842
CsA, steroids	0 (0.00)	3 (1.80)	0 (0.00)	3 (1.23)	.9999
CsA, MMF, steroids	0 (0.00)	3 (1.80)	1 (2.70)	4 (1.65)	.5697
TAC only	12 (30.77)	36 (21.56)	6 (16.22)	54 (22.22)	.2918
TAC, MMF	12 (30.77)	35 (20.96)	5 (13.51)	52 (21.40)	.1806
TAC, mTOR	2 (5.13)	10 (5.99)	0 (0.00)	12 (4.94)	.4209
TAC, steroids, or other	6 (15.38)	16 (9.58)	5 (13.51)	27 (11.11)	.4473
TAC, MMF, mTOR	0 (0.00)	0 (0.00)	1 (2.70)	1 (0.41)	.1523
TAC, MMF, steroids[b]	0 (0.00)	9 (5.39)	6 (16.22)	15 (6.17)	.011
TAC, MMF, mTOR, steroids	0 (0.00)	0 (0.00)	1 (2.70)	1 (0.41)	.1523
MMF only	3 (7.69)	17 (10.18)	4 (10.81)	24 (9.88)	.8966
MMF, mTOR	0 (0.00)	7 (4.19)	3 (8.11)	10 (4.12)	.1712
MMF, steroids	0 (0.00)	2 (1.20)	1 (2.70)	3 (1.23)	.4484
mTOR only	2 (5.13)	9 (5.39)	0 (0.00)	11 (4.53)	.4577
mTOR, steroids	1 (2.56)	1 (0.60)	0 (0.00)	2 (0.82)	.5286
Steroids only	0 (0.00)	2 (1.20)	0 (0.00)	2 (0.82)	>.9999
Most recent values before symptoms					
White blood cells, $10^9/L$	5.1 (4.4–6.5)	5.2 (3.9–6.7)	6.0 (4.3–6.7)	5.2 (4.0–6.7)	.9274
Bilirubin, *mg/dL*	0.8 (0.5–1.0)	0.6 (0.4–1.0)	0.6 (0.5–1.0)	0.7 (0.5–1.0)	.7569
Creatinine, *mg/dL*[a,b]	1.0 (0.9–1.1)	1.1 (0.9–1.5)	1.2 (1.0–1.6)	1.1 (0.9–1.4)	.019
ALT, *U/L*	23.0 (17.0–32.0)	20.0 (15.0–31.0)	23.0 (17.0–34.0)	20.0 (16.0–32.0)	.3607

NOTE. Data are presented n (%) or median (1st–3rd quartile).
ACE, angiotensin converting enzyme; mTOR, mammalian target of rapamycin inhibitors.
[a]*P* value ward vs home ≤.05.
[b]*P* value ICU vs home ≤.05.
[c]*P* value ICU vs ward ≤.05.
[d]Plasma creatinine >2 mg/dL.
[e]Patients can be treated with >1 therapy; therefore, percentages do not sum to 100.

Thromboprophylaxis, mainly with low-molecular-weight heparin, was started on COVID-19 diagnosis in 117 patients (48.2%). Thrombotic events occurred in 7 of 204 (3.4%) hospitalized patients, comprising 3 pulmonary embolisms, 2 deep vein thromboses, and 2 strokes.

An acute liver injury was observed in 56 patients with previous persistently normal ALT levels, being in the flare range in 10 patients. Acute rejection was reported in 3 patients. Notably, CNI had been withdrawn in 2 patients, and the dose of mammalian target of rapamycin had been halved in the third patient.

Forty-nine patients (20.2%) died after a median of 13.5 days (first–third quartile, 10–23 days) from the diagnosis of COVID-19. Causes of death were respiratory failure in 39 patients (77.6%), end-stage liver disease with respiratory failure in 2, end-stage liver disease without respiratory failure in 1, hemorrhagic shock in 2, pulmonary embolism in 1, metastatic cancer in 1 septic shock in 1, and septic complication from tracheal fistula in 1. Overall Kaplan-Meier survival from the date of COVID-19 symptoms is given in Figure 3. Estimated a probability of survival was 88.2% (95% confidence interval [CI], 82.5%–92.1%) at 30 days and 84.4% (95% CI, 77.7%–89.2%) at 90 days.

Clinical Features and Outcomes of Liver Transplant Recipients With COVID-19 Treated at Home, in General Wards, and in Intensive Care Units

Baseline characteristics of patients with less severe symptoms who could be treated at home and those with more severe symptoms requiring hospitalization in general wards and ICUs are reported in Table 2. Patients treated at home were younger, had fewer comorbidities, and were

Table 2. Clinical Presentation and Course After COVID-19 Symptoms

Variable	Place of management			Total (N = 243)	*P* value
	Home (n = 39)	Ward (n = 167)	ICU (n = 37)		
Symptoms: at clinical diagnosis					
Fever >37.2°C[a]	25 (64.10)	137 (82.04)	28 (75.68)	190 (78.19)	.0468
Cough	21 (53.85)	106 (63.47)	16 (43.24)	143 (58.85)	.0609
Polypnea or dyspnea[a,b,c]	4 (10.26)	57 (34.13)	21 (56.76)	82 (33.74)	.0001
Diarrhea[a]	3 (7.69)	46 (27.54)	6 (16.22)	55 (22.63)	.0171
Anosmia and dysgeusia[a]	9 (23.08)	10 (5.99)	2 (5.41)	21 (8.64)	.0061
Muscle pain[a]	13 (33.33)	24 (14.37)	4 (10.81)	41 (16.87)	.0098
Confusion	0 (0.00)	4 (2.40)	3 (8.11)	7 (2.88)	.0969
Thoracic pain	3 (7.69)	11 (6.59)	1 (2.70)	15 (6.17)	.717
Asthenia	11 (28.21)	34 (20.36)	4 (10.81)	49 (20.16)	.1669
Other	4 (10.26)	11 (6.59)	0 (0.00)	15 (6.17)	.1591
Time between symptoms and positive test, *d* [b]	9 (3–19)	5 (2–9)	3 (0–7)	4 (2–10)	.0226
Chest x-ray or thorax CT scan					
No[a,b]	16 (41.03)	8 (4.79)	4 (10.81)	28 (11.52)	<.0001
Yes, normal[b,c]	15 (38.46)	51 (30.54)	0 (0.00)	66 (27.16)	.0002
Yes, ground-glass opacities[a,b,c]	7 (17.95)	106 (63.47)	32 (86.49)	145 (59.67)	<.0001
Yes, lobar opacities[c]	1 (2.56)	6 (3.59)	7 (18.92)	14 (5.76)	.0044
Ground-glass or lobar opacities[a,b,c]	8 (20.51)	108 (64.67)	33 (89.19)	149 (61.32)	<.0001
Respiratory support[c]					<.0001
Oxygen support	1 (50.00)	78 (79.59)	7 (18.92)	86 (62.77)	
Noninvasive ventilation	1 (50.00)	17 (17.35)	8 (21.62)	26 (18.98)	
Mechanical ventilation	0 (0.00)	3 (3.06)	22 (59.46)	25 (18.25)	
Added lung infection					
None[b,c]	39 (100.00)	154 (92.22)	25 (67.57)	218 (89.71)	<.0001
Bacterial[b]	0 (0.00)	11 (6.59)	7 (18.92)	18 (7.41)	.0064
Fungal[c]	0 (0.00)	1 (0.60)	5 (13.51)	6 (2.47)	.0011
Other	0 (0.00)	2 (1.20)	0 (0.00)	2 (0.82)	>.9999
Renal replacement therapy[b,c]	0 (0.00)	10 (5.99)	11 (29.73)	21 (8.64)	<.0001
Vasoactive drugs (NA)[b,c]	1 (2.56)	1 (0.60)	19 (51.35)	21 (8.64)	<.0001
Myocarditis	0 (0.00)	0 (0.00)	1 (2.70)	1 (0.41)	.1523
Peak laboratory values					
Bilirubin, *mg/dL*[c]	0.8 (0.5–1.1)	0.7 (0.4–1.0)	1.2 (0.8–2.7)	0.8 (0.5–1.2)	.0034
International normalized ratio[b,c]	1.1 (1.0–1.2)	1.1 (1.1–1.3)	1.3 (1.1–1.7)	1.1 (1.1–1.3)	.0039
Creatinine, *mg/dL*[b,c]	1.0 (0.9–1.6)	1.2 (0.9–1.8)	2.2 (1.2–4.0)	1.3 (0.9–2.0)	.0009
ALT, *U/L*[b,c]	28.0 (19.0–39.0)	32.0 (19.0–51.5)	59.5 (32.5–134.5)	34.0 (20.0–55.0)	.0014
COVID-19 therapy					
None[a,b]	33 (84.62)	46 (27.54)	15 (40.54)	94 (38.68)	<.0001
Lopinavir/ritonavir[a,b]	0 (0.00)	35 (20.96)	6 (16.22)	41 (16.87)	.007
Hydroxychloroquine[a,b,c]	4 (10.26)	99 (59.28)	13 (35.14)	116 (47.74)	<.0001
High-dose steroids[a,b]	0 (0.00)	26 (15.57)	8 (21.62)	34 (13.99)	.0144
Remdesevir	0 (0.00)	0 (0.00)	1 (2.70)	1 (0.41)	.1523
Tocilizumab	0 (0.00)	11 (6.59)	4 (10.81)	15 (6.17)	.0962
Azythromicin[a]	2 (5.13)	57 (34.13)	8 (21.62)	67 (27.57)	.0009
Other[b]	1 (2.56)	15 (8.98)	8 (21.62)	24 (9.88)	.0215
Immunosuppression changes					
Yes[a,b]	4 (10.26)	71 (42.51)	22 (59.46)	97 (39.92)	<.0001
Stop CNI	0 (0.00)	11 (6.59)	5 (13.51)	16 (6.58)	.0441
25%-50% reduction in CNI	2 (5.13)	28 (16.77)	8 (21.62)	38 (15.64)	.1091
Stop antimetabolites[b]	1 (2.56)	26 (15.57)	8 (21.62)	35 (14.40)	.0455
Stop mTOR inhibitors	0 (0.00)	9 (5.39)	1 (2.70)	10 (4.12)	.3305
Other	1 (2.56)	5 (2.99)	0 (0.00)	6 (2.47)	.1479

Table 2. Continued

Variable	Place of management			Total (N = 243)	*P* value
	Home (n = 39)	Ward (n = 167)	ICU (n = 37)		
Outcome[a,b,c]					<.0001
Alive	39 (100.00)	138 (82.63)	17 (45.95)	194 (79.84)	
Dead	0 (0.00)	29 (17.37)	20 (54.05)	49 (20.16)	
Time between symptoms and last follow-up, *d* [b,c]	70 (48–88)	66 (42–88)	29 (17–75)	65 (35–87)	.007
Missing	3 (7.69)	1 (0.60)	2 (5.41)	6 (2.47)	
Cause of death					
Refractory pneumonia		23 (79.31)	15 (75.00)	38 (77.55)	.7405
Liver-related death					
Without lung failure		1 (3.45)	0 (0.00)	1 (2.04)	>.9999
With lung failure		2 (6.90)	1 (5.00)	3 (6.12)	>.9999
Other		3 (10.34)	4 (20.00)	7 (14.29)	.4221
Heparin[a,b]					<.0001
Missing	13 (33.33)	20 (11.98)	6 (16.22)	39 (16.05)	
No	24 (61.54)	53 (31.74)	10 (27.03)	87 (35.80)	
Yes	2 (5.13)	94 (56.29)	21 (56.76)	117 (48.15)	
Average CNI level pre–COVID-19					.0235
No CNI	4 (10.26)	5 (2.99)	1 (2.70)	10 (4.12)	
CsA ≤50 ng/L	1 (2.56)	6 (3.59)	4 (10.81)	11 (4.53)	
CsA 50–100 ng/L	1 (2.56)	2 (1.20)	0 (0.00)	3 (1.23)	
CsA >100 ng/L	0 (0.00)	35 (20.96)	6 (16.22)	41 (16.87)	
TAC ≤4 ng/mL	3 (7.69)	22 (13.17)	6 (16.22)	31 (12.76)	
TAC 4–6 ng/mL	10 (25.64)	25 (14.97)	6 (16.22)	41 (16.87)	
TAC >6 ng/mL	6 (15.38)	25 (14.97)	6 (16.22)	37 (15.23)	

NOTE. Data are presented n (%) or median (1st–3rd quartile).
CT, computed tomography; mTOR, mammalian target of rapamycin; NA, noradrenaline.
[a]*P* value ward vs home ≤.05
[b]*P* value ICU vs home ≤.05
[c]*P* value ICU vs ward ≤.05

more frequently receiving TAC as the primary immunosuppressant. Kaplan-Meier survival after stratification by place of management, at home, general ward, or ICU is provided in Figure 3. Patients managed at home survived, whereas the probability of survival at 30 days was 93.1% (95% CI, 86.7%–96.5%) and 57.0% (95% CI, 37.6%–72.4%), respectively, for patients in ward and in ICUs, and it declined to 89.8% (95% CI, 82.1%–94.3%) and 46.6% (95% CI, 26.2%–64.6%) at 90 days. Notably, 12 patients with advanced COVID-19 disease were not admitted to an ICU, 8 because they were deemed too sick for the ICU due to a combination of advanced age and severe comorbidities and 4 because ICUs were overwhelmed.

Factors Associated With Death

Factors by univariable analysis significantly associated with death were increased age of the recipient, time from LT, diabetes, chronic kidney disease, number of comorbidities, and use of TAC (Table 3). After multivariable analysis, advanced age (>70 vs <60 years) remained independently associated with an increased mortality risk (hazard ratio, 4.16; 95% CI, 1.78–9.73), whereas use of TAC was confirmed independently associated with a reduced mortality risk (hazard ratio, 0.55; 95% CI, 0.31–0.99). The Kaplan-Meier survival curves stratified by age (>70 or <70) and type of immunosuppressant (TAC vs non-TAC) may be helpful for the clinician to better understand the individual risk (Supplementary Figure 1).

Because the number of comorbidities increased with the increasing age of the recipient, a second model excluding age was constructed. This allowed diabetes and chronic renal failure to emerge as predictors of mortality, their effect having been shadowed in the first model by the dominant effect of age (Supplementary Table 1).

The interplay among age of the recipient, primary immunosuppressant, and chronic renal failure is summarized in Supplementary Table 2 and Supplementary Figure 2, where the negative impact of chronic kidney disease is dramatically evident in recipients not maintained on TAC. Finally, in Supplementary Table 3, patients receiving TAC-based vs non–TAC-based regimens are compared with respect to some relevant clinical variables such as age, time from transplant, chronic renal failure, concurrent exposure to angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and presence of hepatocellular carcinoma. In fact, patients receiving TAC were younger and had fewer comorbidities, these variables being potentially associated

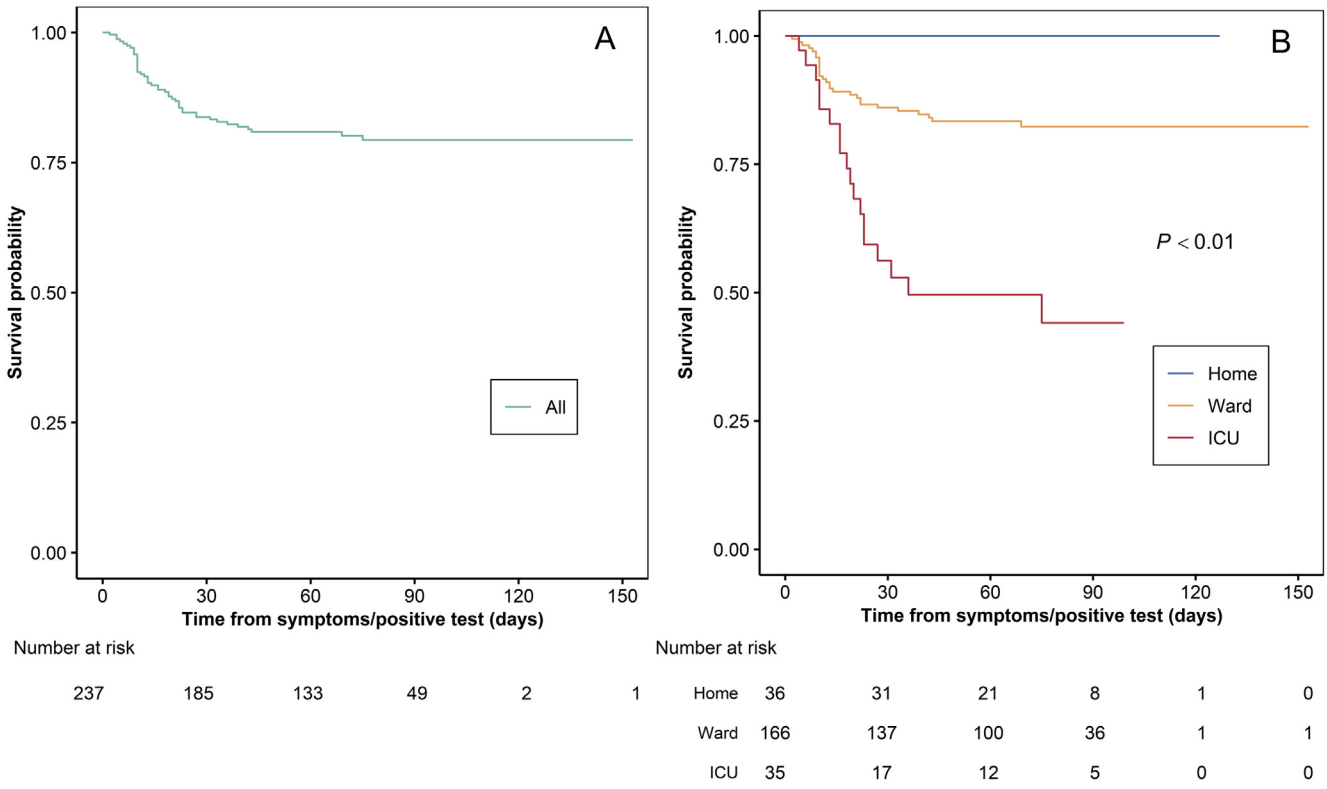

Figure 3. Kaplan-Meier survival curve from the date of COVID-19 symptoms (*A*) overall and (*B*) stratified by place of management.

with a better outcome. Conversely patients on TAC were much less frequently treated with angiotensin-converting enzyme or angiotensin receptor blocker inhibitors, this therapy being associated with a better outcome. All these variables were included in the multivariable analysis that confirmed the independent protective role of TAC.

Discussion

As more than 200 countries worldwide are still struggling with the COVID-19 pandemic, all solid-organ transplant recipients are at risk of infection and poor outcome due to chronic immunosuppression, high rates of comorbidities, advanced age, and frequent hospitalization. We have analyzed the characteristics, management, and outcome of a large multinational European cohort of LT recipients with symptomatic SARS-CoV-2 infection.

Rates of hospitalization and death in the current study were 85% and 20.2%, confirming what we already showed in our preliminary report on the first 103 patients,[7] where some patients were still experiencing their disease course. These findings concur with the 23% mortality risk reported by Webb et al,[6] but compare unfavorably with the 12% mortality risk observed by Becchetti et al,[9] possibly due to the lower percentage of patients requiring hospitalization in this latter study. Our study confirmed that abdominal symptoms and, more specifically, diarrhea are at least twice more frequent than in the general population[9] and are possibly associated to MMF. This hypothesis is supported by the fact that almost 50% of the 26 patients maintained on MMF as the primary immunosuppressant had diarrhea as presenting symptom. Clinicians should therefore be vigilant and consider SARS-CoV-2 testing in transplant recipients presenting with diarrhea, particularly if using MMF.

However, the main finding of the present study is the significant variation in mortality risk with both age of the recipients and use of TAC as immunosuppressant. The role of advanced age confirms what has been extensively observed in the general population, with patients older than 70 having an increased 4-fold mortality risk.[11-14] The lower risk of death for patients maintained on TAC was unexpected and to our knowledge has not been previously reported. In particular Becchetti et al[9] could not explore this association in their prospective cohort of 57 LT recipients with COVID-19 because the great majority of their patients were receiving TAC. Notably, in our analysis, the beneficial impact of TAC was robust and persisted after controlling for various confounders. The biological explanation of the potential favorable role of TAC is unknown but may be dual: inhibition of viral replication and interaction with the immune response. Some studies have shown that CoV replication, depends on active immunophilin pathways and that TAC is capable of strongly inhibiting the growth of some human CoV, notably SARS CoV-1, probably by binding the immunophilin FK506-binding proteins, although not specifically SARS-CoV-2.[10,15,16]

Another potential driver of the TAC protective effect could be related to the immunosuppressive property of this

Table 3. Results From Univariate and Multivariate Analysis of Predictors of Mortality, From Cox's Proportional Hazard Regression Models

	Univariate models		Multivariate models	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age				
Linear (1-year increase)	**1.06 (1.03–1.10)**	**<.0001**		
60–70 vs ≤60 years	**2.58 (1.12–5.94)**	**.0255**	2.20 (0.94–5.13)	.068
>70 vs ≤60 years	**5.49 (2.42–12.48)**	**<.0001**	**4.16 (1.78–9.73)**	**.001**
Sex (male vs female)	1.39 (0.71–2.73)	.3438		
Indication for LT				
Decompensated cirrhosis	1.11 (0.61–2.00)	.736		
Hepatocellular carcinoma	1.25 (0.67–2.34)	.4846		
Other	0.63 (0.25–1.61)	.3362		
Time between LT and COVID-19 symptoms (1-year increase)	**1.05 (1.01–1.09)**	**.0054**		
Body mass index (1-unit increase)	1.00 (0.94–1.07)	.9936		
Comorbidities				
Diabetes	**1.98 (1.11–3.54)**	**.0212**		
Hypertension	1.76 (0.98–3.17)	.0584		
Chronic lung disease	0.55 (0.17–1.76)	.3126		
Chronic kidney disease[a]	**2.20 (1.19–4.08)**	**.0123**	1.72 (0.92–3.22)	.0912
Coronary artery disease	1.37 (0.49–3.81)	.5518		
Other	1.71 (0.89–3.31)	.1095		
Comorbidities, n				
1 vs 0	**3.54 (1.02–12.33)**	**.0468**		
≥2 vs 0	**5.63 (1.72–18.50)**	**.0044**		
Smoking (yes vs no)	1.62 (0.72–3.63)	.241		
Type of immunosuppressant				
CsA vs all other	**2.29 (1.13–4.60)**	**.0209**		
TAC vs all other	**0.43 (0.24–0.77)**	**.0042**	**0.55 (0.31–0.99)**	**.0472**
MMF vs all other	1.30 (0.73–2.33)	.3704		
mTOR inhibitors vs all other	1.37 (0.66–2.84)	.3969		
Treatment with ACE inhibitors or angiotensin II receptor antagonists (yes vs no)	**1.92 (1.06–3.49)**	**.0328**		
Country				
Spain vs Other	1.52 (0.67–3.48)	.3178		
Italy vs Other	1.34 (0.54–3.34)	.5253		
France vs Other	1.48 (0.55–3.94)	.4355		
Center recruiting more than 9 patients vs other centers	1.47 (0.82–2.65)	.1993		

NOTE. Bold values are statistically significant ($P < .05$).
ACE, angiotensin converting enzyme; CT, computed tomography; HR, hazard ratio; mTOR, mammalian target of rapamycin.
[a]Plasma creatinine >2 mg/dL.

CNI.[17] By inhibiting calcineurin and suppressing the early phase of T-cell activation, TAC reduces the production of many cytokines, notably proinflammatory cytokines, as tumor necrosis factor-α and interferon-γ, and possibly mitigates the cytokine storm that characterizes stage III COVID-19. Interestingly, this background recently prompted a group of Spanish investigators to test the effect of TAC in combination with steroids in the management of COVID-19 occurring in immunocompetent individuals (clinicaltrials.gov/ct2/show/NCT04341038). While waiting for studies on larger cohorts of transplant recipients that would allow a more precise estimate of the protective effect of TAC, reducing or withdrawing the doses of TAC during COVID-19 should be discouraged, if not indicated for other clinical reasons.

The role of comorbidities as relevant risk factors for mortality has been clearly demonstrated in the general population with COVID-19.[18] Despite being highly prevalent among LT recipients,[19] neither a specific comorbidity nor a combination of comorbidities emerged as independently associated with outcome. This is at least partly explained by the dominant effect of age as comorbidities

Table 4. European Liver Transplantation Association/ European Liver Transplant Registry COVID-19 Registry for Liver Transplant Candidates and Recipients: Collaborators With Affiliations

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Table 4. Continued

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increased with the increasing age of the recipients. Nevertheless, in our exploratory analysis, chronic renal failure, defined by a serum creatinine >2 mg/dL, maintained a trend of significance ($P < .1$) even if shadowed by the dominant effect of increasing age. Notably, the negative impact of renal failure on survival was particularly relevant in patients who were not receiving TAC, once again pointing to its possible protective role against COVID-19, at least in LT recipients.

Finally, therapy for COVID-19 differed across centers and countries and varied over time with the increasing knowledge in treating this new disease. Because large prospective randomized trials have recently demonstrated that corticosteroids and remdesivir are effective in severe cases, whereas hydroxychloroquine and lopinavir-ritonavir are not, new patients should be treated accordingly.[20,21]

This study has some strengths. It is, at the time of writing, the largest cohort of consecutive transplant recipients affected by COVID-19 with a relatively long median follow-up of approximately 2 months. It focuses only on symptomatic patients and analyzes the role of clinical features at admission and diagnosis on mortality risk. The quality of the data was guaranteed by maintaining constant communications with the contributing centers. Finally, the international multicentered pattern of the study copes with any individual center effect.

Some limitations are also to be acknowledged. Firstly, although we attempted to collect data on major covariables, there remains the possibility of missing confounders. Secondly, we focused on symptomatic patients with confirmed positive SARS-CoV-2 RT-PCR test despite test sensitivity <80%. Thus, some patients were excluded.

Conclusion

This study, including more than 240 LT recipients, confirmed that 25% of patients requiring hospitalization for COVID-19 died, the mortality risk being greater in patients aged older than 70 and with medical comorbidities such as impaired renal function and diabetes. Conversely, the use of TAC was associated with an increased survival probability. Although the biological explanation of this latter finding is currently unknown, our preliminary evidence should encourage clinicians to keep TAC at the usual dose because it may be beneficial when treating COVID-19. A more precise estimate of the protective effect of TAC requires studies on larger cohorts of transplant recipients.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2020.11.045.

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CRediT Authorship Contributions
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Conflicts of interest
The authors disclose no conflicts.

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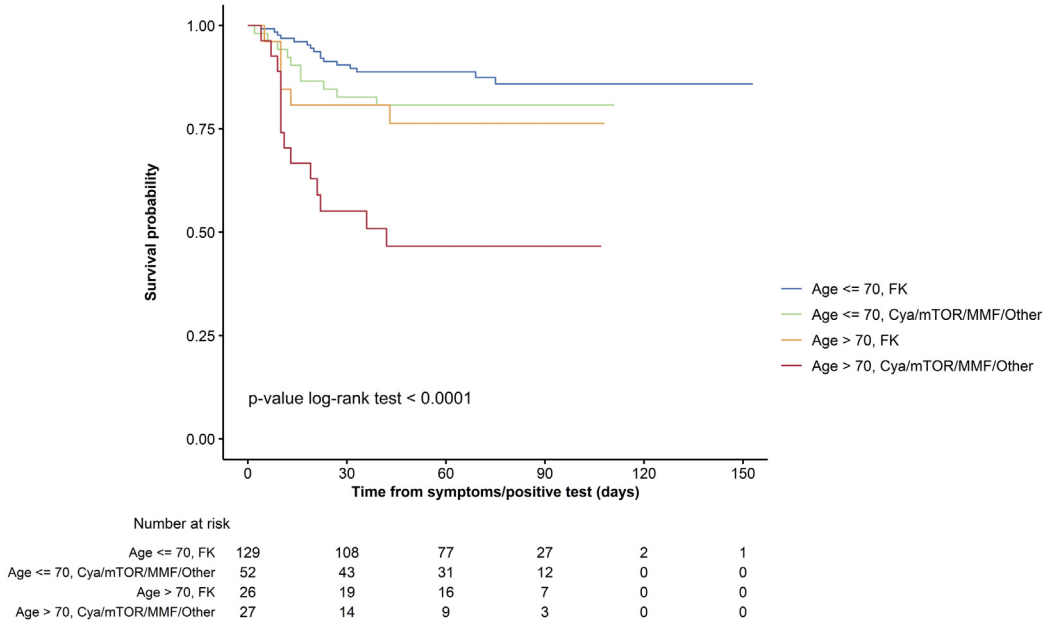
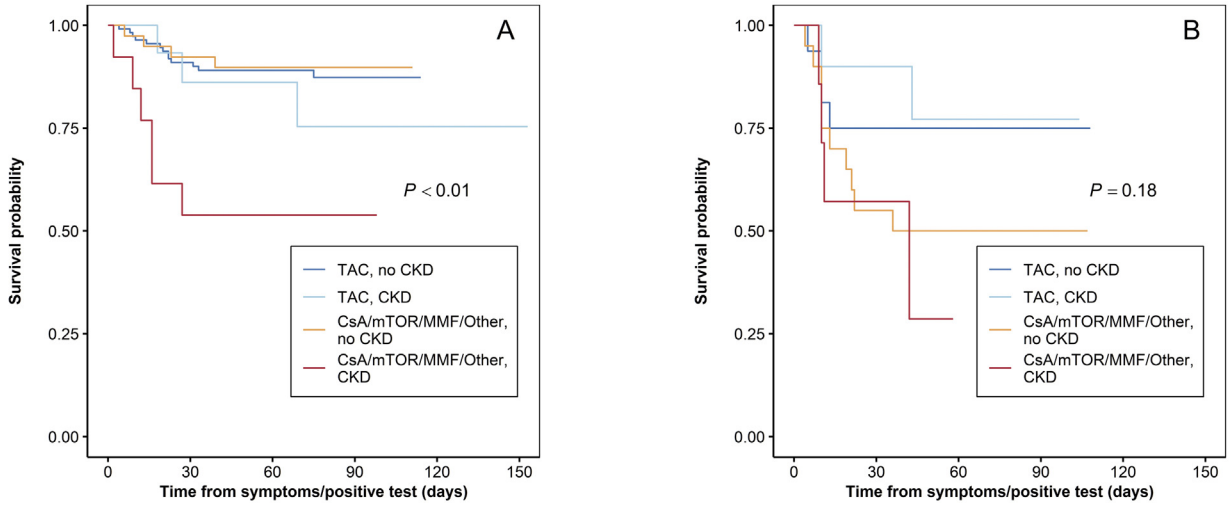


Number at risk

Age <= 70, FK	129	108	77	27	2	1
Age <= 70, Cya/mTOR/MMF/Other	52	43	31	12	0	0
Age > 70, FK	26	19	16	7	0	0
Age > 70, Cya/mTOR/MMF/Other	27	14	9	3	0	0

Supplementary Figure 1. Kaplan-Meier curves for survival from the date of COVID-19 diagnosis, stratified by age (2 categories) and main immunosuppressant. Cya, cyclosporin A; FK, tacrolimus; mTOR, mammalian target of rapamycin.



Number at risk

TAC, no CKD	113	96	68	25	0	0
TAC, CKD	16	12	9	2	2	1
CsA/mTOR/MMF/Other, no CKD	39	36	26	11	0	0
CsA/mTOR/MMF/Other, CKD	13	7	5	1	0	0

Number at risk

TAC, no CKD	16	11	11	5	0	0
TAC, CKD	10	8	5	2	0	0
CsA/mTOR/MMF/Other, no CKD	20	11	9	3	0	0
CsA/mTOR/MMF/Other, CKD	7	3	0	0	0	0

Supplementary Figure 2. Kaplan-Meyer curves for survival from the date of COVID-19 diagnosis show the interplay between age of the recipient, primary immunosuppressant, and chronic renal failure (CRF). mTOR, mammalian target of rapamycin.

Supplementary Table 1. Results From Multivariate Analysis of Predictors of Mortality, From Cox's Proportional Hazard Regression Models, Excluding Age From the Predictors

Variable	HR (95% CI)	*P* value
Comorbidities		
Diabetes	1.95 (1.06–3.58)	.0313
Chronic kidney disease[a]	1.97 (1.05–3.67)	.0336
Other	1.92 (0.97–3.82)	.0608
Main immunosuppressant (TAC vs CsA/mTOR/MMF)	0.52 (0.29–0.95)	.0325

NOTE. Predictors with a *P* value $\leq$.1 were retained in the model. Bold values are statistically significant ($P < .05$).
HR, hazard ratio; mTOR, mammalian target of rapamycin inhibitor.
[a]Plasma creatinine >2 mg/dL.

Supplementary Table 2. Estimated Probability of Survival 50 Days After the Symptoms, Stratified by Age (2 Categories), Main Immunosuppressant and Chronic Kidney Disease

Age	Main Immunosuppressant	Chronic kidney disease[a]	Patients (n)	Probability of survival at 50 days (95% CI)
≤ 70 y	TAC	No	113	0.89 (0.82–0.94)
		Yes	16	0.86 (0.55–0.96)
	CsA/mTOR/MMF/other	No	39	0.90 (0.75–0.96)
		Yes	13	0.54 (0.25–0.76)
>70 y	TAC	No	16	0.75 (0.46–0.90)
		Yes	10	0.77 (0.34–0.94)
	CsA/mTOR/MMF/other	No	20	0.50 (0.27–0.69)
		Yes	7	0.29 (0.01–0.69)

NOTE. Estimates are based on Kaplan-Meier curves.
mTOR, mammalian target of rapamycin inhibitor
[a]Plasma creatinine >2 mg/dL.

Supplementary Table 3. Baseline Characteristics of the Study Population, Stratified by Type of Calcineurin Inhibitor

Variables	Immunosuppressant			
	CsA/other (n = 81)	TAC (n = 162)	Total (N = 243)	*P* value
Male sex	66 (81.48)	105 (64.81)	171 (70.37)	.0073
Age at symptoms, *y*	68 (60.5–73.5)	61 (53.0–68.0)	63 (55.0–69.0)	
Location of patient at occurrence of symptoms				.4631
Home	74 (91.36)	143 (88.27)	217 (89.30)	
Hospital	7 (8.64)	19 (11.73)	26 (10.70)	
Place of management				.0831
Home	7 (8.64)	32 (19.75)	39 (16.05)	
Ward	61 (75.31)	106 (65.43)	167 (68.72)	
ICU	13 (16.05)	24 (14.81)	37 (15.23)	
Time between last LT and COVID-19 symptoms, *y*	12 (6.2–18.9)	7 (2.0–13.3)	8 (3.1–15.0)	
Missing	1 (1.23)	5 (3.09)	6 (2.47)	
Indication for LT				
Decompensated cirrhosis	51 (62.96)	90 (55.56)	141 (58.02)	.27
Hepatocellular carcinoma	21 (25.93)	42 (25.93)	63 (25.93)	>.9999
Other	9 (11.11)	31 (19.14)	40 (16.46)	.1118
Body mass index, kg/m^2	26.3 (23.5–29.7)	25.7 (23.4–29.4)	25.9 (23.4–29.4)	.6612
Chronic kidney disease[a]	22 (27.16)	27 (16.67)	49 (20.16)	.0546
Coronary artery disease	3 (3.70)	14 (8.64)	17 (7.00)	.1548
Comorbidities, n				.0003
0	11 (13.58)	46 (28.40)	57 (23.46)	
1	20 (24.69)	59 (36.42)	79 (32.51)	
≥2	50 (61.73)	57 (35.19)	107 (44.03)	
Drugs				
β-Blockers	20 (24.69)	30 (18.52)	50 (20.58)	.2618
ACE inhibitors or angiotensin II receptor antagonists	33 (40.74)	26 (16.05)	59 (24.28)	<.0001
Type of immunosuppressant				
CsA	29 (35.80)	0 (0.00)	29 (11.93)	<.0001
TAC	0 (0.00)	162 (100.00)	162 (66.67)	<.0001
MMF	50 (61.73)	69 (42.59)	119 (48.97)	.0049
mTOR inhibitor	23 (28.40)	14 (8.64)	37 (15.23)	<.0001
Steroids	14 (17.28)	42 (25.93)	56 (23.05)	.1316
Other	0 (0.00)	1 (0.62)	1 (0.41)	>.9999
Outcome				.0033
Alive	56 (69.14)	138 (85.19)	194 (79.84)	
Dead	25 (30.86)	24 (14.81)	49 (20.16)	
Time between symptoms and last follow-up, *d*	60 (23–83)	66 (39–87)	65 (35–87)	.127
Missing	1 (1.23)	5 (3.09)	6 (2.47)	
Cause of death				
Refractory pneumonia	21 (84.00)	17 (70.83)	38 (77.55)	.2695
Liver-related death				
Without lung failure	0 (0.00)	1 (4.17)	1 (2.04)	.4898
With lung failure	2 (8.00)	1 (4.17)	3 (6.12)	>.9999
Other	2 (8.00)	5 (20.83)	7 (14.29)	.2467

NOTE. Data are presented n (%) or median (1st–3rd quartile).
mTOR, mammalian target of rapamycin.
[a]Plasma creatinine >2 mg/dL.