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ORIGINAL ARTICLE

COVID-19 in lung transplant recipients: A multicenter study

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This study describes the clinical presentation, treatment, and outcomes of SARS-CoV-2 infection in lung transplant recipients (LTRs). This is a multicenter, retrospective study of all adult LTRs with confirmed SARS-CoV-2 infection from March 4 until April 28, 2020 in six Spanish reference hospitals for lung transplantation. Clinical and radiological data, treatment characteristics, and outcomes were reviewed. Forty-four cases were identified in that period. The median time from transplantation was 4.2 (interquartile range: 1.11–7.3) years. Chest radiography showed acute parenchymal abnormalities in 32 (73%) cases. Hydroxychloroquine was prescribed in 41 (93%), lopinavir/ritonavir (LPV/r) in 14 (32%), and tocilizumab in 19 (43%) patients. There was a strong interaction between tacrolimus and LPV/r in all cases. Thirty-seven (84%) patients required some degree of respiratory support and/or oxygen therapy, and 13 (30%) were admitted to intermediate or intensive critical care units. Seventeen (39%) patients had died and 20 (45%) had been discharged at the time of the last follow-up. Deceased patients had a worse respiratory status and chest X-ray on admission and presented with higher D-dimer, interleukin-6, and lactate dehydrogenase levels. In this multicenter LTR cohort, SARS-CoV-2 presented with high mortality. Additionally, the severity of disease on presentation predicted subsequent mortality.

KEYWORDS

clinical research / practice, critical care / intensive care management, drug toxicity, infection and infectious agents - viral, infectious disease, lung disease: infectious, lung transplantation / pulmonology

Abbreviations: AR, acute rejection; CARVs, community-acquired respiratory viruses; CLAD, chronic lung allograft dysfunction; CMV, cytomegalovirus; ICU, intensive care unit; IF β , interferon beta; IgG, immunoglobulin G; IL-6, interleukin-6; LPV/r, lopinavir/ritonavir; LTR, lung transplant recipients; RT-PCR, real-time reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; SOT, solid organ transplant.

1 | INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak has been declared a pandemic due to the high number of cases worldwide. In the World Health Organization report of May 11, 2020, there were more than 4 million confirmed cases of SARS-CoV-2 infection and more than 279,000 deaths.¹ Three stages of the disease have been described: initial early infection, followed by pulmonary involvement, and finally systemic hyperinflammation.² Around 5%–14% of patients develop respiratory failure, and some also develop acute respiratory distress syndrome, multiorgan failure, and death.^{2–5}

The published evidence regarding coronavirus disease 2019 (COVID-19) in solid organ transplant (SOT) recipients is limited to case reports and preliminary data.^{6–15} Lung transplant recipients (LTRs) have the highest risk of community-acquired respiratory viral infections.¹⁶ However, data on COVID-19 in LTRs are scarce.^{9,11,17}

The aim of this study was to analyze the clinical presentation, treatment, and outcomes of COVID-19 in LTRs.

2 | MATERIAL AND METHODS

We conducted a multicenter, retrospective study of all adult LTRs with confirmed SARS-CoV-2 infection from March 4, 2020 when the first national case was diagnosed until the end of the study period on April 28, 2020 in six Spanish hospitals with lung transplantation units that performed a total of 371 lung transplants in 2019. At the end of the study period, there were a total of 2400 LTRs living in Spain (data from the National Transplant Organization Registry). No COVID-19 screening was performed in the stable asymptomatic LTR population. Diagnostic polymerase chain reaction (PCR) was performed in all patients with LTR who presented with symptoms suggestive of COVID-19. All LTRs with confirmed SARS-CoV-2 infection were included in the study. Due to the uncertainties in the clinical course of COVID-19, all but one patient were hospitalized, regardless of their clinical status at presentation, to guarantee close monitoring of their progression. Electronic health records were reviewed for clinical and radiological data, treatment characteristics, immunosuppression management, and outcomes in LTRs. Medical records were reviewed according to a preestablished protocol, and data were entered into a specific database.

The Clinical Research Ethics Committee approved the study (PR(AG)259/2018).

2.1 | Microbiological procedures

Symptomatic LTRs were tested for SARS-CoV-2 infection. In all patients, nasopharyngeal and oropharyngeal swabs were performed by trained medical staff. The presence of SARS-CoV-2 in these swabs was determined using real-time reverse transcription PCR (RT-PCR). We used a commercial CE-IVD-marked, RT-PCR-based assay (Cobas SARS-CoV-2; Roche Diagnostics), on a Cobas 6800 system. Bacterial

and fungal cultures were performed in patients with sputum production and endotracheal aspirates in mechanically ventilated patients. Some patients had access to nonquantitative ELISA assessment of anti-SARS-CoV-2 antibodies 3 weeks after the onset of symptoms.

Treatment was based on the Spanish Ministry of Health guidelines for the general population¹⁸ and adapted to the LTR population. All centers had access to all medications proposed at that time in international publications for the treatment of COVID-19. As a whole, the following management was proposed: in patients without pneumonia, hydroxychloroquine was used with a loading dose of 400 mg twice daily on the first day and 200 mg twice daily for days 2–5. In these cases, mycophenolate mofetil or rapamycin was stopped and tacrolimus doses were adjusted to a trough level of 5 ng/mL. In patients with pneumonia, in addition to hydroxychloroquine at the same dosages, azithromycin (500 mg, once daily for 5 days) was added. Some centers considered using additional antiviral treatment, lopinavir/ritonavir (LPV/r) 400/100 mg twice daily for 7 days or darunavir/cobicistat 800/150 mg daily for 7 days. Immunosuppressive therapy was modified following the protocol described above. In all cases, the corrected QT interval with Bazett's formula was measured at baseline, due to the risk of QT interval prolongation with hydroxychloroquine and azithromycin therapy.

Tocilizumab, an interleukin (IL)-6 inhibitor, was used in cases of respiratory failure (peripheral oxygen saturation/fraction of inspired oxygen <300) with IL-6 levels higher than 40 pg/mL, following the institutional recommendation in that moment.¹⁸ This drug was prescribed as a single dose of 400 mg in patients weighing less than 75 kg or 600 mg in patients weighing >75 kg.

Interferon beta (IF β) was used as a second-line treatment in patients with persistent respiratory failure.

2.2 | Statistical analysis

In order to describe qualitative variables, absolute frequencies and percentages are used. The description of quantitative variables is performed using the mean, standard deviation (SD), median, and quartiles. The Kolmogorov–Smirnov test was used to assess the normality of distributions.

In the case of quantitative variables, the Student *t* test (Mann–Whitney *U* test if normality was not met) was performed. The chi-squared test (Fisher's exact test for frequencies <5) was used to compare categorical variables. For all tests, *p*-values <0.05 were considered statistically significant. Statistical analyses were performed using STATA version 14 (StataCorp, College Station, TX).

3 | RESULTS

As of April 28, 2020, 44 cases of COVID-19 in LTRs had been diagnosed in the participant centers. All but one patient was hospitalized for follow-up regardless of their clinical situation. The median time from transplantation was 4.2 (interquartile range: 1.11–7.3) years.

Demographic and clinical characteristics at baseline are shown in Table 1. All patients were diagnosed following PCR of the nasopharyngeal swab, which in most cases was positive at the first attempt; only four (9.1%) patients required a second test. Table 2 shows the clinical presentation and complementary test results. The most frequent presenting symptoms were fever in 34 (77%) patients, and dyspnea and cough in 26 (59%) patients. Twelve (27.3%) of patients presented with diarrhea. At admission, six (14%) patients presented with respiratory failure, although the median oxygen saturation in the cohort was 95% (interquartile range, 92%–97%). Chest X-ray at diagnosis revealed acute parenchymal abnormalities in 32 (73%) cases, with predominant bilateral infiltrates.

Regarding medical treatment (Table 3), 39 (88.6%) patients had already received azithromycin on an outpatient basis. Hydroxychloroquine was prescribed in 93% of patients, with no adverse events attributable to that treatment. LPV/r was the most commonly used antiviral therapy (14 patients, 31.8%), and led to an increase over the upper limit of the tacrolimus level in 10 patients (71.4%) despite lowering the dose and even stopping tacrolimus therapy. Both hydroxychloroquine and protease inhibitors were prescribed immediately after diagnosis, a few hours after admission. Tocilizumab was used in 19 patients (43.2%) with respiratory failure who fulfilled the tocilizumab treatment criteria. Thirty-four (77.3%) patients received thromboprophylaxis with low molecular weight heparin, and 10 (22.7%) received full anticoagulation treatment.

Thirty-seven (84%) patients required some degree of respiratory support, from isolated supplemental oxygen therapy to ventilatory support in its different modalities (Table 3). Specifically, 20 (45.6%) patient received supplemental oxygen therapy with the highest FiO_2 of 0.4, 10 (22.8%) were treated with different continuous positive airway pressure devices with supplemental oxygen at a maximum FiO_2 of 1, four (9.1%) received noninvasive mechanical ventilation, and three (6.8%) received invasive mechanical ventilation.

Thirteen (30%) patients had to be admitted to intermediate or intensive critical care units, where invasive mechanical ventilation was applied in 3 (6.8%) patients. No patients received extracorporeal membrane support. The most frequent associated complication was acute kidney injury (AKI).¹⁹ This was present in 29 (67.4%) patients, with a median estimated glomerular filtration rate (eGFR) of 40 (19–65) mL/min/m². AKI was associated with high tacrolimus levels (>15 ng/mL) in 60% of patients. Ten (71%) of the patients treated with LPV/r developed related AKI, with a mean eGFR of 16 (4–33) mL/min/m². Tacrolimus levels in this subgroup rose to a mean peak value of 28.5 (5.8–60) ng/mL. Regarding cardiovascular complications, five (11.4%) patients developed cardiac failure,²⁰ which was mild in all but one who had a history of dilated cardiomyopathy. Pulmonary embolism was suspected and confirmed in one patient who recovered well. One patient was diagnosed with noncomplicated lower extremity deep vein thrombosis. No treatment changes were necessary due to changes in the QT interval.

Seven patients developed cytomegalovirus (CMV) replication during hospitalization requiring antiviral treatment, without CMV

organ disease. Three weeks after diagnosis, antibodies against anti-SARS-CoV-2 were assessed in five patients. In four of them, high-specific SARS-CoV-2 immunoglobulin G (IgG) levels were found.

As of April 28, 17 out of the 44 (38.6%) patients had died and 20 out of 44 (45.4%) had been discharged. All deaths were due to COVID-19, but one was attributed to acute rejection (AR). Among the 13 patients admitted to intermediate or intensive critical care units, seven died, two were discharged, and four were still hospitalized at the time of data collection. Two out of the three patients treated with invasive mechanical ventilation died, while the other remained in the intensive care unit (ICU).

Regarding baseline characteristics, patients who died only differed from those who were discharged in baseline FEV1 (Table 1). Patients who died were more likely to have dyspnea, lower oxygen saturation, and worse chest X-ray at admission than those of the discharged group. They also expressed an increase in different biomarkers related to poor prognosis, specifically D-dimer, IL-6, and lactate dehydrogenase (Table 2, Figure 1A,B).

Due to the pandemic situation, bronchoscopy procedures were limited, and bronchial biopsies were not performed in any patient. However, a high clinical suspicion of AR was present in one patient who experienced a relapse after overcoming COVID-19. Specifically, acute severe respiratory failure and new lung infiltrates reappeared on the day he was discharged. Tacrolimus levels under 5 ng/mL, and even undetectable levels in one test, had been identified in the previous 4 days due to troublesome dose adjustment related to LPV/r treatment. Empiric treatment with three doses of methylprednisolone 10 mg/kg was administered, which led to temporary but not decisive improvement, and the patient finally died 29 days after the onset of symptoms.

4 | DISCUSSION

We report a cohort of 44 LTRs diagnosed with COVID-19 admitted to hospital: up to 14% presented with respiratory failure at admission and 84% needed respiratory support during hospitalization. The majority of patients were treated with hydroxychloroquine; protease inhibitors and tocilizumab were also administered in some cases, while remdesivir was not used as it was not available in Spain during the study period. At the time of follow-up, 39% of patients had died. Compared to the discharged patients, those with similar characteristics at baseline had a worse respiratory status at admission and blood markers of poor prognosis.

Community-acquired respiratory viruses (CARVs) are recognized as a major cause of morbidity and mortality in SOT, especially in LTRs.¹⁶ SARS-CoV-2, like other CARVs, causes a variety of direct effects on the LTR allograft with nonspecific clinical presentation. In our cohort, patients mostly presented with fever, dyspnea, and cough, but not classical viral upper respiratory tract symptoms.¹⁶ Two thirds had acute parenchymal abnormalities on chest radiography, mostly described as bilateral diffuse infiltrates. Compared to previously described hospitalized patients from the

TABLE 1 Demographic and baseline characteristics

Demographic characteristics	All (n 44)	Deceased (n = 17)	Discharged (n = 20)	Persistently admitted (n = 7)
Age, years, median (p25-75)	62.8 (56.4, 67.8)	62.9 (60.2, 67.1)	62.0 (55.2, 69.5)	65.9 (49.7, 67.7)
Sex, men, n (%)	26 (59.1)	12 (60)	10 (59)	4 (57)
Type of transplantation, double, n (%)	26 (59.1)	13 (76.5)	8 (40)	5 (71.4)
Lung disease, n (%)				
ILD	23 (54.9)	11 (64.7)	9 (45)	4 (57.1)
COPD	10 (23.8)	4 (23.6)	6 (30)	1 (14.3)
PH	5 (11.9)	2 (11.7)	1 (5)	0
CF/BE	2 (4.7)	0	2 (10)	2 (28.6)
LAM	2 (4.7)	0	2 (10)	0
CLAD, n (%)				
No	27 (61.4)	9 (52.9)	13 (65)	5 (71.4)
BOS	16 (36.3)	7 (41.2)	7 (35)	2 (28.6)
RAS	1 (2.3)	1 (5.9)	0	0
Lung function before infection				
FVC, ml, median (p25-75)	2300 (1800, 3080)	2020 (1620, 2400)	2605 (1990, 3095)	2625 (1800, 3910)
FEV1, ml, mean (SD)*	1751.2 (708)	1441 (473)	1922 (717)	1957 (987)
FEV1/FVC, %, median (p25-75)	70 (60, 78)	70 (59, 79)	69.5 (61, 76)	77.5 (56, 89)
% of FVC compared to posttransplant baseline	86 (81.2, 95.1)	85 (79.5, 90)	89.5 (82, 95.8)	86 (81.3, 93)
% of FEV1 compared to posttransplant baseline	84.5 (71.9, 92.5)	77 (69, 93)	86 (78, 91.5)	71 (61, 100)
Comorbidities, n (%)				
Chronic bronchial infection	15 (34.1)	5 (29.4) ^α	7 (35) ^β	3 (42.8) ^Ω
Diabetes mellitus	18 (40.9)	9 (53)	6 (30)	3 (42.9)
Arterial Hypertension	21 (47.7)	9 (53)	9 (45)	3 (42.9)
Dyslipidemia	24 (54.6)	10 (58.8)	10 (50)	4 (57.1)
Chronic kidney failure	25 (56.7)	10 (58.8)	12 (60)	3 (42.9)
GF, mL/min/m ² , mean (SD)	57.4 (24.9)	55.5 (26)	56.4 (25)	64.9 (25)
BMI, mean (SD)	25.8 (3.7)	26.6 (2.4)	24.8 (4.4)	27 (3.4)
Ischemic heart disease	2 (4.6)	0	1 (5)	1 (14.3)
Cerebrovascular disease	2 (4.6)	1 (5.9)	1 (5)	0
Malignancy	5 (11.4)	1 (5.9)	3 (15)	1 (14.3)
Thromboembolic disease	7 (15.9)	4 (23.5)	2 (10)	1 (14.3)
HBV	1 (2.3)	1 (5.9)	0	0
Myopathy	3 (6.8)	1 (5.9)	0	2 (28.6)
Previous treatment, n (%)				
Calcineurin inhibitors	43 (97.7)	17 (100)	19 (95)	7 (100)
Mycophenolate mofetil	29 (65.9)	11 (64.7)	14 (70)	4 (57.1)
Corticosteroids	44 (100)	17 (100)	20 (100)	7 (100)
mTor inhibitors	11 (25)	4 (23.5)	5 (25)	2 (28.6)
Azithromycin, n (%) *				
No	5 (11.4)	0	3 (15)	2 (28.6)
250 ×3/week	36 (81.8)	14 (82.3)	17 (85)	5 (71.4)
500 ×3/week	3 (6.8)	3 (17.7)	0	0

Abbreviations: COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; CF, cystic fibrosis; BE, bronchiectasis; PH, pulmonary hypertension; LAM, lymphangioleiomyomatosis; CLAD, chronic lung allograft dysfunction; BOS, bronchiolitis obliterans syndrome; RAS, restrictive allograft syndrome; FVC, forced vital capacity; FEV1, forced expiratory volume in the 1st second; GF, glomerular filtrate; BMI, body mass index; HBV, hepatitis B virus; SD, standard deviation.

Chronic bronchial infection microorganisms: ^α*E. coli*, *E. aerogenes*, *P. aeruginosa* (x3). ^β*P. aeruginosa* (x3), *C. albicans* (x2), *A. flavus*. ^Ω*P. aeruginosa* (x2), *E. coli*.

**p* < .05.

***p* < .001 for deceased vs discharged.

TABLE 2 Clinical characteristics of patients admitted with COVID-19

Clinical characteristics	All (n = 44)	Deceased (n = 17)	Discharged (n = 20)	Persistently admitted (n=7)
Days with symptoms at admission, median (p25-75)	2.5 (1, 6.5)	3 (1.5, 7)	2.5 (2, 5)	2 (1, 13.5)
Time from presentation to death/discharge/end-of-follow-up, days, median (p25-75)	—	13.5 (2 - 40)	18.7 (2 - 37)	24 (1 - 48)
Symptoms, n (%)				
Fever	34 (77.3)	13 (76.5)	15 (75)	6 (85.7)
Dyspnea*	26 (59.1)	15 (88)	8 (40)	3 (42.8)
Cough	26 (59.1)	7 (41.2)	14 (70)	5 (71.4)
Asthenia	14 (31.8)	6 (35.3)	6 (30)	2 (28.6)
Diarrhea	12 (27.3)	2 (11.8)	7 (35)	3 (42.8)
Myalgia	10 (22.7)	3 (17.6)	6 (30)	1 (14.3)
Nausea/vomit	9 (20.5)	1 (5.9)	4 (20)	4 (57.2)
Expectoration	8 (18.2)	2 (11.8)	3 (15)	3 (42.8)
Headache	2 (4.6)	1 (5.9)	0	1 (14.3)
Abdominal pain	2 (4.6)	0	0	2 (28.6)
Odynophagia	2 (4.6)	0	2 (10)	0
Chest X-ray at diagnosis, n (%)				
No changes	12 (27.3)	1 (5.9)	7 (35)	4 (57.2)
Consolidation	3 (6.9)	2 (11.8)	1 (5)	0
Bilateral infiltrates	29 (65.9)	14 (82.3)	12 (60)	3 (42.8)
Blood test, median (p25-75)				
Lowest lymphocytes count x10E9/L	0.5 (0.27, 0.91)	0.4 (0.1, 0.6)	0.6 (0.44, 0.9)	0.3 (0.26, 1)
Lowest lymphocytes count, %*	9.3 (4.6, 16)	5.1 (2.6, 11.6)	12 (8.1, 18.1)	7 (4.5, 10.6)
Lowest platelets count x10E9/L	176 (129, 245)	173 (119, 191)	185 (146, 260.2)	230 (86.5, 279)
Highest ferritin, ng/ml	672 (335, 1208)	925 (356, 1282)	604 (249, 922)	975 (575, 1987)
Highest D-dimer, ng/ml*	950 (429, 2571)	1458 (1000, 5112)	696 (413, 1235)	950 (344, 6934)
Highest IL-6, pg/ml*	88.9 (8.7, 133.4)	142.8 (91.8, 309)	14.2 (5.9, 95)	72 (16.6, 105)
Highest LDH, UI/L**	461 (319, 687)	687 (501, 775)	344 (299, 431)	813 (394, 1383)
Highest CPR, mg/dl	13.2 (6.1, 23)	19.2 (9.9, 31.7)	11.8 (5.6, 16.2)	6.4 (5.9, 20.4)
Complications, n (%)				
Atelectasis	1 (2.3)	0	0	1 (14.3)
Renal failure	29 (67.4)	11 (64.7)	12 (60)	6 (85.7)
Heart failure	5 (11.4)	1 (5.9)	2 (10)	2 (28.6)
Associated infections, n (%)				
Bacterial Bronchitis ^α	2 (4.6)	0	1 (5)	1 (14.3)
Bacterial Pneumonia ^β	2 (4.6)	0	2 (10)	0
CMV infection	7 (15.9)	2 (11.8)	4 (20)	1 (14.3)

Abbreviations: CMV, cytomegalovirus; CPR, C-protein reactive; IL-6, interleukin-6; LDH, lactate dehydrogenase.

^αDefined as: sputum, no radiological new infiltrates and positive cultures (both *H.influenza*).

^βDefined as: sputum and newly emerging radiological infiltrates and positive cultures (1 *H.influenza*, 1 *M.pneumoniae*).

**p* < 0.05.

***p* < 0.001 for deceased vs discharged.

general population,⁴ LTRs were more likely to be symptomatic, with fever, dyspnea, and diarrhea seen more frequently. Diarrhea was remarkably higher in our population and in other SOT recipients than in the general population, affecting around 30% and 5% of patients, respectively.^{9,10}

Following the institutional recommendation of the time from the Spanish Drug Administration,¹⁸ almost all patients were treated with hydroxychloroquine, which was complemented by LPV/r or darunavir/cobicistat and tocilizumab in some cases. However, treatment with protease inhibitor antiviral drugs was avoided in most patients,

TABLE 3 Treatment and outcomes

Pharmacological treatment	All (n = 44)	Deceased (n = 17)	Discharged (n = 20)	Persistently admitted (n = 7)
Hydroxychloroquine	41 (93.2)	17 (100)	17 (85)	7 (100)
Protease inhibitors	18 (40.9)	11 (64.7)	5 (25)	2 (28.6)
IF beta	4 (9.1)	3 (17.6)	1 (5)	0
Tocilizumab	19 (43.2)	9 (52.9)	7 (35)	3 (42.8)
Human normal Ig	10 (22.7)	6 (35.3)	2 (10)	2 (28.6)
Anticoagulation	10 (22.7)	4 (23.5)	3 (15)	3 (42.8)
Corticosteroids**	33 (75)	17 (100)	9 (45)	7 (100)
Max dose, median (p25-75), mg/day**	40 (10, 80)	40 (40, 312)	9 (5.75, 17.5)	40 (18, 60)
Antibiotic	40 (90.9)	16 (94.1)	17 (85)	7 (100)
Tacrolimus	37 (86.1)	17 (100)	14 (70)	6 (85.7)
Mean levels, median (p25-75)*	9.5 (6.1, 13.7)	9.9 (8.9, 14.9)	8.1 (3, 11.1)	13.4 (9.6, 17.2)
Min, median (p25-75)	5.2 (3.6, 8.7)	7.5 (3.6, 9.2)	4.9 (3.8, 6)	3.2 (2.3, 6.9)
Max, median (p25-75)*	16.7 (10.4, 22.7)	18 (15.7, 29)	11.6 (8.4, 19.4)	16.8 (16.1, 20.9)
mTor	7 (16.7)	2 (11.8)	4 (20)	1 (14.3)
Respiratory support*				
Room air	7 (15.9)	0	6 (30)	1 (14.4)
O ₂	20 (45.6)	1 (5.9)	14 (70)	5 (71.4)
HFNC	5 (11.4)	5 (29.4)	0	0
CPAP	5 (11.4)	5 (29.4)	0	0
NIV	4 (9.1)	4 (23.6)	0	0
Invasive mechanical ventilation	3 (6.8)	2 (11.7)	0	1 (14.4)
FiO ₂ , median (p25-75)*	92 (31,100)	97.5 (82, 100)	31 (31, 31)	28 (27.5, 46)
Highest level of care				
Home	1 (2.3)	0	1 (5)	0
Low complexity	0	0	0	0
Medical ward	30 (68.2)	10 (58.8)	17 (85)	3 (42.8)
Intermediate critical care	9 (20.5)	5 (29.4)	1 (5)	3 (42.8)
ICU	4 (9.1)	2 (11.8)	1 (5)	1 (14.4)
Length of hospital stay, days, median (p25-75), days	11 (8, 20)	12 (9, 15)	10.5 (7.7, 20.5)	21 (7.5, 24)
Death	17 (38.6)	17 (100)	0	0
*COVID-19	16 (36.3)	16 (100)	0	0

Abbreviations: CPAP, continuous positive airway pressure; FiO₂, fraction of inspired oxygen; HFNC, high flux nasal cannula; ICU, intensive care unit; IF beta, interferon beta; Ig, immunoglobulin; NIV, noninvasive ventilation. Data are shown as n(%) unless specified.

* $p < .05$.

** $p < .001$ comparisons for deceased vs discharged.

prioritizing drug interaction control over an eventual beneficial effect of these drugs. Clinical management included a reduction of immunosuppression by stopping mycophenolate or mTor inhibitor treatment and down-titrating the tacrolimus dose. It has been suggested that immunosuppression might be a protective factor against COVID-19 severity in SOT recipients.²¹ Nonetheless, mortality data in our cohort and in other studies, including different SOT recipients were higher than that in the hospitalized general population.^{9,10}

This is an observational study, which prevents drawing any firm conclusions about the efficacy of these different treatment options; however, it provides insights into their tolerance. While tocilizumab

and IF β were well tolerated, with no cases of drug interaction or secondary effects, the previously described interaction between protease inhibitors and tacrolimus was confirmed in our cohort, resulting in significant AKI that forced a temporary interruption of tacrolimus therapy in all patients to maintain adequate levels. Indeed, most patients did not receive treatment with protease inhibitors in contravention of institutional recommendations for the general population at that time, to prioritize maintaining correct levels of tacrolimus. Afterward, and mostly due to the results of the present study, the use of protease inhibitors for the treatment of SARS-CoV-2 is no longer recommended in our protocols.

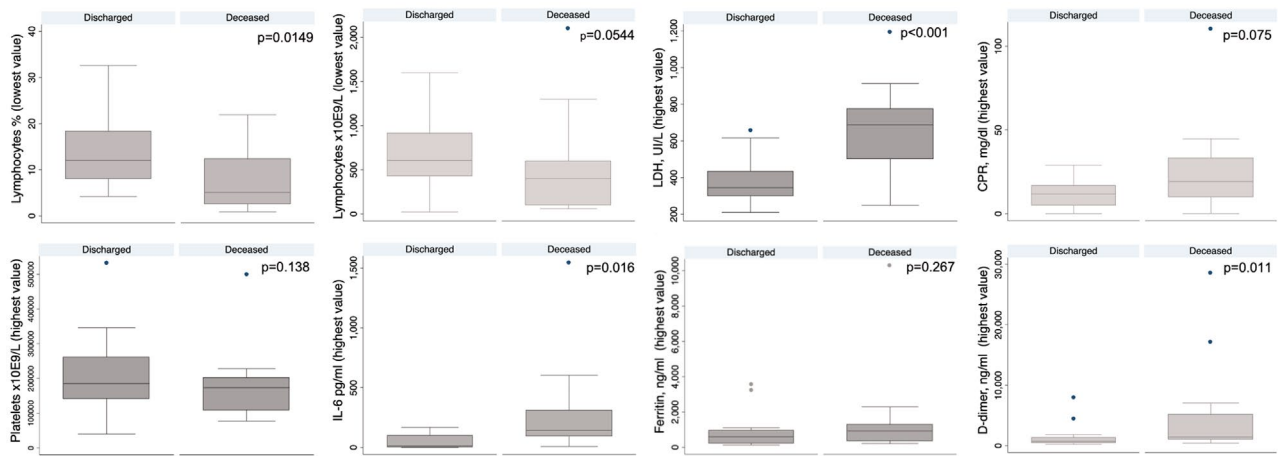


FIGURE 1 Comparison of blood variables between discharged and deceased individuals [Color figure can be viewed at wileyonlinelibrary.com]

When comparing LTRs who were discharged with those who died during hospitalization, the main difference in baseline characteristics was related to functional capacity. Those who died had worse lung capacity as reflected by the FEV1, and half of them had a diagnosis of chronic lung allograft dysfunction (CLAD) compared with 25% in the discharged group. Patients who died had worse respiratory status at admission. As expected, during the progression of the disease, they also had worse blood parameters, including lower lymphocyte counts, and higher ferritin, D-dimer, IL-6, and lactate dehydrogenase levels, as seen in previous studies of COVID-19.⁵ Long-term follow-up of this group will provide more data regarding the effect of COVID-19 on allograft survival; however, the acute phase seems to have a worse prognosis than that in the general population.

Only five patients were tested for anti-SARS-CoV-2 antibodies, and four of them expressed high titers of specific IgG. As far as we know, this is the first evidence suggesting that LTRs develop specific immunity against the virus.

An association between CARV infections and AR has been described.^{22,23} Bronchoscopy was not performed in our cohort; therefore, the possible co-existence of AR phenomena associated with the infection is unknown. The pathogenesis of CARV-mediated AR is not well understood, but it is possible that acute viral replication or inflammatory cytokines released by the damaged parenchyma may trigger circulating leukocytes.²² Moreover, there is a recognized risk of CLAD after lower respiratory tract infection with CARVs.^{22,23} Further study of the effect of SARS-CoV-2 infection on the development of CLAD in surviving LTRs is warranted in the near future.

Spain has a high rate of mortality due to COVID-19 with 247,486 confirmed cases and 28,330 deaths (11.4%) to date.²⁴ In our cohort, 38.6% of the patients with LTR died during admission, a mortality rate higher than that observed in the hospitalized population in different countries.^{25,26} To the best of our knowledge, our cohort is the largest LTR population with COVID-19. Data from LTRs are limited to a report from Leuven of 10 patients of whom eight were hospitalized and one died,¹⁷ a case report with a favorable outcome¹¹ and a

cohort of 90 SOT recipients, where Pereira et al. included 17 LTRs. Although the specific outcome of this subgroup was not reported, overall mortality for the whole group, including kidney transplant recipients, was around 24%.⁹

Our data were recorded at the peak of the pandemic in Spain, when the ICU occupation was over 500% of their capacity in the participant centers. This has toughened the ICU admission criteria for frail and pluripathological patients. In this context, exceptional rationing of care measures had to be taken, and most LTR patients in a critical situation were considered unsuitable for ICU measures due to relevant comorbidities and frailty. No preestablished general ICU admission criteria were created due to the pandemic, and every case was individually evaluated and discussed in a multidisciplinary meeting. In any case, intensive care assistance did not seem to modify the course of the disease, as no differences in survival were observed between those who were and were not treated in ICU. The nature of this study prevents drawing specific conclusions about determinants or mortality, but two clearly differentiable groups are identified with respect to disease behavior: those patients with a mild course of the disease with no or little flux oxygen therapy required, and those with severe respiratory failure that required high flux oxygen therapy plus some degree of respiratory support. This second group includes all those who died but one, suggesting that if the disease expresses this inflammatory phenotype, the prognosis is extraordinarily bad regardless of the treatment used. Moreover, for LTRs, it has been described that pneumonia is a main and independent predictor of mortality upon ICU admission.²⁷

Our study has some limitations that need to be addressed. First, data regarding the outcome of some patients are lacking because they were still hospitalized at the time of last follow-up. Second, the complete clinical spectrum of SARS-CoV-2 might not be represented, as we have only included clinically symptomatic patients, but patients with asymptomatic or mild COVID infections who did not seek health care have not been identified. However, aside from asymptomatic cases, it is unlikely that COVID-19 is significantly underdiagnosed in LTRs, as they are instructed to contact their transplant center if

symptoms of acute respiratory infection appear. Moreover, almost all LTRs were admitted at that time due to the many uncertainties of the disease's progression. Finally, the size of the cohort does not allow for a mortality analysis; therefore, the results comparing outcomes in discharged versus deceased individuals should be evaluated cautiously. Specifically, restrictions on ICU admission due to the extraordinary situation might have worsened survival outcomes in critical patients. Nevertheless, the description of patients' characteristics by outcome could help to better showcase the behavior of LTRs with COVID-19.

Spain has been the world leader in organ donation and transplantation for several years, and at the same time it has been one of the countries more severely affected by the SARS-CoV-2 pandemic. This is one of the strengths of our cohort, which includes all patients diagnosed in all lung transplant centers in Spain but one. Therefore, we believe the sample is a representative of the LTR population.

In conclusion, the clinical presentation of SARS-CoV-2 infection in LTRs is similar to that of the general population, but with worse prognosis and higher mortality. The severity of disease on presentation predicts subsequent mortality. Treatment with protease inhibitors does not seem to be beneficial, as it did not show a positive effect and led to a disbalance in tacrolimus levels and subsequent acute kidney injury.

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DISCLOSURE

The authors of this manuscript have conflicts of interests to disclose as described by the *American Journal of Transplantation*. CB has received speaker fees from Boehringer and consulting fees from Janssen pharma. MB has received speaker fees from Grifols, Menarini, CSL Behring, GSK, and consulting fees from GSK, Novartis, Boehringer Ingelheim, and GebroPharma. MLM has received speaker fees from Janssen Pharma, GSK, and M.S.D. and consulting fees from Janssen Pharma and M.S.D. ERL received a travel grant from Janssen pharma. CAQL received speaker fees from Janssen Pharma and M.S.D. and consulting fees from Janssen pharma, GSK, and M.S.D. VMMC received speaker fees from Janssen Pharma, GSK, Astellas, Boehringer Ingelheim, and Chiesi. BSG received talk fees or travel grants from GlaxoSmithKline, Actelion Pharmaceuticals, Bial, Mundipharma, Novartis, and Astellas Pharma.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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