# COVID-19 and Short- and Medium-term Outcomes in Liver Transplant Patients: A Spanish Single-center Case Series



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Background & aims: The evidence suggests that most vulnerable subjects to COVID-19 infection suffer from patients with comorbidities or immunosuppression, including liver transplant recipients. Liver graft dysfunction may be a rare complication. Some patients complain about the post-COVID-19 syndrome. The aim of this study was to assess medium- and short-term outcomes in liver transplant patients. Patients and methods: A retrospective case series was performed at a tertiary referral center. We screened 845 patients who had liver transplant (LT) in our center. All consecutive LT patients with COVID-19 during the Spanish outbreak from March 2020 to April 2021 were included. Demographics, pre-existing comorbidities, clinical and radiological data of COVID-19 infection, complications, and liver graft function were assessed at diagnosis and 3-month follow-up. Results: Overall, 20 LT patients were diagnosed with confirmed COVID-19. We included 16 patients that met the inclusion criteria, 8 nonhospitalized (50%) and 8 (50%) hospitalized patients were analyzed. The median follow-up was 5.33 months (IQR 3.06-8.26). One patient died during the follow-up. All patients presented some grade of respiratory or functional symptoms. Dyspnea and fatigue were the most prevalent symptoms during the 3-month follow-up. No liver graft dysfunction were reported despite of partial immunosuppression withdrawal in four patients (25%). One patient had cardiovascular complications. Conclusions: Our results suggest the presence of post-COVID-19 syndrome with mild residual physical and psychological dysfunction in this subgroup of patients at 3 months after COVID-19. However, no cases of loss or liver graft dysfunction were reported. (J CLIN EXP HEP-ATOL 2022;12:689-695)

The severe respiratory distress syndrome coronavirus (SARS-CoV-2) is responsible for COVID-19 disease. The liver involvement has been described in various studies,<sup>1</sup> with some potential role of cholangiocytes due to their high expression of virus receptor angiotensin-converting enzyme 2 (ACE2) (2). Liver damage could be induced by cytopathic effect of the virus, cytokine storm or drug toxicity.<sup>2</sup>

The pandemic has affected liver transplantation (LT) units worldwide reducing their activity.<sup>3</sup> However, data about the risk of LT patients for contracting the virus

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are limited, and the role of immunosuppression in the inflammatory response remains unclear.<sup>3</sup>

Regarding immunosuppression, recommendations suggest that changes in immunosuppression should be considered according to severity of disease. However, mycophenolate should be withdrawn in all types of infection, calcineurin inhibitors (CNI) and mammalian target of rapamycin (m-TOR) inhibitors could be reduced or stopped in severe affection keeping some dose of steroids.<sup>4</sup>

Recently, the Spanish experience regarding LT recipients and COVID-19 infection was published, suggesting an increased risk of acquiring the infection without higher mortality rates.<sup>4</sup> An international register found that LT was not independently associated with lower survival. However, worse outcomes following COVID-19 were related to comorbidities.<sup>5</sup>

Some studies have suggested that COVID-19 patients can experience some symptoms after being discharged called "post-COVID-19 syndrome."<sup>6</sup> This syndrome could affect physical and mental health with the need for rehabilitation. Then, even though the short-term outcomes seem to be like the general population, the medium- and longterm outcomes or the possible effect on the graft has not been described yet.

Keywords: SARS-CoV-2, COVID-19, liver transplantation, immunosuppression, sequelae

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*Abbreviations*: CNI: Calcineurin inhibitors; COVID-19: Coronavirus disease 2019; LT: Liver transplantation; m-TOR: Mammalian Target of Rapamycin; RT-PCR: reverse transcriptase polymerase chain reaction; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SD: standard deviation; STAI: State Trait Anxiety Inventory; WHIIRS: Women's Health Initiative Insomnia Rating Scale; WHOQOL: World Health Organization quality of life

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Table 1 Baseline Demographics, Clinical Characteristics, Radiological Feature, Antiviral Therapy and Outcomes of Liver Transplanted Patients at the COVID-19 Diagnosis.

Case	Gender	Age	Major comorbidities	Charlson Index	Interval LT (months)		Baseline IS regimen	COVID-19 symptoms	Radiological features	COVID-19 therapy	Median LoS (days)	Management of IS	Liver allograft dysfunction	Outcomes
#1	Male	59	-	0	33	NO		Fever, dyspnoea, cough	Bilateral consolida tions	HCQ + CS + RDV + LMWH	58	mTOR Withdrawal	NO	Need for oxygen Discharged
#2	Male	59	Diabetes	1	19	YES	CNI + MMF	Fever, dyspnoea		HCQ + CS + LMWH	14	Reduction MMF	NO	Need for oxygen Discharged
#3	Male	60	-	0	4	YES	CS + CNI + MMF	Cough	No findings	None	-	No change or mild reduction	NO	Non- hospitalized
#4	Male	62	Diabetes	1	74	NO	CNI	Fever, cough		HCQ + CS + LPV/r + LMWH	11	No change or mild reduction	NO	Need for oxygen Discharged
#5	Male	69	Diabetes, COPD	2	53	NO		Dyspnoea, cough	Bilateral consolida tions	None	2	MMF Withdrawal	NO	No need for oxygen Discharged
#6	Male		Diabetes, CLD, CKD, neoplasia, mild dementia	5	190	NO	mTOR	Fever, dyspnoea, cough	Bilateral consolida tions	TZA + CS + LMWH	16	No change or mild reduction	NO	No need for oxygen Discharged
#7	Female	54	-	0	26	NO	CNI + MMF	Asymptomatic	No findings	None	-	No change or mild reduction	NO	Non-hospitalized
#8	Female	66	Diabetes	1	47	NO	CNI + MMF	Cough	No findings	None		No change or mild reduction	NO	Non-hospitalized
#9	Female		PVD, CLD, CKD, Hypertension	3	102	NO	CNI + mTOR	Asymptomatic	No findings	None	-	No change or mild reduction	NO	Non-hospitalized
#10	Male	39	HIV, CLD	2	46	NO	CNI + mTOR	Asymptomatic	No findings	None		No change or mild reduction	NO	Non-hospitalized

Case	Gender	Age	Major comorbidities	Charlson Index	Interval LT (months)		Baseline IS regimen	COVID-19 symptoms	Radiological features	COVID-19 therapy	Median LoS (days)	Management of IS	Liver allograft dysfunction	Outcomes
#11	Male	69	COPD, Hypertension	1	28	NO	CNI	diarrhea	Bilateral consolida tions	CS + LMWH + Antibiotics	10	No change or mild reduction	NO	No need for oxygen Discharged
#12	Female	46	Diabetes	1	116	NO	CNI	Cough	No findings	None	-	No change or mild reduction	NO	Non-hospitalized
#13	Male	66	Diabetes	1	52	NO	CNI + MMF	Asymptomatic	No findings	None	-	No change or mild reduction	NO	Non-hospitalized
#14	Male	57	Diabetes, PUD	2	75	NO	CNI + MMF	Fever	Bilateral consolida tions	CS + LMWH + Antibiotics	22	MMF Withdrawal	NO	IMV and UCI (8 days) No need for oxygen Discharged
#15	Male	49	Diabetes, Hypertension	1	81	NO	CNI + mTOR	Asymptomatic	No findings	None	-	No change or mild reduction	NO	Non-hospitalized
#16	Female	69	CHF, CTD, hypothyroidism	2	180	NO		Fever, dyspnoea, cough, anosmia headache	Bilateral consolida tions	CS + LMWH	7	No change or mild reduction	NO	No need for oxygen Discharged

COPD, chronic obstructive pulmonary disease; CLD, chronic liver disease; CKD, chronic kidney disease; PVD, Peripheral vascular disease; CHF, Congestive heart failure; PUD, Peptic ulcer disease; CTD, Connective tissue disease; LT, liver transplantation; IS, immunosuppression; CS; corticosteroids; mTOR, mammalian target of rapamycin; CNI, calcineurin inhibitor; HCQ, hydroxychloroquine; RDV, remdesivir; LPV/r, Lopinavir/Ritonavir; TZA, Tocilizumab; LMWH, Low Molecular Weight Heparin; LoS, length of stay; IMV, invasive mechanic ventilation; ICU, intensive care unit; ARDS, acute distress respiratory syndrome.

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Thus, the aim of this study was to assess short- and medium-term outcomes in LT patients with COVID-19.

#### **METHODS**

#### Design and study population

This was a single-center retrospective study including all adult ( $\geq$ 18 years) LT recipients routinely followed at Hospital Universitario Rio Hortega (Valladolid, Spain) and diagnosed with COVID-19 from March 2020 to April 2021. We screened 845 LT patients at our center. Patients whose follow-up was less than 1 month after the COVID-19 diagnosis were excluded. The study protocol was approved by the local ethics committee.

All LT recipients with confirmed SARS-CoV-2 infection were placed on droplets precautions and no visits were allowed. Patients were treated with antiviral and immunomodulatory therapy according to clinical practice guidelines and protocols by Spanish Ministry of Health.<sup>7</sup> Patients with mild pneumonia were treated with lopinavir/ritonavir, hydroxychloroquine, IFN- $\beta$ , or remdesivir combined with antibiotics (azithromycin for 5 days and ceftriaxone for 7 days) after oral informed consent. Tocilizumab and boluses of steroids were prescribed in patients with acute distress respiratory syndrome. The management of immunosuppression in LT patients were performed by transplant physicians, according to clinical guidelines of the Spanish Society of Liver Transplantation<sup>8</sup>; mycophenolate withdrawal or conversion to CNI or mTOR was considered. Complete immunosuppression withdrawal was not recommended.

All patients were followed up until the last medical assistance or death.

#### Study definitions

- Confirmed SARS-CoV-2 infection was defined as a positive result of real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swabs or a positive serology test.
- Respiratory insufficiency was defined as an arterial oxygen partial pressure less than 60 mmHg.
- Liver allograft dysfunction was defined as raised bilirubin >4 times from baseline values or international normalized ratio >1.4, according to Colmenero et al.<sup>4</sup>

#### Data collection

Demographical data (i.e., age and gender), comorbidities according to Charlson Comorbidity Index,<sup>8</sup> LT data (i.e., LT date, immunosuppression, and the rate of liver graft dysfunction), clinical data at the diagnosis, 1- and 3-month followup, radiological features and the antiviral drugs administered (see above) were collected. Moreover, the length of stay and

Case	Weight change (%)	mMRC for dyspnoea	Fatigue		Arthralgia and myalgia	Anxiety		WHIIR scale for	WHOQOL- BREF					
		scale				STAI- trait	STAI- state		Total	Physical health	Psychological	Social relations	Environment	
#1	-3.8	Moderate	Yes	No	Yes	2	3	2	96	20	31	12	33	
#2	+2.5	Mild	No	No	Yes	6	3	3	107	32	25	14	36	
#3	-1	Mild	Yes	No	Yes	9	2	15	114	33	26	15	40	
#4	-10	Mild	Yes	No	No	5	3	3	104	30	25	15	34	
#5	-5.1	Mild	Yes	No	No	6	6	14	94	30	20	9	35	
#6	_	_	-	_	-	_	-	_	_	_	_	_	_	
#7	0	No	Yes	Yes	No	36	40	17	88	25	23	11	29	
#8	+4	No	No	No	No	2	3	3	108	32	25	15	36	
#9	+2	No	No	No	Yes	5	3	4	105	28	26	14	37	
#10	-4	Mild	Yes	No	Yes	8	6	12	88	23	22	11	32	
#11	-1	Mild	Yes	No	No	5	5	7	93	25	24	12	32	
#12	0	Mild	No	Yes	No	4	3	7	96	28	24	14	30	
#13	0	No	Yes	No	Yes	6	4	11	108	30	27	15	36	
#14	-6	Moderate	Yes	No	Yes	20	18	15	91	22	30	9	28	
#15	-1	Mild	Yes	Yes	No	12	17	13	92	27	21	13	31	
#16	+1	Mild	Yes	No	No	3	3	7	97	29	22	15	31	

 Table 2 Features at 3-Month Follow-up after COVID-19 Infection.

mMRC, modified Medical Research Council; STAI, State-Trait Anxiety Inventory; WHIRS, Women's Health Initiative Insomnia Rating Scale; WHOQOL, World Health Organization Quality of Life.

the need of noninvasive ventilation administration or intensive care unit were reviewed in hospital inpatients.

At the 3-month follow-up, clinical data such as fatigue, headache, arthralgia, myalgia, and dyspnea (mMRC score<sup>9</sup>), insomnia (WHIIRS, Women's Health Initiative Insomnia Rating Scale  $\geq 9^{10}$ ), and anxiety (STAI-state and STAI-trait scores  $\geq 40^{11}$ ); liver graft dysfunction and medium-term vascular complications were collected. Finally, the impact of the COVID-19 on the quality of life was assessed by WHOQOL scores.<sup>12</sup>

#### Statistical analysis

Descriptive statistics were used to report characteristics of patients. Normally distributed values were shown as mean  $\pm$  standard deviation (SD), otherwise as median and interquartile range whenever appropriate. Student *t*-test or nonparametric test was used to compare continuous variable and  $X^2$  test or Fisher's exact test was used for categorical variables, wherever appropriate. Statistical analyses were performed using IBM SPSS Statistic for Windows (version 24.0. IBM Corp, NY, USA). *P*-values <0.05 were considered statistical significance.

# RESULTS

From March 2020 to April 2021, a total of 20 LT patients (2 Re-LT patients) were diagnosed with COVID-19. Two patients died due to acute respiratory distress syndrome during hospitalization, and two hospitalized patients had not been discharged at the time of writing this manuscript and were therefore excluded for the present analysis.

All included patients (n = 16) had a positive SARS-CoV-2 RT-PCR test result. Eight of them (50%) were hospitalized, and the median length of stay was 14 days (IQR 2-24). The demographics, clinical characteristics, radiological feature, the antiviral therapy, and outcomes at the COVID-19 diagnosis are shown in Table 1. Median age was 63 years (IQR 59-69) with predominance of male patients (85.7%), and median interval time from LT to COVID-19 was 52 months (IQR 19-94). The CNI- and MMF-based immunosuppression regimen was the most frequent baseline LT therapy (43.8%). Fever, cough, and dyspnea were present in most cases (n = 11, 68.8%), and only one (6.3%) patient had gastrointestinal symptoms (diarrhea and abdominal pain); eight patients (50%) had bilateral (n = 7, 43.8%) or unilateral (n = 1, 6.3%) pneumonia on a chest radiography. One patient required mechanical ventilation or transfer to intensive care unit.

Most of hospitalized patients received boluses of steroids (n = 7, 43.8%) as antiviral therapy combined hydroxychloroquine (n = 3, 18.8%), remdesivir (n = 1, 6.3%) or lopinavir/ritonavir (n = 1, 6.3%) or tocilizumab (n = 1, 6.3%). All hospitalized patients were treated with subcutaneous lowmolecular-weight heparin. Rest of the patients received symptomatic treatment. Antibiotic therapy was associated with antiviral treatment when bacterial co-infection was suspected. Modifications of immunosuppression therapy were registered in four patients: mycophenolate withdrawal (two patients, 50%), mycophenolate reduction (one patient, 25%), and mild reduction of CNI/mTOR inhibitors (one patient, 25%).

Following a median period of 5.33 months (IQR 3.06–8.26), all patients had some physical or psychological sequelae: dyspnea according to mMRC score (11 patients), fatigue (11 patients), arthralgia/myalgia (7 patients), head-ache (3 patients), insomnia according to WHIIRS (7 patients) and anxiety measured by STAI-state and STAI-trait scores (1 patient) were reported. Hospitalized patients had a higher weight loss, especially those with longer length of stay (except patient #3), than nonhospitalized patients. The median weight change was -2.8% (IQR -6.33 to 0.63). None of them needed pulmonary rehabilitation. More detailed data are shown in Table 2.

Moreover, patients with a higher insomnia or anxiety score had lower WHOQOL scores at 3-month follow-up. They admitted a worse quality of life at the expense of psychological and social relation domains (see Table 2).

Short- and medium-term LT complications or liver graft dysfunction were not reported at 3-month followup. All patients resumed baseline immunosuppression after resolution of COVID-19.

During the follow-up, one patient with comorbidities died 39 days after COVID-19 hospitalization discharge due to cardiac insufficiency secondary to acute coronary syndrome and cardiac dysfunction as COVID-19 cardiovascular complication.

#### DISCUSSION

Many uncertainties remain about the impact of COVID-19 infection in LT population, including the recovery and short- and medium-term outcomes. We present a case series to report the partial physical and psychological recovery after COVID-19 infection in LT patients in a Spanish region with a high COVID-19 incidence.

The incidence of COVID-19 among LT recipients in our center was 2.37% (20/845). All patients were followed up using COVID-19 screening tests, telephone interviews, or conventional clinic visits. COVID-19 cases were registered in local database.

Despite the heterogeneity of time interval from LT (4-190 months) and age (ranging from 54 to 74 years), the short- and medium-term outcomes of COVID-19 infection were associated with comorbidities and respiratory failure. In addition, hospitalized patients were older and had more comorbidities than nonhospitalized patients.

The rates of hospitalization, pneumonia, and ICU admission were similar to other published series of solid organ transplant recipients.<sup>13</sup>

As recent published data,<sup>14</sup> despite clinical recovery at discharge, many patients had physical and psychological problems when evaluated after 3 months. For example, two-third of them complained of dyspnea and fatigue. The presence of physical sequalae was associated with longer hospital length of stay and more severe infection. However, the impact on the quality of life and mental health as anxiety or insomnia were not associated with severity of COVID-19 infection.

Chronic cardiovascular damage is associated with SARS-CoV-2 infection.<sup>15</sup> In our cohort, one patient died due to cardiovascular complications during the follow-up.

Therefore, a multidisciplinary strategy could be offered to LT patients to avoid physical and psychological dysfunction during the follow-up. Besides, a cardiovascular care in the management of COVID-19 should be recommended to improve long-term outcomes in LT patients.

On the other hand, the relationship between immunosuppression and COVID-19 outcome is a double-edged sword. No evidence-based guidelines for managing immunosuppression in LT patients with COVID-19 but complete immunosuppression withdrawal may not justify.<sup>4</sup> In our cohort, despite of partial immunosuppression withdrawal, none of LT patients developed liver allograft dysfunction during the hospitalization or the follow-up. So, it could be a chance to use strategies to minimize immunosuppression, especially in older patients and patients with longer time interval from LT.

There are some limitations that should be mentioned, as a retrospective study. Despite screening the database thoroughly, we cannot exclude some degree of underreporting. Secondly, our study was conducted at a single LT center with a small sample size. Future larger studies are needed to validate our results and determine longterm outcomes.

In conclusion, our analysis reveals that all LT patients had a partial recovery with residual medical problems at 3 months. Moreover, this report highlights the need of physical and psychological follow-up and monitoring the liver allograft function after COVID-19 in LT patients.

#### **ETHICS APPROVAL**

This study was approved by the local Institutional Review Board at Hospital Universitario Rio Hortega, Valladolid.

# AVAILABILITY OF DATA AND MATERIAL

The authors confirm that the data supporting the findings of this study are available within the manuscript.

#### CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Javier Tejedor-Tejada: Conceptualization, acquisition of data, Methodology, interpretation of data, Writing -

original draft, Writing - review & editing, technical support. **Esteban Fuentes-Valenzuela:** Conceptualization, design, Methodology, interpretation of data, Writing - review & editing, technical support. **Carmen Alonso-Martin:** Writing - original draft, Writing - review & editing, technical support. **Carolina Almohalla-Alvarez:** Writing - original draft, Writing - review & editing, technical support. **Felix Garcia-Pajares:** Writing - original draft, Writing - review & editing, technical sup-

# **CONFLICTS OF INTEREST**

The authors have none to declare.

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