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Incidence and Impact of COVID-19 Cases in Brazilian Liver Transplant Recipients: An Academic, Single-center Experience

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ABSTRACT

Background. Current literature reports diverge on the impact of COVID-19 in liver transplant (LT) recipients. Literature findings often report conflicting results, relying on small sample sizes, limited ethnic variability, and nonstandardized methodologies. Notably, there are no studies on this topic regarding Latin American populations. This study seeks to report the impact of COVID-19, disease characteristics, and progression in LT recipients in a Latin American academic center environment.

Methods. The study design was a historic cohort, including adult LT recipient patients with suspected or confirmed COVID-19 who sought care between December 2019 to October 2021. The primary end point was defined as COVID-19−related death. Demographic, clinical, and laboratory data was also collected.

Results. Twenty-seven patients were included, representing a 3.5% incidence within 752 patients in the follow-up. The mean age and years from transplantation were 54 (SD ± 11) and 6.3 years (SD ± 5.4), respectively. Most patients were white (23 - 85.2%) and male (21 - 25.2%). The hospitalization rate was 55.6%, and 5 patients (18.5%), all of whom subsequently died, were admitted to the intensive care unit. Neither the presence of comorbidities nor advanced age were related to lethality. Patients with immunosuppression modifications (P = 0.039) or isolated tacrolimus suspension (P = 0.006) were associated with increased mortality.

Conclusions. This study described COVID-19 infections in LT recipients in Latin American populations. This group was not affected by common factors associated with higher lethality, and displayed a tendency toward lower hospitalization rates. Our study concurred with previously reported evidence of a protective association of tacrolimus maintenance during treatment in LT recipients affected by COVID-19.

AMID the COVID-19 pandemic, solid organ transplant centers have been subjected to a severe decline in the number of undertaken procedures and novel challenges in the follow-up and management of solid organ transplant (SOT) recipients. In this scenario, the consequences of infection by SARS-CoV-2 virus in these patients is of particular concern, due to the perceived added risk of immunosuppression and comorbidity burden.

Current literature reports diverge on the impact of COVID-19 in liver transplant (LT) recipients. Some authors have observed increased lethality associated with older age and an increased number of comorbidities in these patients [1−4], while other reports, including meta-analyses, did not achieve such results [5−7]. A single study even reported a seemingly protective effect of immunosuppressive therapies on lethality in SOT recipients [2].

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This study seeks to report the impact of COVID-19, disease characteristics, and progression in LT recipients, providing hypotheses of the pathogenesis of the infection in a Latin American academic center.

MATERIALS AND METHODS

We designed this study as a historic cohort, analyzing patient records submitted by an online standardized questionnaire. The study included adult, LT recipient patients with suspected or confirmed COVID-19 who sought care between December 2019 and October 2021. The primary endpoint was defined as COVID-19−related death, and follow-up was maintained until either death or the submission of data to analysis.

We collected demographic, clinical, and laboratory data regarding the presentation, disease progression, and outcome of the infection (survival and death). All participants consented to the collection of this data by agreeing to a standardized term approved by the institution's ethics committee.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) program, version 23.0 (IBM, Armonk, NY, USA), with descriptive analysis and parametric or nonparametric comparative tests according to variable normality. Mann-Whitney test was used for nonnormal continuous variables while the Student t test and ANOVA were used for normal variables. The χ^2 test was used for

Table 1. Demographic, Clinical, and Laboratorial Information

	Survived (n = 22)	Died (n = 5)	*P* value
Age (mean)	60 (± 12)	56 (± 10)	0.75
≥60 years old (%)	12 (54.5)	2 (40)	0.64
Male (%)	17 (77.3)	4 (80)	0.89
Ethnicity (%)			
White	19 (86.4)	4 (80)	(reference)
Asian	2 (9.1)	0 (0)	-
Black	1 (4.5)	1 (20)	0.30
COVID-19 *wave (%)*			
First wave	4 (18.2)	3 (60)	0.91
Second wave	18 (81.8)	2 (40)	
Comorbidities			
Charlson Comorbidity Index (mean)	1.55 (± 1.18)	1.2 (± 1.10)	0.25
Hypertension (%)	10 (45.5)	2 (40)	0.61
Diabetes mellitus (%)	12 (54.5)	2 (40)	0.46
Obesity (%)	4 (18.2)	2 (40)	0.30
Chronic kidney disease (%)	5 (22.7)	0 (-)	0.32
Years from transplantation (mean)	6.3 (± 3.8)	3.4 (± 4.8)	0.22
Immunosuppressor Use at Admission (%)			
Cyclosporine	5 (22.7)	0 (-)	-
Tacrolimus	13 (59.1)	4 (80)	0.62
Mycophenolate	13 (59.1)	3 (60)	0.684
Azathioprine	2 (9.1)	1 (20)	0.47
Steroids	0 (-)	0 (-)	0.23
Everolimus	7 (31)	2 (40)	0.53
Symptoms on Admission (%)			
Fever	11 (50)	4 (80)	0.34
Cough	11 (50)	2 (40)	1.0
Dyspnea	3 (13.6)	2 (40)	0.22
Fatigue	5 (22.7)	2 (40)	0.58
Myalgia	9 (40.9)	1 (20)	0.62
Nausea or vomiting	1 (4.5)	1 (20)	0.34
Odynophagia	1 (4.5)	0 (-)	1.0
Abdominal pain	1 (4.5)	0 (-)	1.0
Laboratory Values at Admission			
Lymphocyte count, cells/μL	1102 (± 616)	635 (± 177)	0.35
AST (UI/L)	48 (± 47)	84 (± 98)	0.43
ALT (UI/L)	43 (± 53)	93 (± 111)	0.34
C-reactive protein	96 (± 0)	167 (± 99)	0.59
Hospitalization (%)	12 (54.5)	5 (100)	0.47
ICU admission (%)	0 (-)	5 (100)	**< 0.001**
Intubation (%)	0 (-)	5 (100)	**< 0.001**
Immunosuppressive Regimen Modifications (%)			
Partial or total suspension	8 (33.6)	5 (100)	**0.039**
Suspension of tacrolimus (either alone or with other drugs)	3 (75)	1 (25)	**0.006**

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ICU, intensive care unit.

Table 2. Detailed Characteristics of Recorded Deaths

Patient	Sex	Age	Years from Transplant	Comorbidities	AST/ALT at admission (UI/L)	Immunosuppressive Regimen on Admission	Immunosuppression Modifications	ICU Stay (Days)
1	Male	57	2.43	Hypertension Diabetes Obesity	45/41	Tacrolimus, Mycophenolate, Everolimus	Total suspension	14
2	Male	41	1.68	Obesity	195/221	Tacrolimus, Mycophenolate	Tacrolimus Suspension	11
3	Female	67	1.56	Diabetes	12/18	Azathioprine, Tacrolimus, Mycophenolate	Total suspension	19
4	Male	54	1.95	None	-	Everolimus	Total suspension	16
5	Female	63	12.59	Hypertension	-	Tacrolimus	Total suspension	1

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ICU, intensive care unit.

normal and nonnormal discrete binary variables and multinomial logistic regression for nonbinary categorical variables.

RESULTS

We included 27 patients in the final analysis. All cases were confirmed by reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2. These cases represented a 3.5% incidence rate within our 752 LT recipients currently in follow-up. Demographic and clinical data on these cases is displayed in Table 1. The mean follow-up time was 92.04 days (SD ± 95.8 days).

The mean age in our sample was 54 years old (SD ± 11 years), with a mean time from transplantation of 6.3 years (SD ± 5.4 years). Most patients were white (23 - 85.2%) and male (21 - 25.2%). Fifteen patients (55.6%) required inpatient treatment, with 5 subsequently admitted to the intensive care unit.

Five deaths were recorded in our sample, all from patients in the intensive care unit. These represent a 33.4% lethality rate in hospitalized patients and an 18.5% lethality rate overall. All recorded deaths were due to acute COVID-19 complications. Detailed characteristics of the recorded deaths are displayed in Table 2.

Only 2 patients displayed liver enzyme elevations (aspartate aminotransferase and alanine aminotransferase of 195/221 and 151/162 in each case, respectively). Despite that, there were no reports of liver function alterations and no graft losses in our sample.

Immunosuppression modifications correlated with increased mortality, with all deaths occurring within the 13 patients whose regimen had alterations ($P = 0.039$).

Lastly, 4 deaths were reported in patients using tacrolimus at admission, accounting for 23.52% mortality. Only 1 death was reported within the 9 patients not using tacrolimus at admission. This difference did not correlate with mortality ($P = 0.62$). There was, however, an increase in mortality related to tacrolimus suspension after admission, compared to its maintenance, with no deaths in the former group and 3 in the latter ($P = 0.006$).

DISCUSSION

In this study, we observed that, although the SARS-CoV2 infection in LT recipients mainly displayed similar characteristics to those reported in previous studies in the same populations, some crucial aspects, such as the association of greater lethality to advanced age and comorbidities [1−4,8,9], were not observed in our study.

In our study, the hospitalization rate (55.6%) was not as high as reported in other studies, which displayed rates of up to 88% in LT recipients [8−10]. Unlike other reports in literature [2−5,10−12], the lethality rate observed in our sample (18.51%) was quite elevated. Yet, our study has not found any causal factors that justify such increased lethality.

Although previous evidence indicates advanced age and the presence of comorbidities as factors associated with increased mortality in SOT recipients [1,2,4,9,13], none of these variables displayed such correlations in our study.

Nevertheless, similarly to a study by Coll et al, we found a tendency to lower lethality from the first wave of COVID-19 to the second, dropping from 42.8% to 10% between both peaks of infections [3].

In our study, 17 patients (62.96%) used tacrolimus at admission. Although the use of tacrolimus at admission was not associated with increased mortality, the discontinuation of tacrolimus therapy in users at admission was associated with higher mortality, which is a result in line with that reported by Belli et al [2].

When interpreting the results in this study, the study's limitations should be taken into account. These are notably, the retrospective, noncontrolled design and the use of patient records to extract information. These limitations may hinder the reproduction of results and require more complementary studies. Conversely, the novel population, number of variables collected, and inclusion of patients from all phases of the pandemic attest to the validity of our analysis.

CONCLUSIONS

In conclusion, this study showed that LT recipients with COVID-19 in Latin America were not as affected by common factors associated with mortality and had lower hospitalization rates. Moreover, our study concurred with previously reported evidence suggesting a protective association of tacrolimus maintenance during treatment of these patients.

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