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Liver Injury in Liver Transplant Recipients with Coronavirus Disease 2019 (COVID-19): US Multicenter Experience

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ABBREVIATIONS

ACE2- angiotensin-converting enzyme 2; ALT- Alanine aminotransferase; ALD-alcoholic liver disease; AST- aspartate aminotransferase; CI-confidence interval; COVID-19- Coronavirus disease -2019 ; DM- Diabetes Mellitus; HCV- Hepatitis C virus; HTN- Hypertension; ICU-intensive care unit; IQR- interquartile range; LT- Liver transplantation; NAFLD- Nonalcoholic fatty liver disease; OR- odds ratio; ULN- upper limit of normal

ABSTRACT

Background

Coronavirus disease 2019 (COVID-19) is associated with liver injury, but the prevalence and patterns of liver injury in liver transplant (LT) recipients with COVID-19 is not defined.

Approach and Results

We conducted a multicenter study in the US of 112 adult LT recipients with COVID-19. The median age was 61 years (IQR 20), 54.5% (n=61) were male, and 39.3% (n=44) Hispanic. The mortality rate was 22.3% (n=25); 72.3% (n=81) were hospitalized and 26.8% (n=30) admitted to the ICU. Analysis of peak values of alanine aminotransferase (ALT) during COVID-19 showed moderate liver injury (ALT 2-5x ULN) in 22.2% (n= 18) and severe liver injury (ALT > 5x ULN) in 12.3% (n= 10). Compared to age and gender matched non-transplant patients with CLD and COVID-19 (n=375), the incidence of acute liver injury was lower in LT recipients (47.5% vs.

34.6%; p=0.037). Variables associated with liver injury in LT recipients were younger age (p= 0.009, odds ratio (OR) 2.06 [1.20-3.54]), Hispanic ethnicity (p= 0.011; OR 6.01 [1.51-23.9]), metabolic syndrome (p= 0.016; OR 5.87 [1.38-24.99]), vasopressor use (p= 0.018; OR 7.34 [1.39-38.52]) and antibiotic use (p= 0.046; OR 6.93 [1.04-46.26]). Reduction in immunosuppression (49.4%) was not associated with liver injury (p= 0.156) or mortality (p= 0.084). Liver injury during COVID-19 was significantly associated with mortality (p= 0.007; OR 6.91 [95% CI: 1.68-28.48]) and ICU admission (p=0.007; OR 7.93[1.75-35.69]) in LT recipients.

Conclusion

Liver injury is associated with higher mortality and ICU admission in LT recipients with COVID-19. Hence, monitoring liver enzymes closely can help in early identification of patients at risk for adverse outcomes. Reduction of immunosuppression during COVID-19 did not increase risk for mortality or graft failure.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has now claimed over 750,000 lives around the world, with more than 170,000 deaths in the US alone (1). Data on clinical outcomes and disease severity of COVID-19 in liver transplant (LT) recipients is limited, but initial reports raise concern for high rates of adverse outcomes (2–4). Bhoori et al first reported the death of three LT recipients in the epicenter of COVID-19 in Lombardy, Italy in March 2020, and postulated that post-transplant metabolic complications may drive adverse outcomes with COVID-19 rather than immunosuppression (5). A subsequent study of 38 LT recipients from the international SECURE-CIRRHOSIS registry showed a mortality rate of 24% (6). Other recent studies have reported mortality rates ranging from 12-20% and have identified factors like older age, comorbid active cancer or renal injury to be predictive of adverse outcomes (2–4). The dose or type of immunosuppression does not appear to be associated with adverse outcomes, and most guidelines recommend continuing immunosuppression during COVID-19 (7). However, real-world data on how immunosuppression was modified during COVID-19 and the impact of these changes on graft function or outcomes are not yet clear.

Early studies have reported that COVID-19 is associated with liver injury, which, in turn, is predictive of severe disease (8–10). However, it is not clear if SARS-CoV-2, the virus that causes COVID-19, causes liver injury in a direct fashion, or if other factors like hepatotoxic medications and comorbid metabolic conditions play a major role. LT recipients present a unique challenge since they are immunosuppressed and hence might not be able to mount an adequate immune response against the virus. Moreover, their immunosuppression is likely to be modified during COVID-19, placing them at risk for acute rejection. In addition, the propensity for drug-drug interactions is higher in these patients, raising concern for hepatotoxicity from medications used during the management of COVID-19. More studies are needed to understand the risk for graft injury in liver transplant recipients who acquire COVID-19.

Here, we report data from a large US multi-center study of LT recipients with COVID-19, and define their patterns of liver enzyme abnormalities, determine the impact of changes in immunosuppression, and identify predictors of liver injury and mortality.

METHODS

Study Design

This is a multicenter observational cohort study on clinical outcomes of COVID-19 in patients who have undergone liver transplantation. This study was carried out by the consortium of investigators to study COVID-19 in chronic liver disease (COLD) (registered Clinicaltrials.gov NCT04439084). Inclusion criteria for this study constituted: age over 18 years, laboratory confirmed diagnosis of COVID-19 and history of liver transplantation(Fig S1). The COLD registry collected de-identified data on patients within the inclusion criteria diagnosed with COVID-19 before May 30, 2020. Only patients with COVID-19 confirmed by PCR-based laboratory diagnosis were included. All participating institutions independently identified patients meeting inclusion criteria and collected data. Death was attributed to COVID-19 if it was clinically related to the COVID-19 illness and there were no other unrelated causes of death (11).

Data collection

We collected de-identified data using 170 structured and text variables in 10 different categories: demographic data, clinical course of COVID-19, comorbidities, laboratory tests within 6 months before the diagnosis of COVID-19, at diagnosis of COVID-19, and after COVID-19, transplant status, immunosuppression, hepatotoxic medications, vasopressor use (if >12 hours) and treatment of COVID-19. For the analysis on liver injury, only patients who had laboratory values for liver tests prior to- and during COVID-19 infection were included. A control group of nontransplant patients with chronic liver disease (CLD) who also had laboratory values for liver tests at the same points was employed (Fig S1).

Statistical analysis

A predefined statistical data analysis plan was used. Continuous variables are expressed as medians and interquartile ranges (IQR) or mean and standard deviation, as appropriate. Categorical variables are summarized as counts and percentages. The statistical significance of differences between groups was evaluated using the independent *t*-test or the Mann-Whitney U test for continuous variables, and the chi-square test for categorical variables.

The primary outcome studied was the presence of acute liver injury. Since changes in AST, bilirubin or albumin can be due to multiple non-hepatic factors, we used ALT, a more specific marker for acute liver injury, to define liver injury. ALT values at the peak of COVID-19 disease were used to define acute liver injury as follows: no liver injury = ALT values <2 times the upper limit of normal (ULN); moderate liver injury 2-5 times ULN; severe liver injury > 5x ULN (10). Patients with both moderate and severe liver injury were classified as having acute liver injury. The cutoffs for normal values of ALT were 19 U/L for women and 30 U/L for men (12). The secondary outcome was all-cause mortality. Severe COVID-19 was defined as admission to the ICU, receipt of vasopressors or mechanical ventilation. To determine the independent risk factors for the primary outcome, we performed multinomial logistic regression analyses. After considering the number of outcome events, the multivariable-adjusted models were confined to variables that were based on clinical plausibility, statistical significance in the univariate model, and had less than 10% missingness.

RESULTS

Demographic and clinical characteristics of Liver Transplant Recipients with COVID-19

We identified 112 liver transplant recipients who were diagnosed with COVID-19 before May 30, 2020 from 15 US medical centers. The median age of the cohort was 61 years (IQR 20), and 54.5% (n = 61) were male. This racially and ethnically diverse study cohort was 39.3% (n = 44) Hispanic, 27.7% (n = 31) non-Hispanic white, and 25.9% (n = 29) non-Hispanic African American. The median follow-up period for the cohort was 20.0 (IQR 19) days. The most common comorbidities were hypertension (53.2% [n = 59]), diabetes mellitus (45.5% [n = 51]), obesity (23.4% [n = 26]) and hyperlipidemia (20.7% [n = 23]). The most common indication for LT was hepatitis C-related cirrhosis (28.6% [n = 32]) followed by non-alcoholic fatty liver disease (NAFLD) (14.3% [n = 16]) and alcohol-related liver disease (ALD) (14.3% [n = 16]). The median time from liver transplant to diagnosis of COVID-19 was 4.0 (IQR 11) years; 12.5% (n = 14) had been transplanted within one year prior to COVID-19 diagnosis.

Clinical outcomes of COVID-19 in liver transplant recipients

The all-cause mortality in our cohort was 22.3% (n = 25). Overall, 72.3% (n = 81) were hospitalized and the median length of hospital stay was 6.5 days (IQR 10). Among the hospitalized patients, 37.0% (n = 30) were admitted to the intensive care unit (ICU) and 29.6% (n=24) received vasopressors. Supplemental oxygen was given to 52.7% (n=59) and 23.2% (n=26) were placed on mechanical ventilation. The most common medications used for treatment of COVID-19 were hydroxychloroquine (37.5%) or azithromycin alone (27.7%). Table 1 shows the clinical and demographic features of the cohort stratified by clinical outcomes.

Patterns of Liver Injury in Liver Transplant Recipients with COVID-19

Our objective was to study the patterns and predictors of acute liver injury in transplant recipients, so we included 82 (73.2%) patients who had the following three longitudinal values of liver enzymes: 1) values prior to the diagnosis of COVID-19, 2) values at the time of diagnosis of COVID-19 and 3) peak values during COVID-19. One patient had a documented diagnosis of acute cellular rejection and, hence, was excluded from further analysis of etiology of liver

injury. We compared the incidence of liver injury with a control group of 375 non-transplant patients with chronic liver disease (CLD). The LT cohort and the control group were matched for median age (63 [IQR 14] vs. 60 [IQR 19]; p=0.10), gender (males 52.4% vs. 56.9%; p=0.669) and incidence of comorbidities like diabetes (47.6% vs. 47.1%, p=1.000), hypertension (57.3% vs. 59.3%, p=0.804) and obesity (26.8% vs. 37.5%, p=0.075). At baseline, prior to the diagnosis of COVID-19, LT recipients and nontransplant patients with CLD had similar median ALT (23 [IQR 22] vs. 25 [IQR 24]; p=0.380). Peak ALT during COVID-19 was higher in non-transplant patients with CLD than LT recipients than (41 [IQR 60] vs. 32.5 [IQR 44]); p=0.043). Correspondingly, the incidence of acute liver injury (peak ALT > 2 ULN) was higher in non-transplant patients with CLD than LT recipients (47.5% vs. 34.6%; p=0.037).

Amongst LT recipients, all three liver enzymes (AST, ALT and alkaline phosphatase) showed significant increases from baseline during COVID-19 (Figure 1a). The pattern of liver injury was predominantly hepatocellular, with the highest increases between baseline and peak values seen in AST (median 19 vs. 41 IU/L , $p < 0.001$) and ALT (median 23 vs. 32 IU/L , $p < 0.001$), followed by alkaline phosphatase (median 100 vs. 120, $p = 0.007$). AST and ALT values closely correlated at all three timepoints ($p<0.0001$ all three). Bilirubin also increased slightly (median 0.6 vs. 0.7, $p = 0.03$) during COVID-19, while albumin significantly decreased (3.7 vs 2.8, $p < 0.001$) (Figure 1a). Further, we evaluated a subgroup of 33 patients who had clinical resolution of COVID-19. A significant decrease in AST (44.9 vs 29.0; $p = 0.005$), ALT (40.3 vs. 29.8; $p = 0.06$) and alkaline phosphatase (212.8 vs 156.3; $p = 0.04$) was noted upon COVID-19 resolution in this cohort. On review of other parameters, a decrease in both leukocytes (6.00 vs 5.18, $p = 0.03$) and platelets (198 vs 158, $p < 0.001$) was observed during COVID-19.

Predictors of Liver Injury in Transplant Recipients during COVID-19

We wanted to determine predictors of liver injury during COVID-19 in LT recipients. The majority of LT recipients had peak ALT < 2x ULN (65.4% [n = 53]); while moderate elevation in ALT 2-5x ULN was seen in 22.2% (n = 18) and severe elevation > 5x ULN in 12.3% (n = 10). Table 2 shows the proportion of liver injury seen in the different clinical and demographic subgroups.

On univariate analysis, patients with more severe COVID-19 i.e. patients who were admitted to the ICU (p = 0.002), received vasopressors (p < 0.001) or were mechanically ventilated (p < 0.001) were more likely to have acute liver injury (ALT <2x ULN). We obtained a detailed list of several classes of potentially hepatotoxic medications the patients had received (Table S1). Among them, receipt of antibiotics was associated with risk for liver injury (p = 0.016), while use of statins, proton pump inhibitors (PPI) or acetaminophen was not. None of the medications used to treat COVID-19 were associated with liver injury.

Multivariate logistic regression was performed to identify independent predictors of liver injury (ALT >2x ULN). Non-Hispanic white transplant recipients had a lower risk for liver injury during COVID-19 (p = 0.016; odds ratio (OR) 0.13 [95% CI: 0.02-0.68]). Younger age (p = 0.009, OR 2.06 [1.20-3.54]), Hispanic ethnicity (p = 0.011; OR 6.01[1.51-23.9]), metabolic syndrome (p = 0.016; OR 5.87 [1.38-24.99]), receipt of vasopressors (p = 0.018; OR 7.34 [1.39-38.52]) and antibiotic use (p = 0.046; OR 6.93 [1.04-46.26]) were associated with independent risk for liver injury (Figure 1b).

Changes in Immunosuppression were not associated with Liver Injury during COVID-19

Tacrolimus (90.1% [n = 73]) was the most common immunosuppressant used, followed by mycophenolate (50.6% [n = 41]) and low dose (<20 gm/day) prednisone (27.2% [n = 22]) (Fig S2a). Immunosuppression was modified in approximately half the patients during COVID-19 (49.4%, [n = 40]). Immunosuppression was mostly changed in patients who had more severe COVID-19 with a higher likelihood of modification in those who were admitted to the ICU (p = 0.020), received vasopressors (p = 0.008) or were on mechanical ventilation (p = 0.012) (Fig S2b). The most common change was holding mycophenolate (33.3% [n = 27]), followed by decrease in tacrolimus dose (25.9% [n = 21]) or holding tacrolimus (4.9% [n = 4]). Acute cellular rejection was reported only in one patient in our cohort, and that patient's tacrolimus dose had been reduced during COVID-19. Reducing tacrolimus (p = 0.735) or holding mycophenolate (p = 0.617) were not associated with liver injury (Table 2). Overall, reduction in immunosuppression during COVID-19 was not associated with liver injury (p = 0.156) or risk for mortality (p = 0.084).

Acute Liver Injury is Associated with Mortality in Transplant Recipients and COVID-19

We evaluated predictors of overall mortality in LT recipients with COVID-19 (Table 4). After adjusting for age, gender, race, ethnicity, comorbidities, time since transplantation and immunosuppression, presence of liver injury was significantly and independently associated with higher overall mortality (p = 0.007; OR = 6.91 [1.68-28.48]) (Figure 1b). The other factor independently associated with overall mortality was diabetes mellitus (p = 0.04; OR = 3.73 [1.04-13.45]). Further, we confirmed that baseline ALT prior to COVID-19 (non-survivors 33.8% vs. survivors 29.2%; p = 0.530) or ALT at diagnosis (non-survivors 38.4% vs. survivors 34.0%; p = 0.641) of COVID-19 did not predict higher mortality. However, peak ALT was significantly higher in non-survivors than survivors (149.8 vs. 43.5; p = 0.001).

We analyzed predictors of ICU admission among LT recipients with COVID-19. Incidence of liver injury was associated with significant and independent risk for ICU admission (p=0.007; OR 7.93 [1.75-35.69]) (Table S2).

DISCUSSION

Liver injury has been reported in a significant proportion of nontransplant patients with COVID-19 but data on transplant recipients is scarce. Liver transplant recipients are at particular risk for graft injury given their immunocompromised state, high prevalence of metabolic comorbidities, and risk for drug-drug interactions leading to hepatotoxicity. Our multicenter observational study of 112 patients explores clinical outcomes and patterns of liver injury in LT recipients with COVID-19. We found that 34.6% of the LT recipients had liver injury during COVID-19, with liver enzyme elevations predominantly in a hepatocellular pattern. Age, Hispanic ethnicity, metabolic syndrome, vasopressor and antibiotic use predicted liver injury, highlighting the multifactorial nature of this process. Moreover, liver injury was independently associated with risk for mortality and ICU admission. Hence following liver enzymes closely can help in the early identification of LT recipients at risk for adverse outcomes with COVID-19. Type of immunosuppression did not have an impact on mortality or liver injury. Real-world data

from our study shows that immunosuppression was modified in 50% of the patients during COVID-19, but only one patient experienced acute rejection and none of the patients experienced graft failure. These data are reassuring and will hopefully guide physicians taking care of LT recipients with COVID-19.

Recent studies in the non-transplant general population have shown that liver injury is relatively common during COVID-19 with rates ranging from 15-53% (8,10). In our study, we show that around a third of LT recipients sustained acute liver injury during COVID-19, but despite being immunocompromised, this rate was lower than that of our non-transplant cohort with CLD (47.5%). There has been significant concern that SARS-CoV-2 may cause cholestatic liver injury since angiotensin-converting enzyme 2 (ACE2), the host cell receptor for the virus, has been reported to be expressed on cholangiocytes (13). But data, including results from our study, consistently show a predominantly hepatocellular pattern of injury (13–15). This raises the possibility that SARS-Co-V2 may cause direct hepatocellular damage, as recently reported by Wang et al (16). Other non-hepatotropic viruses have also been shown to be associated with similar pattern of liver injury. In fact, the rate of liver injury in viral infections from SARS (50.3%) and other human coronaviruses (HCoV) (36.0%) were higher than COVID-19 (22.5%)(8). However, most of this data is from non-transplant patients. In transplant recipients, even though SARS-Co-V and MERS-Co-V have rarely been reported to cause transaminitis (17,18), our study clearly shows that SARS-Co-V2 is associated with liver injury in a substantial proportion of LT recipients.

Drug induced liver injury (DILI) is a major cause for abnormal liver tests. We collected extensive history of various classes of potentially hepatotoxic medications used during the clinical course of COVID-19. We show that patients in the ICU who received vasopressors were more likely to have liver injury, highlighting the association of liver injury with hypotension in severe COVID-19. We identified use of antibiotics, several of which are known to cause DILI, to be another risk factor for liver injury. However, use of acetaminophen, PPIs and statins were not associated with liver injury and these medications can be safely continued during COVID-19. Moreover,

medications commonly used to treat COVID-19 were not associated with significant liver injury, and this should encourage physicians to continue to offer such treatment in this patient population even in the presence of mild to moderate ALT elevations.

The overall mortality in our study was 22.3% (n=25). A similar mortality rate of 20.5% has been reported from 482 solid organ transplant (SOT) recipients in the US (19). The CDC reports that the general US population has a COVID-19 mortality rate of 5% (20). However, the median age of LT recipients who acquire COVID-19 is higher at 60.1 years compared to the reported median age of 48 years in the general population (20). Furthermore, metabolic comorbidities like diabetes and hypertension, which are known to increase COVID-19 severity, were present in almost 50% of the LT recipients in our cohort while it was present in less than a third of the general population with COVID-19 (20). A recent study does report that mortality among COVID-19 SOT recipients is similar to the general population, after controlling for age and other comorbidities (21). Another study from Spain of 111 LT recipients, showed that the mortality rates were actually lower in LT recipients than the matched general population (22). Based on these studies, it appears that transplant itself is not a risk factor of higher COVID-19 mortality, but coexisting comorbidities are. In our study, we report that liver injury is associated with COVID-19 severity. Thus, closely monitoring liver tests can enable earlier identification of patients at risk for adverse outcomes. New promising treatment directed against SARS-Co-V2 which reduces the severity of COVID-19 can potentially also decrease the incidence of liver injury.

During the initial phases of the COVID-19 pandemic, it was not clear how, or if, immunosuppression should be reduced in LT recipients with COVID-19. Following evaluation of early reports, several societies published guidelines recommending continuation of immunosuppression at stable doses for most patients (7,23,24). Real-world data from our study shows that immunosuppression was actually modified in 50% of the patients, but only one patient experienced acute rejection. As expected, immunosuppression was more likely to have been reduced in patients with more severe COVID-19 i.e. those who were in the ICU on

vasopressors. Nonetheless, decreases in immunosuppression were not associated with liver injury or mortality. These data are reassuring and will hopefully guide physicians taking care of LT recipients with COVID-19.

To our knowledge, our study represents one of the largest multicenter cohorts of LT recipients from the US. Another strength of our study is that we evaluated serial changes in ALT to more accurately identify those with liver injury. Different studies have used varying definitions of liver injury, we used standard definitions for ALT cut-offs (12) that have also been used by other groups (8,10). We believe that ALT is a more specific marker of liver injury in this context since AST can originate from the heart, which is also known to be affected during COVID-19 (25). One limitation of our study is potential referral bias, since most of the centers contributing patients to our cohort are tertiary referral centers, but we did include both outpatients and inpatients in this cohort and have captured patients with mild and severe COVID-19. Another limitation is the lack of a control group of the general population with COVID-19, which prevents us from analyzing whether transplant recipients are at higher risk for mortality. Nonetheless, our study furthers our understanding of patterns and incidence of liver injury in LT recipients when compared to a control group of non-transplant patients with CLD. Lastly, longer term follow up will be needed to study the course of liver injury after COVID-19 resolution, but we do present reassuring data from a subgroup of patients who have already recovered.

In conclusion, we show that liver injury is common and is independently associated with mortality with COVID-19. We recommend that liver enzymes should be closely monitored in LT recipients with COVID-19, as they can serve as predictors of outcome. We perform a detailed analysis of various potentially overlapping causes of liver injury and determine that it is mostly driven by hepatotoxic medications and severity of COVID-19. Although antibiotics have been commonly utilized in the direct management of COVID-19, as well as secondary infections, judicious antibiotic stewardship remains a target in infected LT recipients and may reduce risk of liver injury. Further, avoiding hypotension in patients admitted to ICU can potentially mitigate liver injury. Decisions regarding modifications to immunosuppression regimens in LT

recipients with COVID-19 need to be made on a case-by-case basis, but our study shows that immunosuppression can be safely reduced, if necessary. While our subgroup analysis shows that liver injury appears to be transient and mostly resolves following recovery from COVID-19, extended follow up will be needed to understand long term effects.

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TABLE LEGENDS

Table 1 Demographics and Clinical Outcomes in Liver Transplant Recipients with COVID-19

COPD-chronic obstructive pulmonary disease; COVID-19- 2019 Coronavirus Disease; HCQ-hydroxychloroquine; HIV- human immunodeficiency virus; ICU- intensive care unit; MMF-mycophenolate; mTOR-mammalian target of rapamycin; NH- Non-Hispanic

Table 2 Liver Injury during COVID-19 in Liver Transplant Recipients

ALT-alanine transaminase; APAP- acetaminophen; COVID-19- 2019 Coronavirus Disease; ICU-intensive care unit; IQR-interquartile range; MMF- mycophenolate; NH- Non-Hispanic; PPI-proton pump inhibitor; ULN-upper limit of normal

Table 3 Multivariate Analysis of Predictors of Acute Liver Injury in Liver Transplant Recipients with COVID-19

APAP- acetaminophen; CI-confidence interval; COVID-19- 2019 Coronavirus Disease; PPI-proton pump inhibitor

Table 4 Multivariate analysis of Predictors of Mortality in Liver Transplant Recipients with COVID-19

CI-confidence interval; COVID-19- 2019 Coronavirus Disease; DM- diabetes mellitus; HLD-hyperlipidemia; HTN- hypertension; MMF-mycophenolate

FIGURE LEGENDS

Figure 1 Liver Injury in Liver Transplant recipients with COVID-19

a. Pattern of liver test elevations comparing baseline values with values at diagnosis of COVID-19 and peak values during COVID-19.
b. Predictors of liver injury in LT recipients with COVID-19
c. Risk for overall mortality in LT recipients with COVID-19 with patients stratified by presence of liver injury.

COVID-19- 2019 Coronavirus Disease; AST- aspartate transaminase; ALT- alanine transaminase
*$p<0.05$, ***$p<0.001$*

Table 1 Demographics and Clinical Outcomes in Liver Transplant Recipients with COVID-19

Variable	Sub-category	All n=112 (100%)	Death n=25, (22.3%)	Hospitalization n=81, (72.3%)	ICU Admission n=30, (26.8%)
Demographics					
Age	<65	64 (57.1%)	10 (15.6%)	43 (67.2%)	13 (20.3%)
	>/=65	48 (42.9%)	15 (31.3%)	38 (79.2%)	17 (35.4%)
Gender	Male	61 (54.5%)	15 (29.4%)	40 (65.6%)	13 (21.3%)
	Female	51 (45.5%)	10 (16.4%)	41 (80.4%)	17 (33.3%)
Race/Ethnicity	NH White	31 (27.7%)	6 (19.4%)	22 (71.0%)	7 (22.6%)
	NH Black	29 (25.8%)	6 (20.7%)	20 (69.0%)	8 (27.6%)
	NH Asian	5 (4.5%)	2 (40.0%)	4 (80.0%)	2 (40.0%)
	NH Other	3 (2.7%)	1 (33.3%)	1 (33.3%)	1 (33.3%)
	Hispanic or Latino	44 (39.3%)	10 (22.7%)	34 (77.3%)	12 (27.3%)
Indication for Liver Transplantation					
	Hepatitis C	32 (28.6%)	3 (18.8%)	11 (68.8%)	6 (18.8%)
	Hepatitis B	8 (7.1%)	1 (12.5%)	7 (87.5%)	1 (12.5%)
	Alcohol related liver disease	16 (14.3%)	6 (18.8%)	22 (68.8%)	5 (31.3%)
	Non-alcoholic fatty liver disease	16 (14.3%)	9 (56.3%)	15 (93.8%)	10 (62.5%)
	HCC	17 (15.2%)	6 (35.3%)	14 (82.1%)	7 (41.2%)

Comorbidities					
	Diabetes mellitus	51 (45.5%)	18 (35.3%)	40 (78.4%)	18 (35.3%)
	Hypertension	59 (52.6%)	20 (33.3%)	45 (75.0%)	20 (33.3%)
	Hyperlipidemia	23 (20.5%)	8 (34.8%)	21 (91.3%)	9 (39.1%)
	Obesity	26 (23.2%)	6 (23.1%)	19 (73.1%)	9 (34.6%)
	Coronary artery disease	9 (8.0%)	4 (44.4%)	8 (88.9%)	3 (33.3%)
	Congestive heart failure	6 (5.4%)	2 (33.3%)	5 (83.3%)	2 (33.3%)
	HIV	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	COPD	4 (3.6%)	1 (25.0%)	4 (100%)	2 (50.0%)
	Asthma	7 (6.3%)	2 (28.6%)	6 (85.7%)	2 (28.6%)
	Other cancer	7 (6.3%)	5 (71.4%)	7 (100%)	4 (57.1%)
	Obstructive sleep apnea	7 (6.3%)	2 (28.6%)	3 (42.9%)	2 (28.6%)
	Metabolic syndrome	22 (19.6%)	8 (36.4%)	17 (77.3%)	9 (40.9%)
Substance use					
Alcohol use	Current daily drinking	1 (0.9%)	0 (0.0%)	1 (100.0%)	0 (0.0%)
	Social drinking	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Do not drink currently	108 (96.4%)	5 (4.6%)	78 (72.2%)	30 (27.8%)
Tobacco	Current smoker	5 (4.5%)	0 (0.0%)	5 (100.0%)	1 (20.0%)
	Former smoker	39 (34.8%)	10 (25.6%)	26 (66.7%)	12 (30.8%)

	Never smoker	68 (60.7%)	15 (22.1%)	50 (73.5%)	17 (25.0%)
Other	Opioid use	1 (0.9%)	1 (100.0%)	1 (100.0%)	1 (100.0%)
Treatment for COVID-19					
	Remedesivir	3 (2.7%)	1 (33.3%)	3 (100.0%)	2 (66.7%)
	Steroids	4 (3.6%)	2 (50.0%)	4 (100.0%)	3 (75.0%)
	HCQ+ Azithromycin	26 (23.2%)	12 (46.2%)	26 (100.0%)	16 (61.5%)
	HCQ alone	42 (37.5%)	18 (42.9%)	42 (100.0%)	23 (54.8%0
	Azithromycin alone	31 (27.7%)	12 (38.7%)	23 (90.3%)	17 (54.8%)
Immunosuppression					
	Tacrolimus	103 (91.9%)	24 (23.3%)	73 (70.9%)	28 (27.2%)
	Cyclosporine	7 (6.3%)	0 (0.0%)	6 (85.7%)	1 (14.3%)
	MMF	56 (50.0%)	15 (26.8%)	41 (73.2%)	21 (37.5%)
	Azathioprine	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Prednisone-Low Dose*	27 (24.1%)	8 (29.6%)	25 (92.6%)	11 (40.7%)
	Prednisone-High Dose$	7 (6.3%)	1 (14.3%)	6 (85.7%)	2 (28.6%)
	mTOR inhibitors	4 (3.6%)	2 (50.0%)	4 (100.0%)	2 (50.0%)
	Other	3 (2.7%)	1 (33.3%)	3 (100.0%)	1 (33.3%)

*COPD-chronic obstructive pulmonary disease; COVID-19- 2019 Coronavirus Disease; HCQ- hydroxychloroquine; HIV-human immunodeficiency virus; ICU- intensive care unit; MMF- mycophenolate; mTOR-mammalian target of rapamycin; NH- Non-Hispanic; HCC-Hepatocellular carcinoma * Low dose<20 mg/day. $High dose >20 mg/day*

Table 2: Liver Injury during COVID-19 in Liver Transplant Recipients

Variable	Covariate	All Patients (n=81)	ALT <2xULN (n=53, 65.4%)	ALT 2-5x ULN (n=18, 22.2%)	ALT > 5xULN (n=10, 12.3%)	p value
Age	Median (IQR)	63 (14)	65.0 (13)	57.5 (23)	62 .0 (11)	0.406
Gender	Male	38 (46.9%)	29 (54.7)	8 (44.4)	5 (50.0)	0.747
	Female	42 (51.9%)	24 (45.3)	10 (55.6)	5 (50.0)	
Race/Ethnicity	NH White	39 (48.1%)	18 (34.0)	2 (11.0)	1 (10.0)	**0.038**
	NH Black	21 (25.9%)	15 (28.3)	6 (33.3)	1 (10.0)	
	NH Asian	22 (27.2%)	3 (5.7)	1 (5.6)	0 (0)	
	Hispanic or Latino	33 (40.7%)	17 (32.1)	9 (50.0)	7 (70.0)	
Comorbidities	Diabetes Mellitus	38 (46.9%)	20 (37.7)	12 (66.7)	6 (60.0)	0.071
	Hypertension	46 (56.8%)	26 (49.1)	11 (61.1)	9 (90.0)	0.050
	Hyperlipidemia	20 (24.7%)	9 (17.0)	7 (38.9)	4 (40.0)	0.086
	Obesity	21 (25.9%)	11 (20.8)	6 (33.3)	4 (40.0)	0.319
	Metabolic Syndrome	17 (21.0%)	7 (13.2)	6 (33.3)	4 (40.0)	0.056
	Coronary Artery Disease	9 (11.1%)	5 (9.4)	1 (5.6)	3 (30.0)	0.115
Severity of COVID-19	Hospitalization	71 (87.7%)	44 (83.0)	17 (94.4)	10 (100.0)	0.199

	ICU admission	28 (34.6%)	12 (22.6)	7 (38.9)	9 (90.0)	**0.002**
	Mechanical Ventilation	24 (29.6%)	9 (17.0)	6 (33.3)	9 (90.0)	**<0.001**
	Vasopressor use	23 (28.4%)	9 (17.0)	5 (27.8)	9 (90.0)	**<0.001**
	Supplemental Oxygen	54 (66.7%)	33 (62.3)	11 (61.1)	10 (100.0)	0.057
	Death	25 (30.9%)	10 (18.6)	6 (33.3)	8 (80.0)	**0.003**
Hepatotoxic medication	Yes	65 (80.2%)	40 (75.4)	16 (88.8)	9 (90.0)	0.331
	Any Antibiotics	60 (74.1%)	34 (64.15)	16 (88.8)	10 (100.0)	**0.016**
	Cephalosporin	40 (49.4%)	21 (40.4)	10 (55.6)	9 (90.0)	**0.012**
	APAP	29 (35.8%)	16 (49.1)	8 (44.4)	5 (50.0)	0.335
	Statins	16 (19.8%)	9 (17.0)	4 (22.2)	3 (30.0)	0.610
	PPI	33 (40.7%)	21 (39.6)	8 (44.4)	4 (40.0)	0.936
COVID-19 Treatment	Hydroxychloroquine +Azithromycin	23 (28.4%)	13 (24.5)	6 (33.3)	4 (40.0)	0.246
	Hydroxychloroquine	16 (19.8%)	8 (15.1)	5 (27.8)	3 (30.0)	0.347
Immunosuppression	Tacrolimus	73 (90.1%)	46 (86.7)	17 (94.4)	10 (100.0)	0.344
	Cyclosporine	6 (7.4%)	6 (11.3)	0 (0)	0 (0)	0.181
	MMF	41 (50.6%)	28 (52.8)	6 (33.3)	7 (70.0)	0.153
	Prednisone-Low Dose	22 (27.2%)	14 (45.3)	4 (18.2)	4 (40.0)	0.586

Change in Immunosuppression	Decreased Tacrolimus	21 (25.9%)	12 (22.6)	4 (22.2)	5 (50.0)	0.735
	Held MMF	27 (33.3%)	18 (34.0)	4 (22.2)	5 (50.0)	0.617
Labs (peak COVID-19)	Creatinine	1.9 (2.3)	1.6 (2.3)	1.8 (1.7)	4.1 (2.3)	**0.026**
	WBC	5.3 (4.6)	5.0 (3.8)	5.5 (7.4)	14.1 (20.6)	0.237
	Neutrophil	3.4 (4.1)	3.3 (3.8)	4.2 (5.0)	2.7 (10.5)	0.792
	Lymphocyte	0.8 (0.7)	0.8 (0.6)	0.9 (1.4)	0.6 (2.1)	0.145

ALT-alanine transaminase; APAP- acetaminophen; COVID-19- 2019 Coronavirus Disease; ICU- intensive care unit; IQR-interquartile range; MMF- mycophenolate; NH- Non-Hispanic; PPI-proton pump inhibitor; ULN-upper limit of normal

Table 3: Multivariate Analysis of Predictors of Acute Liver Injury in Liver Transplant Recipients with COVID-19

Covariate	**Univariate analysis**			**Multivariate analysis**		
	p value	OR	95% CI	p value	OR	95% CI
Age (years)	0.286	1.21	0.85-1.71	**0.009**	2.06	1.20-3.54
Female Sex	0.494	0.72	0.28-1.79	0.333	1.93	0.51-7.33
Race- White	**0.016**	0.26	0.08-0.79	**0.016**	0.13	0.024-0.68
Ethnicity- Hispanic	**0.035**	2.82	1.09-7.26	**0.011**	6.01	1.51-23.90
Metabolic Syndrome	**0.024**	3.65	1.20-11.07	**0.016**	5.87	1.38-24.99
Antibiotics	**0.007**	7.27	1.55-34.02	**0.046**	6.93	1.04-46.26
Vasopressors	**0.004**	4.88	1.74-13.71	**0.018**	7.34	1.39-38.52

Oxygen requirement	0.324	1.81	0.65-5.04
Immunosuppression modified	0.156	2.07	0.81-5.37
Hydroxychloroquine	0.157	2.250	0.74-6.85
Azithromycin	0.312	1.8	0.68-4.77
Any Hepatotoxic	0.240	2.71	0.70-10.46
APAP	0.223	2.000	0.78-5.16
Statins	0.396	1.630	0.53-4.98
Creatinine (peak during COVID-19)	0.799	0.971	0.77-1.22
PPI	0.815	1.140	0.45-2.89

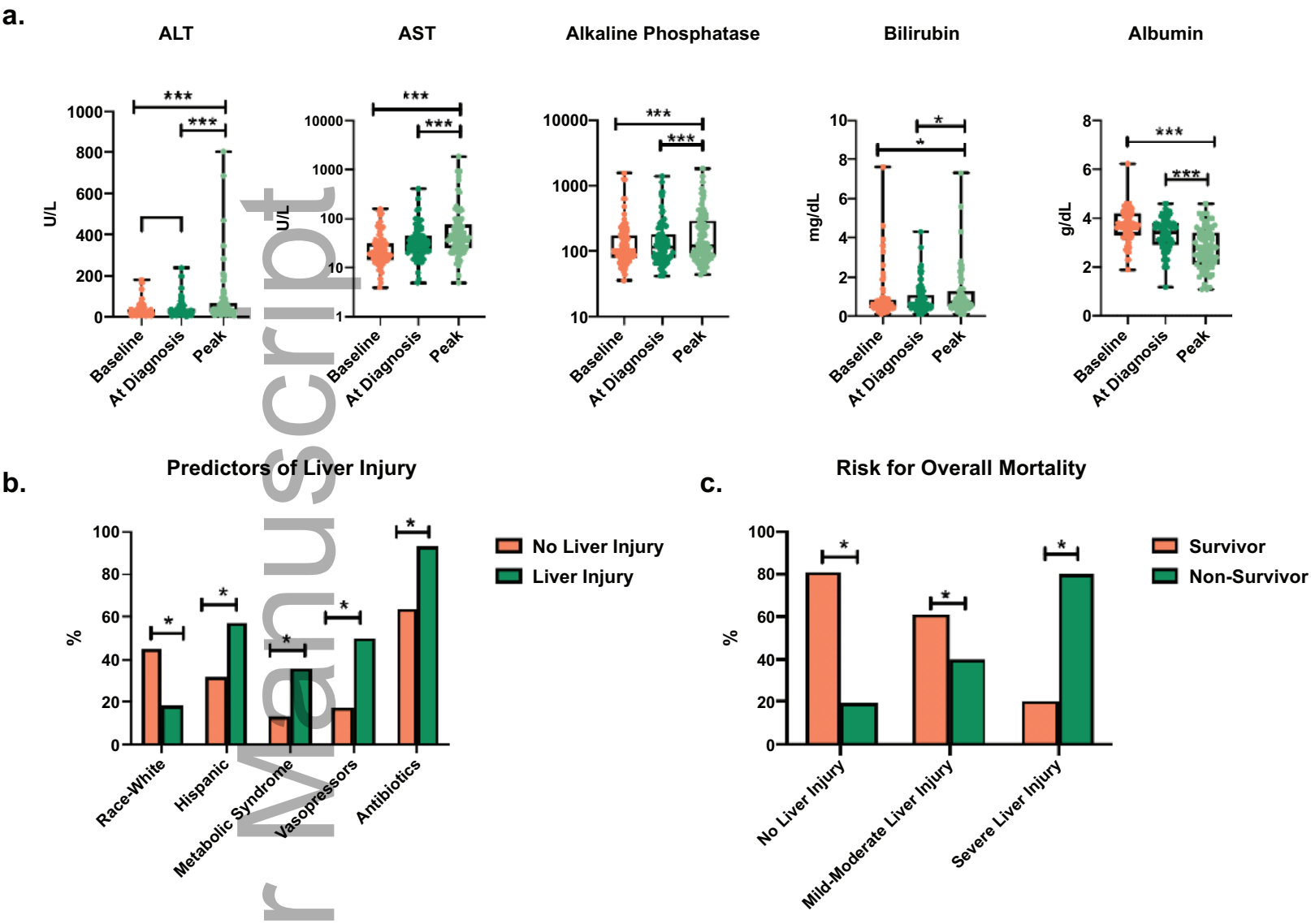
APAP- acetaminophen; CI-confidence interval; COVID-19- 2019 Coronavirus Disease; PPI-proton pump inhibitor

Table 4: Multivariate Analysis of Predictors of Mortality in Liver Transplant Recipients with COVID-19

	Univariate			Multivariate		
	p value	**Odds Ratio**	**95% CI**	**p value**	**Hazard Ratio**	**95% CI**
Liver Injury	**0.002**	4.96	1.80-13.65	**0.007**	6.91	1.67-28.48
Age (>65 years)	0.150	2.15	0.82-5.63	0.130	2.93	0.73-11.81
Sex (Female)	0.229	0.5	0.19-1.30	0.066	3.69	1.11-12.21
Race- Non-Hispanic White	0.803	0.78	0.28-2.13	0.224	1.17	0.35-3.86
Ethnicity-Hispanic	1.000	1	0.36-2.50	0.153	2.01	0.67-13.38

Diabetes Mellitus	**0.004**	4.630	1.65-12.96	**0.044**	3.7	1.04-13.09
Hypertension	**0.028**	3.41	1.18-9.78	0.763	2.04	0.61-6.94
Active Cancer	**0.027**	6.75	1.21-37.63	0.127	10.86	1.04-113.47
Hyperlipidemia	0.404	1.72	0.60-4.92			
Obesity	1.000	0.86	0.29-2.57			
Metabolic Syndrome	0.140	2.45	0.82-7.44			
Time Transplant (<1 year)	1.000	0.91	0.35-2.40			
Immunosuppression Modified	0.084	2.51	0.90-6.95			
Tacrolimus	0.424	3.45	0.39-29.47			
Cyclosporine	0.332	0.75	0.67-0.84			
MMF	0.337	1.73	0.66-4.51			
Prednisone-Low Dose	0.592	1.41	0.50-3.96			

CI-confidence interval; COVID-19- 2019 Coronavirus Disease; DM- diabetes mellitus; HLD- hyperlipidemia; HTN-hypertension; MMF-mycophenolate



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