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The Long-Term Effects and Outcomes of Covid-19 on Elevated Liver Function Tests

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Abstract

Background/Aim: Although Coronavirus disease 2019 (COVID-19) primarily involves the respiratory system, it can also progress to a multisystem illness frequently involving the gastrointestinal tract. It is commonly observed that COVID elevates Liver Function Tests (LFTs) during an acute infection, but not much has been published about the effects once the infection clears. We investigated outcomes of elevated LFTs during a COVID infection as well as long-term LFTs.

Methods: A retrospective cohort study was performed examining patients with COVID between 7/1/2020-11/30/2020 within our hospital system. Of the 1370 patients, we compared LFTs at minimum 3 months prior to COVID, during COVID, and a minimum 3 months after COVID as well as their outcomes.

Results: A total of 1352 patients infected with COVID delta were analyzed. 249 patients were found to have elevated LFTs during hospitalization. Patients with elevated LFTs were more likely to have a longer length of stay, be admitted to the MICU, and intubated as compared to patients with normal LFTs. Patients with elevated LFTs also had significantly lower survival compared to patients with normal LFTs. There was a significant difference between AST, ALT, and ALP during COVID as compared to before and after COVID infection. After a mean 17-month follow-up, patients with elevated LFTs had normalized levels.

Conclusion: Hospitalized COVID patients with elevated LFTs exhibited less survival, longer hospital stay, and more mechanical ventilator use. These patients had elevated LFTs several months after resolution from the respiratory symptoms. Larger prospective observational studies are needed to confirm these associations.

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Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) otherwise known as coronavirus disease-2019 (COVID [-19]) was initially discovered and named due to the significant respiratory distress it ensued. As more people became infected, it was rapidly realized that COVID leads to multiorgan involvement, and commonly involves the gastrointestinal (GI) tract. Common symptoms of these patients included nausea, vomiting, diarrhea, abdominal pain, and loss of appetite [1]. Patients with GI symptoms were also found to have more severe cases of the infection [2,3].

Liver function tests (LFTs) monitor hepatic and bile duct injury, cholestasis, synthetic ability but are not exclusive to the liver. However, the pattern of liver injury seen in patients with COVID is most commonly hepatocellular, with mild elevation of aminotransferases, hyperbilirubinemia, hypoalbuminemia, and elevated γ-glutamytransferase [4]. The initial understanding of elevated LFTs was due to myositis and inflammation [5].

Bertolini et al performed a meta-analysis to review the possible pathogenesis of COVID infecting the GI tract. They observed elevated LFTs were more inflated in the American population in comparison to Asians, included patients with and without chronic liver disease [6,7]. GI epithelial cells express angiotensin-converting enzyme 2 (ACE2), the receptor for SARS-CoV-2, and possess transmembrane serine protease 2 (TMPRSS2) which cleaves the spike protein allowing entrance into hepatocytes and cholangiocytes [8,9,10]. Viral replication occurs on the brush border of the small intestine where ACE2 receptors are expressed and transport the virus into portal circulation and the liver [11]. It is hypothesized that Kupffer cells attempt to clear the infection and cause an inflammatory process causing a cytokine storm, coagulopathy, and/or organ damage [12].

In addition, studies report a correlation between COVID-19 severity and liver function test abnormalities [13]. Although many studies have reported the acute effects of COVID-19 on LFTs, not much information is known regarding the long-term effects of COVID-19 on LFTs. Here, we present a retrospective cohort study which investigates the long-term effects of LFTs in COVID-19 patients at our hospital. To our knowledge, this is the first report of long-term liver enzyme elevations in COVID patients.

Methods

A retrospective cohort study was performed examining hospitalized patients with an active COVID infection between 7/1/2020-11/30/2020 within our hospital system. There were 1370 patients hospitalized during this time and no individual was excluded from the initial study. We obtained data points at the beginning of their hospitalization to exclude confounding factors.

We defined elevated liver function tests to be twice the upper limit of normal at our hospital. The liver tests being monitored were total bilirubin, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), and Alkaline Phosphatase (ALP). The upper limit of normal from our institution was total bilirubin is 1.0mg/dL, AST 40 U/L, ALT 44 U/L, ALP 135 U/L. Eighteen patients were excluded as they were outliers based upon the interquartile range. We stated a patient had elevated liver function tests if they had an elevation in one of the four LFTs being monitored. We compared liver function tests at a minimum of 3 to 12 months prior to their COVID infection, the day of admission with their positive COVID infection, and a minimum of 3 to 12 months after discharge. We also compared outcomes between cohorts during their hospitalization. The outcomes included initial level of care, ventilator use, length of stay, and survival.

We used pairwise Wilcoxon rank sum test with Benzamini Hochberg continuity correction to compare continuous variables and Chi-Square test to compare categorical variables. Unadjusted and adjusted association of elevated LFTs were analyzed using logistic regression model. The mean was calculated to compare the changes in the different liver tests prior, during, and after COVID infection. We subsequently followed patients with elevated LFTs until January 2023 to determine if there any alterations in LFTs.

Results

A total of 1352 patients were analyzed from the 1370 because 18 were excluded as they were outliers. Baseline characteristics between the two groups and additional information can be found on **Table 1**. There were 657 (48.5%) males and 695 (51.5%) females. 249 patients were found to have elevated LFTs during initial hospitalization. Females were more likely to develop elevated LFTs than males (p <0.001).

There were 125 patients admitted to the MICU of which 39 (15.7%) of the patients had elevated LFTs in comparison to the 86 (7.8%) with normal LFTs. There were 111 patients requiring mechanical ventilation of which 35 (14.1%) patients had elevated LFTs as compared to 76 (6.9%) patients with normal LFTs. The mean length of stay for patients with normal LFTs was 7.65 days and 9.1 days for those with elevated LFTs. Overall, patients with elevated LFTs were more likely to have a longer length of stay (aOR 1.02, 95% CI 1.002 – 1.029, p=0.0093), more likely to be admitted to the MICU (aOR 1.55, 95% CI, 1.251 – 1.899, p=0.0017) and more likely to be intubated (aOR 2.34, 95% CI, 1.051 – 3.6, p=0.0005) as compared to patients with normal LFTs. Patients with elevated LFTs also had significantly lower survival compared to patients with normal LFTs (aOR 0.39, 95% CI 0.26-0.59, p<0.0001). **Table 2** shows adjusted and univariate analysis of elevated versus normal liver function tests.

Pairwise comparisons of LFTs at minimum 3 months before and after COVID infection showed no statistically significant difference between AST, ALT, ALP, and total bilirubin, p = 0.43, 0.062, 0.25, and 0.58, respectfully. However, there was a significant difference between AST, ALT, and ALP during COVID when compared to before and after COVID infection (p<0.0001). **Table 3** shows the mean values for each liver function test before, during, and after COVID for all patients until December 2021. **Table 4** shows the mean values of patients with elevated LFTs during their COVID infection and on average 21 months after infection; data reviewed through January 2023. Patients were followed between 4-30 months after their infection. Several patients were either lost to follow or were deceased. Of the patients followed, 10 had continued elevated total bilirubin likely from underlying sickle cell disease, pancreatic cancer, or choledocholithiasis found on ultrasound imagining per chart review. 2 patients had elevated ALT likely from rosuvastatin use and non-alcoholic fatty liver disease found on ultrasound per chart review.

Table 1: Baseline Characteristics of Patients.

	Overall	Normal LFTs	Elevated LFTs	P-value
Patients	1352	1103	249	
Age in years (SD)	62.3 (15.6)	62.7 (15.3)	60.8 (16.5)	
Gender				
Male (n, %)	657, (48.5%)	560 (50.8%)	97 (39%)	0.00075
Female (n, %)	695 (51.5%)	543 (49.2%)	152 (61%)	
Race				0.224
African American	535 (39.6%)	436 (39.5%)	100 (40.2%)	
Caucasian	665 (49.2%)	551 (50%)	114 (45.8%)	
Other	151 (11.2%)	116 (10.5%)	35 (14.1%)	
BMI (mean, SD)	33.5 (9.7)	33.5 (9.73)	33.3 (9.74)	
Comorbidities				
HTN	996, 73.7%	826 (74.9%)	170 (68.3%)	0.038
DM	577, 42.7%	468 (42.4%)	109 (43.8%)	0.72
HLD	644, 47.6%	540 (49%)	104 (41.8%)	0.042
CKD	239, 17.7%	196 (17.8%)	43 (17.3%)	0.926
CAD	260, 19.2%	216 (19.6%)	44 (17.7%)	0.53
CHF	228, 16.9%	186 (16.9%)	42 (16.9%)	1
GERD	256, 18.9%	213 (19.3%)	43 (17.3%)	0.53
CVA	106, 7.8%	92 (8.3%)	14 (5.6%)	0.191
OSA	159, 11.8%	136 (12.3%)	23 (9.2%)	0.192
Cancer	152, 11.2%	118 (10.7%)	34 (13.7%)	0.184
Liver Cirrhosis	18, 1.3%	13 (1.2%)	5 (2%)	0.35
OUTCOMES				
Level of care on admission				0.00025
Floor	1227, 90.8%	1017 (92.2%)	210 (84.3%)	
ICU	125, 9.2%	86 (7.8%)	39 (15.7%)	
Treatment				
Mechanical Ventilation used	111 (8.2%)	76 (6.9%)	35 (14.1%)	0.0005
Mean (SD) length of Stay (days)	7.95 (9.33)	7.65 (9.08)	9.1 (9.91)	<0.0001
Disposition				<0.0001
Discharged	1226, 90.7%	1018 (92.3%)	208 (83.5%)	
Expired	126, 9.3%	85 (7.7%)	41 (16.5%)	

Table 2: Outcomes of Elevated LFTs versus Non-elevated LFTs.

	Univariate OR (95% CI)	p-value	Adjusted OR* (95% CI)	p-value
Length of Stay*	1.015 (1.001 – 1.028)	<0.0001	1.016 (1.002 – 1.029)	0.0093
Level of Admission*	1.482 (1.204 – 1.81)	0.0003	1.546 (1.251 – 1.899)	0.0017
Ventilation*	2.21 (1.429 – 3.362)	0.0005	2.343 (1.051 – 3.6)	0.0005
Survival*	0.424 (0.285-0.638)	0.0001	0.388 (0.257 – 0.594)	<0.0001

*Adjusted for age, gender, race, BMI, comorbidities

Table 3: Variations in Liver Function Tests in Respect to Time.

	Total Bilirubin	AST	ALT	ALP
Before COVID^{+}	0.89	24	25	87
During COVID^{+*}	0.65	58	50	87
After COVID^{+}	0.7	38	34	89

$^{+}$Depicts mean liver function tests of study population.

*The mean differences for AST, ALT, ALP during an active COVID infection as compared to baseline and post infection, p<0.001. While comparing differences in total bilirubin before, during and after infection, there were no statistically significant changes seen, p=0.27, p= 0.17 respectfully.

Table 4: Long-term Differences in Liver Function Tests of Patients with Elevated LFTs during COVID.

	Total Bilirubin	AST	ALT	ALP
During COVID+	1.07	119	111	119
After COVID+	0.81	28	31	93

+Depicts mean liver function tests of study population with elevated LFTs during and after COVID infection.

Discussion

We had 1352 patients analyzed in this study of which 249 patients (18.4%) had elevated liver function tests. This number is lower than the reported average of 25-48% [14,15,17,18]. This is a unique finding given that comorbidities and obesity have been associated with worse outcomes and higher liver dysfunction [16,18]. The findings from our COVID patients with elevated LFTs during hospitalization exhibited longer hospital stay and higher use of ventilators as well as lower survival. These findings are commonly seen in other studies; however, our patients had a lower risk in outcomes [15]. Interestingly, the risk is higher when compared to studies in China [17]. This could be due to the lower percentage of patients developing elevated LFTs in our study population, but when compared to Asian countries, there might be a higher prevalence of undiagnosed Chronic Liver Disease (CLD) such as non-alcoholic fatty liver disease.

We observed that hypertension and hyperlipidemia are associated as comorbidities increasing the likelihood of elevated LFTs, but there are other comorbidities that are commonly found in patients with elevated LFTs such as diabetes, chronic kidney disease, coronary artery disease, congestive heart failure, and cancer. There were only 18 patients included in the study who had a diagnosis of liver cirrhosis in our patient population, and we did not include other chronic liver diseases. We studied the mean values in liver function tests prior to patients being infected with COVID, during the first day of testing positive for COVID, and after the infection. The mean differences for AST, ALT, ALP during an active COVID infection as compared to baseline and post infection, $p<0.001$. While comparing differences in total bilirubin before, during and after infection, there were no statistically significant changes seen, $p=0.27$, $p= 0.17$ respectfully. This suggests a hepatocellular or mixed type of injury over cholestatic. These results are consistent with prior studies which suggest that COVID may induce parenchymal changes to the liver leading to chronic liver disease. However, larger prospective observational studies are needed to confirm these associations. Mani et al evaluated challenges facing patients with chronic liver disease and discovered the prevalence of chronic liver disease patients will only increase due to the lack of screening and educational programs as well as delays in treatment [19].

We also studied patients with elevated LFTs from July 2020 to January 2023. We found that most patients who developed elevated LFTs during their COVID infection would have normalized liver function tests in the future. Several patients had normalized levels within a year, but on average these patients were followed for 21 months (4-30 months). A limitation to this study was only 52% of patients with elevated LFTs were followed outside of their hospitalization within our hospital system. Several patients were lost to follow-up due to possible fear of seeing doctors or having repeat infection, having other privative practitioners, or died in hospital with the initial infection. The significant loss of patients to follow-up could have introduced bias into the long-term LFT values.

We had other limitations in this study. Another parameter we should consider is past medical history not inquired about such as tobacco, alcohol, drug use, or any immunosuppression and if they had any effect on LFTs or outcomes. Future directions of this study could include researching the effects of other COVID variants, vaccination status influence on outcomes, and if obesity has an underlying liver pathology contributing to elevated LFTs in COVID patients.

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