

Increased Serum Aminotransferase Activity and Clinical Outcomes in Coronavirus Disease 2019



Preethi Ramachandran^{*}, Abhilash Periseti[†], Mahesh Gajendran[‡], Abhishek Chakraborti[§], Joshua T. Narh[§], Hemant Goyal[†]

^{*}Brookdale University Hospital and Medical Center, Brooklyn, NY, 11212, USA, [†]Department of Gastroenterology and Hepatology, University of Arkansas for Medical Sciences, Little Rock, AR, USA, [‡]Texas Tech University, Paul L Foster School of Medicine, El Paso, TX, 79905, USA, [§]Department of Internal Medicine, Brookdale University Hospital and Medical Center, Brooklyn, NY, 11212, USA and [†]The Wright Center for Graduate Medical Education, 501 S. Washington Avenue, Scranton, PA, 18503, USA

Aim: Elevation of hepatic aminotransferases (aspartate aminotransferase [AST]/alanine aminotransferase [ALT]) is commonly noted among COVID-19 patients. It is unclear if they can predict the clinical outcomes among hospitalized COVID-19 patients. We aim to assess if elevations in AST/ALT were associated with poor outcomes in hospitalized COVID-19 patients. **Methods:** We retrospectively evaluated hospitalized COVID-19 patients with clinically significant elevated aminotransferases (defined as >2 times upper limit of normal) and compared them with COVID-19 patients without an elevation in aminotransferases. **Results:** The prevalence of elevation in AST/ALT was found to be 13.7% (20/145). The two groups were similar in baseline demographics, comorbidities, and the majority of laboratory tests. There was no difference in the mortality (50% vs. 36.8%, $P = 0.32$) and median hospital stay (7 days vs. 7 days, $P = 0.78$). However, there was a statistically significant increase in the rates of mechanical ventilation among elevated aminotransferases group compared with individuals without elevation (50% vs. 24%, $P = 0.028$). However, this difference was not observed after adjusting for inflammatory markers such as ferritin, lactate dehydrogenase, and lactic acid levels. **Conclusion:** Elevated aminotransferases among hospitalized COVID-19 patients is associated with higher rates of mechanical ventilation but did not achieve statistical significance after controlling for inflammatory markers. Also, patients with elevated aminotransferases did not have higher rates of mortality or prolonged length of stay. (J CLIN EXP HEPATOL 2020;10:533-539)

The Coronavirus Disease 2019 (COVID-19) is caused by novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). It started as a cluster of pneumonia cases in Wuhan, China and subsequently spread to the rest of the world.¹ During the initial outbreak of COVID-19, respiratory manifestations were the primary symptoms at the time of presentation. As more data emerged, gastrointestinal (GI) and hepatic involvements

were increasingly recognized as important manifestations of COVID-19 patients.¹⁻⁵

SARS-CoV-2 binds to its functional receptor-angiotensin-converting enzyme 2 (ACE-2) and gets internalized into the target cells.⁶ ACE-2 receptor levels are highly expressed in the small intestine (including terminal ileum). It could explain the pathogenesis of GI manifestations such as nausea, vomiting, and diarrhea. Moreover, ACE-2 receptors are also expressed in cholangiocytes and hepatocytes, indicating that SARS-CoV-2 might directly bind to these cells resulting in hepatic dysfunction.^{7,8} Patients with preexisting liver diseases are at increased risk of COVID-19, possibly because of their immunocompromised status, but it is unclear if these individuals are at increased risk of mortality too.⁹

Elevated aminotransferases are commonly identified in COVID-19 patients. The precise definition of elevated aminotransferases remains unclear as studies have used variable levels of AST/ALT to define liver injury.^{5,10-12} It could explain the differences in reported prevalence of deranged liver chemistries in patients with COVID-19 (ranging from 14% to 53%).¹³ Additionally, aminotransferases levels at presentation may differ from levels during the course of the disease. Though the minimal rise in aminotransferases is expected primarily because of sepsis,

Keywords: COVID-19, aminotransaminase, abnormal liver chemistries, SARS-CoV-2, mortality, length of stay, clinical outcomes, coronavirus
Received: 15.5.2020; Accepted: 14.6.2020; Available online 30 June 2020

Address for correspondence: Hemant Goyal. Tel.: +570 591 5175

E-mail: doc.hemant@yahoo.com

Abbreviations: angiotensin-converting enzyme 2: [ACE-2]; angiotensin-converting enzyme inhibitor: [ACEI]; alanine aminotransferase: [ALT]; angiotensin receptor blocker: [ARB]; aspartate aminotransferase: [AST]; body mass index: [BMI]; coronary artery disease: [CAD]; chronic obstructive pulmonary disease: [COPD]; Coronavirus Disease 2019: [COVID-19]; creatine phosphokinase: [CPK]; C-reactive protein: [CRP]; gastrointestinal: [GI]; international normalized ratio: [INR]; interquartile range: [IQR]; lactate dehydrogenase: [LDH]; Length of stay: [LOS]; nonsteroidal anti-inflammatory drugs: [NSAIDs]; severe acute respiratory syndrome coronavirus-2: [SARS-CoV-2]; white blood cell count: [WBC]

<https://doi.org/10.1016/j.jceh.2020.06.009>

clinically significant elevation of at least twice the upper limit of normal (ULN) levels is crucial to recognize.¹⁴ Furthermore, it remains to be studied if such significantly elevated liver biochemistries predict outcomes in COVID-19 patients.

Owing to these gaps in current knowledge, we aim to measure the prevalence of clinically significant (twice the ULN) elevation of aminotransferase levels in hospitalized COVID-19 patients. We also assessed if this elevation is associated with poor outcomes during hospitalization when compared with the COVID-19 patients without significantly elevated aminotransferases.

METHODS

Study design and data source

It is a retrospective study from a single tertiary care academic medical center in New York, which is profoundly affected during the pandemic. This study has been approved by the institutional review board. All consecutive adult patients admitted to the Brookdale University Hospital and Medical Center with confirmed COVID-19 from March 18, 2020 to March 31, 2020 were analyzed. Inclusion criteria were all hospitalized patients with a positive nasopharyngeal swab for SARS-CoV-2, adults age 18 years or older. Exclusion criteria were individuals who were not hospitalized or treated on an ambulatory basis, pregnancy, and unavailability of nasopharyngeal testing or laboratory data.

Data related to patient characteristics such as presenting symptoms, comorbidities, home medications, and initial laboratory tests were obtained. Demographic variables such as age, sex, race, smoking status, and median body mass index (BMI) were recorded. Multiple comorbid conditions such as a history of hypertension, dyslipidemia, coronary artery disease (CAD), diabetes (DM), history of any cancer, chronic liver disease, chronic obstructive pulmonary disease (COPD), and asthma were noted. Respiratory symptoms, such as cough, fever, dyspnea, fatigue, and myalgia, were noted. Medication history of use of angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB), nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, or statin use were collected. Furthermore, laboratory data such as median hemoglobin level, white blood cell count (WBC), lymphocyte count, platelet count, ferritin, C-reactive protein (CRP), lactate, and lactate dehydrogenase (LDH) were obtained.

Stratification of study cohort and outcomes

In our study, a significant elevation of aminotransferases was defined as 2 times elevation of either ALT (normal 21–72 international units per liter [IU/L]) or AST (normal 17–59 IU/L) or both from the upper normal limit.¹⁴ Based

on these criteria at presentation, the study cohort was stratified into 2 groups, COVID-19 patients with elevated aminotransferases (cases) and COVID-19 patients without elevated aminotransferases (controls).

The primary outcome in this study is hospital mortality from any cause, and the secondary outcomes are mechanical ventilation and the total length of stay (LOS) in the hospital. The patients who required mechanical ventilation or died in the hospital were considered to have severe COVID-19 in our study. Statistical analysis was performed using IBM SPSS software, version 26 (SPSS Inc, Armonk, NY). Descriptive summary statistics are presented as median with interquartile range (IQR) for the continuous variables, because most of the variables are non-normally distributed and as frequencies with percentages for categorical variables. Categorical and continuous variables were tested for statistical significance using chi-square tests and nonparametric tests, respectively. Multivariate logistic regression analysis was done for the primary dichotomous outcome variable to adjust for confounding variables. Univariate predictor variables with $P < 0.05$ were included in the multivariate analysis.

RESULTS

Study population and baseline demographics

A total of 150 hospitalized COVID-19 patients were analyzed. Five patients were excluded because of the unavailability of labs and key outcome variables. A total of 145 patients met the inclusion criteria and formed our final study population (Figure 1). Of them, 13.7% (20/145 patients) had elevated aminotransferases (cases), and 125 patients were without elevated aminotransferases (controls). The patients in the elevated aminotransferases group had a median AST of 169 IU/L (IQR 131–264.3 IU/L) and a median ALT of 99.5 IU/L (IQR 65–166.8 IU/L).

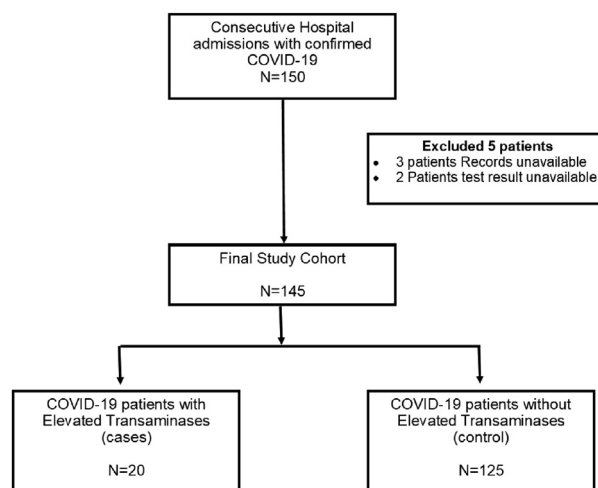


Figure 1 Study flow chart.

L). The patients in the control group had a median AST of 50.37 IU/L (IQR 34–65 IU/L) and a median ALT of 39.91 IU/L (IQR 27–47 IU/L).

Table 1 outlines the baseline demographics and comorbidities between the 2 groups. Among cases, the median age was 59.5 years (IQR 46–70.8 years) compared with 63 years (IQR 53.5–74 years) in controls ($P = 0.88$). The predominant population in our study was African Americans, consisting of 80% of cases and 74% of controls. The median BMI was higher in cases when compared with controls (32.3 vs. 28.3, $P = 0.02$). Comorbidities such as hypertension, dyslipidemia, COPD, asthma, CAD, DM, and cancer were similarly distributed between both groups (**Table 1**). None of the patients in either groups had a documented history of chronic liver disease including alcohol liver disease and nonalcoholic steatohepatitis. The utilization of home medications such as NSAIDs and statins were similar between the 2 groups.

Laboratory data

Table 2 outlines the laboratory values between the two groups. Other liver chemistries as such as albumin, international normalized ratio, total bilirubin, and alkaline phosphatase levels did not differ among the 2 groups. Median hemoglobin, WBC, lymphocyte count, and platelet counts were noted with no statistical difference between the 2 groups. The median ferritin level was 1680 ng/ml in cases (IQR 517.8–3037.5 ng/ml) and 400 ng/ml in the controls (IQR 145–896 ng/ml), but was not statistically significant ($P = 0.11$). Median lactic acid and LDH levels were significantly higher in the cases, as noted in **table 2**. However, D-dimer, creatine phosphokinase, and CRP were similar in both groups.

Outcomes

The outcomes of the study are outlined in **Table 3**. There were no statistically significant differences in the mortality rates between the cases and controls (50% vs. 36.8%, $P = 0.32$). There was a statistically significant increase in rates of mechanical ventilation among elevated aminotransferases group when compared with the control group (50% vs. 24%, $P = 0.028$). There was no difference found in other secondary outcomes: median hospital LOS (7 [IQR 4.3–10.3] days vs. 7 [IQR 5–10] days, $P = 0.78$), and frequency of patients who had shock during hospitalization (45% vs. 30.4%, $P = 0.21$) were not different between the two groups.

Multivariate analysis was performed for outcome variables by including statistically significant covariates ($P < 0.05$) in the univariate analysis, which includes ferritin, LDH, and WBC. The elevated aminotransferases did not become statistically significant for mechanical ventilation as an outcome when adjusted with the variables, as mentioned earlier.

DISCUSSION

Based on our study, 13.7% of patients admitted for COVID-19 had significantly elevated aminotransferases at presentation. Elevated aminotransferases were associated with an increased rate of mechanical ventilation but did not achieve statistical significance after controlling for inflammatory markers. However, there was no increase in the mortality rate or length of stay among patients with elevated aminotransferases.

Our study findings are similar to prior studies with abnormal liver tests. However, the prevalence of abnormal aminotransferases was found to be a lower range^{1,8,10,11,15,16,17}, which could probably be because of strict criteria of inclusion of patients with clinically significant aminotransferase elevation (twice the ULN). A recent meta-analysis reported that 15% of the patients with COVID-19 had abnormal aminotransferases, and 16.7% had abnormal bilirubin, both of which are defined as any value above the upper limit of normal.¹⁸ Also, the aminotransferases were significantly higher in COVID-19 patients with the severe disease when compared with nonsevere disease.^{10,19,20} In a study by Cholankeril et al., 40% of the patients (26/65) had elevated liver enzymes, and most of these patients had normal liver enzymes at baseline.¹⁶ Guan et al. studied 1099 patients in China during an outbreak with COVID-19 and noted that any elevated AST or ALT was noted in 22% of patients.⁵ Total bilirubin was elevated in 11%, and LDH elevation was noted in 41% of patients. It is unclear about the degree of elevation (if 2 times or 3 times ULN) in these patients. Similarly, a descriptive study of 99 patients by Chen et al. noted elevated AST in 35% and ALT in 28% cases.¹⁰ Zhang et al. reported AST elevations in 15% (17/115 patients) and ALT in 10% (11/115 patients).¹¹ These elevations in aminotransferases correlated with markers of inflammation (CRP and neutrophilic lymphocyte ratio) but did not show an independent association with severe COVID-19. Huang et al. analyzed 41 patients with COVID-19 and reported AST elevation in 37% (15/41) of the patients.¹ A retrospective study of 148 patients at Shanghai Health center, China showed that AST was elevated in 22% and ALT in 18% of cases.²¹ In this study, authors noted that 45 patients with normal liver tests on admission developed abnormal tests at a median of 7 days after admission, indicating that multiple interventions, medications, and hemodynamic changes could contribute to these findings.

It is unclear if abnormal liver enzymes could predict severe disease and poor outcomes in COVID-19 patients. In a study by Hajifathalian et al., liver injury at presentation was associated with a 2.3 times higher risk for ICU admission and death.¹⁷ In a study, Cai et al. significantly elevated (defined as 3 times the ULN) AST, and ALT levels at admission were associated with higher odds of progressing to severe disease.¹² Xie et al. reported that patients with elevated

Table 1 Baseline Demographics of the Study Population^a.

Patients' Characteristic	COVID-19 patients with elevated aminotransferases N = 20	COVID-19 patients without elevated aminotransferases N = 125	P-value
Age in years, median (IQR)	59.5 (46,70.8)	63 (53.5, 74)	0.88
Age > 60 years	10 (50%)	80 (64%)	0.32
Female gender	10 (50%)	56 (44.8%)	0.81
BMI, median (IQR)	32.3 (28.3, 39.8)	28.3 (25.6, 33.5)	0.02
Race			0.86
• White	0 (0%)	6 (4.8%)	
• African American	16 (80%)	92 (73.6%)	
• Hispanic	2 (10%)	11 (8.8%)	
• Asian	1 (5%)	6 (4.8%)	
• Unknown	1 (5%)	10 (8%)	
Comorbidities			
• Hypertension	15 (75%)	84 (67.2%)	0.61
• Dyslipidemia	7 (35%)	44 (35.2%)	1
• CAD	4 (20%)	20 (16%)	0.75
• Diabetes Mellitus	6 (30%)	56 (44.8%)	0.24
• Cancer	2 (10%)	13 (10.4%)	1
• COPD	3 (15%)	10 (8%)	0.39
• Asthma	3 (15%)	20 (16%)	1
Immunocompromised Status	3 (15%)	18 (14.4%)	1
Smoker	1 (5%)	15 (12%)	0.69
Medications			
• ACEI/ARB	6 (30%)	43 (34.4%)	0.8
• NSAID	1 (5%)	30 (24%)	0.08
• Aspirin	3 (15%)	42 (33.6%)	0.12
• Statin	8 (40%)	59 (47.2%)	0.63
• PPI	7 (35%)	51 (40.8%)	0.81
• H2B	6 (30%)	29 (23.2%)	0.58
Symptoms			
• Cough	12 (60%)	86 (68.8%)	0.45
• Fever	10 (50%)	89 (71.2%)	0.07
• Dyspnea	15 (75%)	81 (64.8%)	0.45
• Fatigue	9 (45%)	68 (54.4%)	0.47
• Myalgia	4 (20%)	54 (43.2%)	0.053
• GI symptom	5 (25%)	25 (20%)	0.57
Pneumonia	20 (100%)	124 (99.2%)	1

IQR: Interquartile Range; BMI: Body Mass Index; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; ACEI: Angiotensin-converting enzyme inhibitors; ARB: angiotensin-receptor blockers; NSAID: Nonsteroidal anti-inflammatory drugs; PPI: Proton pump inhibitors; H2B:H2 blockers.

^α Ferritin 38% missing variable.

^β D-dimer 78% missing variable.

^aNonparametric test (Mann–Whitney test) used for non-normal distributed continuous variable, and Chi-square test was used for the categorical variable.

COVID-19

Table 2 Laboratory Data.

Patients' laboratory values	COVID-19 patients with elevated a minotransferases N = 20	COVID-19 patients without elevated a minotransferases N = 125	P-value
Hemoglobin	12.8 (12.0, 13.7)	13.2 (11.8,14.2)	0.58
Ferritin*	1680 (517.8, 3037.5)	400 (145,896)	0.11
D-dimer*	2251.5 (316.8, 5240.8)	570 (189,2434)	0.65
WBC	8.2 (6.5, 9.7)	6.3 (5.1, 8.3)	0.03
Lymphocyte count	1.1 (0.8, 1.8)	1 (0.7,1.4)	0.55
Platelet count	201.5 (168.8, 276)	187 (149, 241)	0.19
Creatinine	1.3 (0.7, 1.8)	1.1 (0.8, 1.8)	0.78
Albumin	3.8 (3.4, 4.2)	3.8 (3.4, 4.1)	0.87
INR	1.2 (1.1, 1.3)	1.2 (1.1, 1.3)	1
CPK	215 (89, 905)	204 (107.5, 457)	1
Lactate	2.1 (1.8, 6.2)	1.5 (1.1, 1.9)	0.007
LDH	1648.5 (1317, 2989.8)	916 (698.8, 1198.5)	<0.001
CRP	16.5 (5.5, 21.8)	7.1 (4.3, 17)	0.35
Bilirubin	0.8 (0.6, 1.4)	0.6 (0.4,0.8)	0.89
Alkaline phosphatase	81 (67, 158)	75 (59, 90)	0.09

WBC: White Blood Cells; INR: International Normalized Ratio; CPK: Creatine Phosphokinase; LDH: Lactate Dehydrogenase; CRP: c-Reactive Protein. [€] Nonparametric test (Mann–Whitney test) used for non-normal distributed continuous variable.

liver enzymes had longer LOS.²² Also, the extent of pulmonary lesions on CT scan was a predictor of liver function abnormality in the same study.²⁰

Similarly, Fan et al. noted that patients with abnormal liver function tests had longer LOS.²¹ It is essential to recognize that patients in abnormal liver function groups also had higher levels of procalcitonin, CRP, and LDH, which could indicate that these patients were sicker at the time of admission. In our study, there was no increase in mortality or LOS in patients with elevated aminotransferases. However, we found that the rate of mechanical ventilation was significantly higher in patients with elevated aminotransferases, but the statistical significance was lost when adjusted for confounding variables.

None of the studies have reported a detailed workup of abnormal liver tests in the setting of COVID-19. Furthermore, the mechanism of liver involvement in COVID-19 is unclear, although various mechanisms have been proposed. ACE-2 is expressed in biliary epithelium and hepatocytes. Biliary epithelial ACE-2 expression can be as high as 20 times that of hepatocytes.¹⁵ This could expose hepatic and biliary epithelium to direct viral entry with ACE-2 receptors. Other possible mechanisms include SARS-CoV-2-induced direct hepatotoxicity, immune-mediated damage in the setting of excess cytokine release.²³ Drug-induced liver injury and reactivation of undiagnosed preexisting liver disease have also been thought to be the possible mechanisms.^{7,24} Histologically, reports of direct viral cytotoxicity (such as microvesicular steatosis, mild lobular, and portal activity) and drug-induced liver injury have been noted.^{11,25} In our study population, we did not find any

differences in use of home medications that can cause liver injury nor increased frequency of chronic liver disease. We observed that the patients with elevated liver enzyme groups had higher inflammatory markers (such as ferritin and LDH), which could indicate a higher inflammatory burden in these patients. However, we did not have the data to report the trends of the aminotransferases and the inflammatory markers through the hospital course.

The main strength of this study is the inclusion of only clinically significant elevation aminotransferases levels (2 times the ULN). Additionally, we included data on multiple comorbidities, including medications such as NSAIDs and ACEI/ARB. Multivariate analyses for potential confounders were performed. However, some of the limitations are worth being noted. It is a single-center retrospective study which could introduce bias and limit its generalizability. Even

Table 3 Outcome Data^a.

Patients' outcome	COVID-19 patients with transaminitis N = 20	COVID-19 patients without transaminitis N = 125	P-value
Shock	9 (45%)	38 (30.4%)	0.207
Mechanical ventilation	10 (50%)	30 (24%)	0.028
Died	10 (50%)	46 (36.8%)	0.324
Length of stay in days, median (IQR)	7 (4.3,10.3)	7 (5,10)	0.78

^aNonparametric test (Mann–Whitney test) used for non-normal distributed continuous variable, and Chi-square test was used for the categorical variable.

though none of the patients in the study population reported a history of chronic liver disease, we did not have previous records to validate this. We did not perform a trend analysis of the liver enzymes and the inflammatory markers to see if they correlate. Finally, owing to the small sample size of the current study, especially in the elevated transaminases group, there is a possibility of type II error.

CONCLUSION

Abnormal liver enzymes are commonly encountered in hospitalized COVID-19 patients. The results of our study show that clinically significant elevation of aminotransferases (2 X ULN) was noted in 13.7% of hospitalized COVID-19 patients. Elevated aminotransferases were associated with an increased rate of mechanical ventilation on univariate analysis but was not statistically significant when adjusted for confounders. Aminotransferase elevation was not associated with increased mortality nor hospital LOS. Further, more extensive prospective studies are needed to evaluate if elevations in aminotransferase could predict the clinical outcomes in COVID-19 patients.

CONFLICTS OF INTEREST

The authors report no conflict of interest.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Preethi Ramachandran: Resources, Validation, Visualization, Writing - review & editing. **Abhilash Perisetti:** Writing - original draft, Writing - review & editing. **Ma-hesh Gajendran:** Formal analysis, Methodology, Writing - review & editing. **Abhishek Chakraborti:** Data curation, Validation, Visualization, Writing - review & editing. **Joshua T. Narh:** Data curation, Validation, Visualization, Writing - review & editing. **Hemant Goyal:** Conceptualization, Supervision, Writing - review & editing.

ACKNOWLEDGMENTS

None.

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