Outcomes in COVID-19 Patients with and without Preexisting Chronic Liver Disease: A Retrospective Study

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The novel Coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 strain has resulted in more than 107 million confirmed cases of infection worldwide and more than 2 million deaths as of February 2021.[1] Preliminary studies of the disease and its outcomes showed that patients with preexisting cardiovascular disease, pulmonary disease such as COPD or asthma, and diabetes had more severe COVID-19 outcomes than those without comorbid conditions.[2] While the virus is mainly characterized by respiratory symptoms and the potential progression to acute respiratory distress syndrome (ARDS), additional organ involvement has also been identified as a sequela of the virus. An estimated 20-30% of people infected with COVID-19 also present with liver injury, which can manifest as an elevation in liver enzymes and even pathological changes to the liver found during autopsy.[3] A retrospective study conducted in Italy by Piano, et al., showed that abnormal liver function tests (LFTs) were significantly associated with a higher rate of transfer to the ICU and mortality compared to patients with COVID-19 who did not have any LFT abnormalities.[4] A few studies have demonstrated that levels of ACE-2, the cell receptor that SARS-CoV-2 binds to for cell entry, become upregulated by chronic hepatobiliary disease. This theoretically could result in an increased susceptibility to COVID infection in patients with preexisting chronic liver disease. Additionally, significant pro-inflammatory cytokine responses induced by the acute phase of the SARS-CoV 2 infection could subsequently result in liver damage.[5] Despite these findings, there has not been much literature evaluating the clinical sequelae of SARS-CoV-2 infection in the setting of chronic liver disease. It is unclear whether preexisting chronic liver disease plays a role in the progression of SARS-CoV-2 disease in terms of morbidity and mortality. We believe that evaluation of outcomes, especially mortality rates, in this subset of patients is warranted due to the rapid and severe nature of viral infection with COVID-19. Chronic liver disease may be a risk factor for severe clinical outcomes.

Problem Statement

In patients with active COVID-19 infection, demographic data and characteristics of the clinical COVID-19 disease course have not been adequately compared for patients with and without preexisting chronic liver disease.

A retrospective cohort study at LVHN, evaluating 147 patients with and 147 patients without chronic liver disease, all of whom were infected with COVID-19 during March 22nd, 2020 to August 1, 2020.

- Patient Identification via EPIC tool Slicer Dicer
  - Diagnosis “COVID-19 (ICD-10-CM:U07.1)
  - Age range: “18 years or more and 100 years or less,”
  - 20 slices classified by a diagnosis qualifying as chronic liver disease were then applied to the query in Slicer Dicer.
    - ❖ 322 patients were identified in this list as having one or more of these diagnoses of chronic liver disease (LD). The 6403 patients remaining were identified as not having chronic liver disease (NLD).
- Finalizing patient list
  - These two lists were propensity matched on the basis of age, sex, and BMI and sorted into 150 pairs
  - The initial decision to review 150 patient charts per cohort was made given the allotted time frame and what was believed to be feasible for data collection.
    - ❖ **147 patients in each cohort** after inclusion criteria applied
- Data collection
  - Demographic and baseline clinical data was collected for these 294 charts, as well as post-COVID-19 infection clinical data
  - Chart review of these patients included follow-up data for 90 days after their COVID-19 diagnosis to capture 3-month mortality
- Statistics
  - Descriptive statistics for demographics and clinical data
  - Bivariate analyses- to determine if any demographics or baseline clinical characteristics were statistically significantly different between groups
  - Chi-square tests were used to determine if there was a statistically significant difference in the percentage of patients admitted to the hospital or ICU, who require mechanical ventilation, renal replacement therapy, pressor therapy, and 30-day mortality

Table 1: Demographic Characteristics for All Patients and By Group

Characteristics	Total Patients N=294	Chronic Liver Disease (LD) N=147	No Chronic Liver Disease (NLD) N=147	p-value
Age (years) *mean ± SD*	59.32 ± 14.39	59.26 ± 14.40	59.39 ± 14.44	-
Gender (n, %)				
Male	144 (48)	72(48.98%)	72 (48.98%)	-
Female	150 (52)	75 (51.02%)	75 (51.02%)	
Race/Ethnicity (n, %)				
Caucasian	161 (54.76)	78 (53.06)	83 (56.46)	0.5882[a]
Black or African American	32 (10.88)	16 (10.88)	16 (10.88)	
Hispanic	72 (24.49)	39 (26.53)	33 (22.45)	
Asian	8 (2.72)	6 (4.08)	2 (1.36)	
Multi-racial	10 (3.40)	4 (2.72)	6 (4.08)	
Other	2 (0.68)	0	2 (1.36)	
Unknown	9 (3.06)	4 (2.72)	5 (3.40)	
BMI *mean ± SD*	31.27 ± 5.72	31.30 ± 5.81	31.25 ± 5.64	-

Table 2: Past Medical History For All Patients and By Group

Characteristics	Total Patients N=294	Chronic Liver Disease (LD) N=147	No Chronic Liver Disease (NLD) N=147	p-value[a]
Chronic Liver Disease (n, %)	147 (50)	147 (100)	0	-
NAFLD	-	92 (62.59)	-	
Alcoholic Fatty Liver	-	8 (5.44)	-	
Hepatitis B	-	6 (4.08)	-	
Hepatitis C	-	30 (20.41)	-	
Autoimmune Liver Disease (AIH, PBC, PSC)	-	4 (2.72)	-	
Cirrhosis	-	23 (15.65)	-	
Other	-	9 (6.12)	-	
Hypertension (n, %)	183 (62.24)	106 (72.11)	77 (52.38)	**0.0005**
Hyperlipidemia (n, %)	143 (48.64)	85 (57.82)	58 (39.46)	**0.0016**
Diabetes Mellitus (n, %)	103 (35.03)	59 (40.14)	44 (29.93)	0.0667
Alcohol Use (n, %)	83 (28.33)	48 (32.65)	35 (23.97)	0.0992
Smoking History (n, %)	125 (42.66)	74 (50.34)	51 (34.93)	**0.0077**
Statin Use at Time of COVID Diagnosis (n, %)	97 (32.99)	58 (39.46)	39 (26.53)	**0.0184**

Table 3: Symptoms Present at any Time During Infection Course, All Patients and By Group

	Total Patients N=293	Chronic Liver Disease (LD) N=146	No Chronic Liver Disease (NLD) N=147	p-value[a]
Symptoms (n, %)				
Fever	184 (62.80)	88 (60.27)	96 (65.31)	0.3729
Cough	195 (66.55)	93 (63.70)	102 (69.39)	0.3021
Chest Pain	34 (11.60)	17 (11.64)	17 (11.56)	0.9831
N/V	53 (18.09)	35 (23.97)	18 (12.24)	**0.0091**
Diarrhea	54 (18.43)	33 (22.60)	21 (14.29)	0.0664
SOB	164 (55.97)	71 (48.63)	93 (63.27)	**0.0116**
Hypoxia	77 (26.28)	34 (23.29)	43 (29.25)	0.2462

Table 4: Imaging Information, Rate of Hospitalization, and Complications- All Patients and by Group

	Total Patients N=294	Chronic Liver Disease (LD) N=147	No Chronic Liver Disease (NLD) N=147	p-value
Received Chest X-ray (n, %)	199 (67.69)	94 (63.95)	105 (71.43)	0.1701[a]
Abnormal findings (n, %)	151 (75.88)	68 (72.34)	83 (79.05)	0.2695[a]
Received Chest or Abdominal CT (n, %)				
Abnormal findings (n, %)	95 (32.31) 86 (90.53)	51 (34.69) 46 (90.20)	44 (29.93) 40 (90.91)	0.3827[a] 1.0000[d]
Positive Findings New Onset Liver Involvement on Imaging (n, %)	18 (20.93)	9 (19.57)	9 (22.50)	0.7386[a]
Hospitalized (n %)	150 (51.02)	73 (49.66)	77 (52.38)	0.6407[a]
Hospital LOS, Median (IQR) (n=150)	7 (4-15)	8 (4-15)	7 (4-12)	0.5552[b]
ICU (n, %)	49 (32.67)	25 (34.25)	24 (31.17)	0.6879[a]
ICU LOS, Median (IQR) (n=150)	11 (6-18)	10 (6-17)	11.50 (7-19)	0.7492[b]
Hospice (n, %)	13 (4.42)	8 (5.44)	5 (3.40)	0.3947[c]
Ventilation (n, %)	36 (73.47)	19 (76)	17 (70.83)	0.6822[a]
RRT (n, %)	14 (9.33)	7 (9.59)	7 (9.09)	0.9165[a]
Pressors (n, %)	30 (61.22)	18 (72)	12 (50)	0.1141[a]
Thrombosis (n, %)	10 (3.40)	6 (4.08)	4 (2.72)	0.5199[a]
DVT (n, %)	7 (70)	5 (83.33)	2 (50)	0.5000[c]
PE (n, %)	4 (40)	2 (33.33)	2 (50)	1.0000[d]
SBP (n, %)	1 (0.34)	1 (0.68)	-	-
GI Bleed (n, %)	9 (3.06)	5 (3.40)	4 (2.72)	1.0000[c]
Varices cause of bleed (n, %)	1 (11.11)	1 (20)	0	1.0000[d]
H. Encephalopathy (n, %)	0	0	-	-
Mortality (n, %)	31 (10.54)	12 (8.16)	19 (12.93)	0.1838[a]
Mortality Cause (n=31)				
COVID-19 Related	29 (93.55)	10 (83.33)	19 (100)	0.1419[b]
COVID-19 Unrelated Medical (n, %)	2 (6.45)	2 (16.67)	0	
Not Medically Related	-	-	-	
Length of Follow Up (days), Median (IQR)	164.50 (92-198)	173 (120-199)	157 (47-198)	**0.0180**[e]

Patient population demographics:
- Average age of 59 years, a breakdown of 52% female to 48% male, and average BMI of 31.27
- Chronic liver disease: non-alcoholic fatty liver disease (NAFLD) (62.59%), followed by Hepatitis C (20.41%) and cirrhosis (15.65%)
- LD patients were more likely to also have comorbid conditions such as hypertension, hyperlipidemia, type II diabetes, and alcohol and tobacco use than those without chronic liver disease, as well as higher proportion of cardiovascular risk factors than what has been documented by the county’s data of similar risk factors

COVID-19 Disease Symptoms:
- Higher percentage of those in the LD group experienced GI symptoms such as nausea, vomiting, and diarrhea
- Alternatively, a higher percentage of the NLD group seemed to have experienced respiratory symptoms such as cough, SOB, and hypoxia
- Possible mechanism of GI symptom manifestation- ACE2 receptors in the small intestine

Complications:
- Patients in the NLD group were more likely to be hospitalized, but patients in the LD group were slightly more likely to be placed in the ICU and progressed to hospice care (not statistically significant)
  - With regards to the high rates of hospitalization for all our patients (51.02%) and ICU placement (32.67%), we suggest that this could be due to the higher BMI and older age in our overall patient cohort, resulting in a higher rate of complications
  - It is possible that while treatment modalities and interventions were still being formulated, patients had higher hospitalization and ICU placement rates in general
- Patients with liver disease were more likely to have initiation of mechanical ventilation, renal replacement therapy, pressor initiation for low volume status, thrombotic events, or a gastrointestinal bleed (whether variceal or not)
  - None of the differences in complications between the groups were statistically significant
  - Possible that the increased complication rates are due to the LD group having more comorbidities and a decreased health status at baseline

SELECT:
- Vulnerable populations already facing barriers to care could have been disproportionately affected by the changes in care delivery during the pandemic
- A study done by the University of Pennsylvania evaluated how the COVID-19 pandemic affected the volume of nationwide cirrhosis hospitalizations, noting that many patients who suffered from liver disease lacked proper access to care at baseline.
- Hospital centers faced more of a challenge in managing their high risk and chronically ill patients, with some implementing risk stratification models
- We hope that identification of prognostic factors of COVID-19 disease severity will enable care centers to establish a more standardized management protocol for patients with liver disease and prevent vulnerable patients from slipping through the cracks during this tenuous time.
- Future directions- subgroup analyses by race to understand if there are any racial disparities in relation to outcomes from COVID-19 in patients with LD
- From a health systems standpoint, it would also be interesting to evaluate the relationship of insurance and socioeconomic status of our study cohort receiving care.

Limitations:
- Internal validity
- External validity
- Time frame to complete the study
- 89.46% of patients were censored after time frame for data collection
- Lastly, this study was a single-center, retrospective study with a moderate sample size

The overall goal of our study, in obtaining mortality and outcome data, was to improve management of patients with chronic liver disease at LVHN and other institutions. The results of our study found that patients with chronic liver disease were more likely to have comorbid conditions, such as metabolic disease, that could predispose these patients to more complications during the COVID infection course. The study also found that these patients are more likely to experience gastrointestinal symptoms than respiratory symptoms, a finding that may help us identify possible COVID infection for liver disease patients with those symptoms. Longer follow up for these patients would help strengthen our understanding of the mortality rates in patients with and without liver disease. Further investigation into which chronic liver disease predisposes to certain outcomes would also be helpful to our study. Given the high-risk nature of this population, we hope to use this information from our study to better triage patients with liver disease who are presenting with COVID-19 infection.

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