Journal Pre-proof

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US Multi-center Study

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ABSTRACT

Background

Chronic liver disease (CLD) represents a major global health burden. We undertook this study to identify the factors associated with adverse outcomes in patients with CLD who acquire the novel coronavirus-2019 (COVID-19).

Methods

We conducted a multi-center, observational cohort study across 21 institutions in the United States (US) of adult patients with CLD and laboratory-confirmed diagnosis of COVID-19 between March 1, 2020 and May 30, 2020. We performed survival analysis to identify independent predictors of all-cause mortality and COVID-19 related mortality, and multivariate logistic regression to determine the risk of severe COVID-19 in patients with CLD.

Results

Of the 978 patients in our cohort, 867 patients (mean age 56.9±14.5 years, 55% male) met inclusion criteria. The overall all-cause mortality was 14.0% (n = 121), and 61.7% (n = 535) had severe COVID-19. Patients presenting with diarrhea or nausea/vomiting were more likely to have severe COVID-19. The liver-specific factors associated with independent risk of higher overall mortality were alcohol-related liver disease (ALD) (hazard ratio [HR] 2.42, 95% confidence interval [CI] 1.29-4.55), decompensated cirrhosis (HR 2.91 [1.70-5.00]) and hepatocellular carcinoma (HCC) (HR 3.31 [1.53-7.16]). Other factors were increasing age, diabetes, hypertension, chronic obstructive pulmonary disease and current smoker. Hispanic

ethnicity (odds ratio [OR] 2.33 [1.47-3.70]) and decompensated cirrhosis (OR 2.50 [1.20-5.21])

were independently associated with risk for severe COVID-19.

Conclusions

The risk factors which predict higher overall mortality among patients with CLD and COVID-19

are ALD, decompensated cirrhosis and HCC. Hispanic ethnicity and decompensated cirrhosis are

associated with severe COVID-19. Our results will enable risk stratification and personalization

of the management of patients with CLD and COVID-19.

Clinicaltrials.gov number NCT04439084

Key words- COVID-19; Cirrhosis; Alcohol; Mortality

INTRODUCTION

Chronic liver disease (CLD) is a major international public health concern and its prevalence has been increasing over the past two decades [1,2]. Around 1.5 billion people have CLD worldwide, and it causes more than 2 million deaths per year [3,4]. With the rapid spread of the global pandemic of coronavirus disease-2019 (COVID-19), there has been significant concern that patients with CLD represent a vulnerable population at higher risk for complications.

Initial concerns were based on the observation that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, is genetically related to SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), both of which impair liver function [5,6]. These concerns appear to have been substantiated with early studies reporting elevations in liver enzymes in up to 50% of patients with COVID-19, with higher prevalence in those with worse prognosis [7,8]. Preliminary studies from the United States (US) and Europe also suggest that patients with CLD who acquire COVID-19 have high rates of hospitalization and mortality [9–11]. While these reports raise the alarm, it is not known if all patients with CLD are affected equally or if there are specific subgroups at higher risk for COVID-19 related mortality and morbidity.

Identifying predictors of mortality will allow for risk stratification of patients with CLD affected by COVID-19 and help improve healthcare delivery. To comprehensively characterize the clinical outcomes of COVID-19 in patients with CLD, we undertook a multicenter, observational study of patients with CLD who were diagnosed with COVID-19 in 21 centers across the US.

METHODS

Study Design

This is a multicenter observational cohort study. The consortium of investigators to study COVID-19 in chronic liver disease (COLD) study was formed on April 14, 2020, and accrual of data started immediately (registered Clinicaltrials.gov NCT04439084). A total of 21 centers from the US participated in the study (Table S1). The institutional review board (IRB) of each participating center reviewed and approved the study protocol. Inclusion criteria constituted: age over 18 years, laboratory-confirmed diagnosis of COVID-19 and presence of pre-existing CLD (according to predefined ICD-10 codes listed in Table S2 and confirmed by manual chart review). Patients who had undergone liver transplantation were excluded. Patients with COVID-19 diagnosis based on clinical suspicion were excluded. All participating institutions independently identified patients meeting inclusion criteria by searching their electronic medical records and collected data as per the previously established data accrual plan. The study retrospectively identified cases diagnosed between March 1 and April 14th, and subsequent cases diagnosed with COVID-19 between April 15th and May 30, 2020 were identified prospectively. All data was collected until death or date of last follow up. Death was attributed to COVID-19 if it was clinically related to COVID-19 illness and there were no other unrelated causes of death [12].

Data collection

We collected de-identified data using 170 structured and text variables in 10 different categories. Complete details on the data collection tool are available in Table S3. Diagnosis of

cirrhosis was confirmed by documentation of fibrosis either by MR elastography, fibroscan, FIB-4 or biopsy, which was available in 75% (655/867) of patients. Diagnosis of cirrhosis was ascertained in other patients by detailed chart review for clinical, radiological, or biochemical evidence of liver cirrhosis. Alcohol use was defined as - no drinking, social drinking (2 drinks/day for men and up to 1 drink/day for women), or current daily drinking (drinking more than social drinking limits on a daily basis)[13]. Data on decompensation was collected from chart review for clinical events. The presence and severity of ascites, encephalopathy, variceal bleeding and other major decompensating events at baseline and during COVID-19 were collected. If patients developed acute worsening of ascites, hepatic encephalopathy or variceal bleeding during COVID-19 they were deemed to have decompensated during COVID-19.

Statistical analysis

A pre-defined statistical data analysis plan was followed. Continuous variables are expressed as medians and interquartile ranges 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. No imputation was made for missing data. The primary outcome studied was overall survival. The secondary outcomes were COVID-19-related mortality and a composite endpoint for severe COVID-19 (either death, hospitalization, oxygen requirement, ICU admission, requirement of vasopressors or mechanical ventilation)[14].

To determine the independent risk factors for the outcome, we performed univariate Cox

proportional hazards analysis. Variables were selected for inclusion in the models based on

clinical plausibility, statistical significance in the univariate model, and availability in more than

90% of the patients. Multivariate analysis was performed using Cox proportional hazards

analysis for outcomes regarding all-cause mortality and deaths due to COVID-19. To investigate

the independent determining factors for mortality among patients with and without cirrhosis,

analyses were performed using backward stepwise logistic regression (probability to enter =

0.05 and probability to remove = 0.1) due to insufficient outcome events. All analyses were

performed using STATA 15.1 (StataCorp, College Station, TX, USA). Two-sided P values were

used and considered statistically significant if $P \leq 0.05$. All authors had access to the study data

and reviewed and approved the final manuscript.

RESULTS

Demographic and Clinical Features of the Study Cohort

We collected data from 21 institutions across thirteen states representing all five regions of the United States (Table S1). Data were collected from a total of 978 patients with CLD, of which 867 patients met the inclusion criteria (Figure S1). The largest proportion of the cases were from the Northeast (41.8%) and Southeast (28.4%) regions of the US. The overall all-cause mortality in the cohort was 14.0% (n = 121), and 61.7% (n = 535) patients experienced the composite endpoint of severe COVID-19. Table 1 shows the demographic and clinical characteristics of the patients in the overall cohort and also their proportional distribution based on clinical outcomes. The mean age at the time of COVID-19 diagnosis was 56.9 ± 14.5 years, and 271 patients (31.3%) were ≥ 65 years (Figure S2). Patient ethnicity was relatively evenly distributed- non-Hispanic white (268 [30.9%]), non-Hispanic black (267 [30.8%]) or Hispanic (219 [25.3%]) (Figure S3). The overall median follow-up of patients was 38 (IQR 15-94) days. Most patients (776 [89.5%]) had at least one comorbid medical condition in addition to CLD, while (261 [30.1%]) had more than three non-hepatic comorbidities. The most common comorbidities were hypertension (492 [56.8%]), diabetes mellitus (372 [42.9%]), obesity (365 [42.1%]) and hyperlipidemia (335 [38.6%]) (Figure S4).

The most common cause of CLD was nonalcoholic fatty liver disease (NAFLD) (456 [52.6%]), followed by hepatitis C virus (HCV) infection (190 [21.9%]), alcohol-related liver disease (ALD) (94 [10.8%]) and hepatitis B virus infection (HBV) (62 [7.2%]) (Figure S5, S6). The majority of patients had non-cirrhotic stage disease (620 [71.5%]); 227 (26.2%) patients had a diagnosis of

cirrhosis. Most patients with cirrhosis were well compensated at the time of inclusion (134 [59.1%]), with 93 (40.9%) patients having decompensated cirrhosis prior to diagnosis with COVID-19. Among patients with decompensated cirrhosis, 71 (76.3%) had ascites, 51 (54.8%) had hepatic encephalopathy, 24 (25.8%) had history of variceal bleeding and 10 (10.8%) had other decompensating events. Among the patients with pre-existing hepatocellular carcinoma (HCC) (22 [2.5%]), eight (36.4%) of them had received locoregional therapy, two (9.1%) had received immunotherapy and none of them were on tyrosine kinase inhibitors.

Clinical course of COVID-19 in Patients with CLD

The majority of patients were tested for COVID-19 because they presented with symptoms (772 [89%]) (Figure S7). The top three risk factors for acquiring COVID-19 were exposure to sick contacts (255 [29.4%]), recent visit to a healthcare facility (95 [11.0%]) or nursing home stay (73 [8.4%]). The most common presenting symptom was cough (620 [77.4%]), followed by fever (561 [69.3%]), shortness of breath (494 [61.8%]), fatigue (341 [49.9%]) and diarrhea (190 [26.6%]) (Table 2, Figure S8). Patients presenting with GI symptoms of diarrhea (OR 1.89, 95% CI: 1.30-2.74) or nausea/vomiting (OR 1.84, 95% CI: 1.27-2.68) were more likely to have severe COVID-19 than patients without GI symptoms (Table 2). Also, patients presenting with respiratory symptoms like shortness of breath, sore throat, runny nose or confusion were at higher risk both for mortality and severe COVID-19.

Among patients with CLD and COVID-19, 60.4% (n = 524) were hospitalized, 49.9% (n = 433) required supplemental oxygen, 23.0% (n = 199) were admitted to the ICU, 15.7% (n = 136)

received vasopressors, and 17.8% (n = 154) required mechanical ventilation. The majority of the deaths were due to COVID-19 (86.7%, n = 105). Sixteen patients had non-COVID-19 related mortality, and the cause of death was available in 37.5% (n = 6) of these patients. Two of them died of cardiac failure, two from acute liver failure due to acute alcoholic hepatitis, one from bleeding complications due to coagulopathy and one from septic shock in the setting of acute cholecystitis. New or worsening hepatic decompensation during COVID-19 was noted in 67 (7.7%) of patients- 23 (34.3%) patients had severe hepatic encephalopathy, 11 (16.4%) had severe ascites and 7 (10.4%) had variceal bleed during the clinical course of COVID-19. Median baseline liver tests prior to COVID-19 were- AST IU/L 28.0 (IQR 25), ALT 27.0 IU/L (IQR 27), alkaline phosphatase 88 IU/L (IQR 59) and bilirubin 0.5 mg/dl (IQR 0.5). As shown in previous studies [15], peak values of all liver tests were significantly elevated during COVID-19 (Fig S9).

The combination of azithromycin and hydroxychloroquine (135 [15.6%]), azithromycin alone (101 [11.6%]), hydroxychloroquine alone (87 [10.0%]) were the most commonly used medications for COVID-19. A higher proportion of patients who received medications directed against COVID-19 had more severe disease (Figure S10).

Predictors of All-cause Mortality and COVID-19-related Mortality in Patients with CLD

To identify the predictors of all-cause mortality and COVID-19 related mortality, we performed univariate and multivariate survival analysis (Table 3). The multivariate model for all-cause mortality was adjusted for age, sex, race/ethnicity, etiology of CLD, cirrhosis, hepatic decompensation, HCC, diabetes, hypertension, cardiovascular disease, chronic obstructive

pulmonary disease (COPD), smoking status, and alcohol consumption, all of which were statistically significant in the univariate model and are plausibly clinically relevant.

The liver-specific predictors of all-cause mortality were ALD (hazard ratio [HR] 2.42, 95% confidence interval [CI]: 1.29-4.55), presence of hepatic decompensation at baseline (HR 2.91, 95% CI: 1.70-5.00) and HCC (HR 3.31, 95% CI: 1.53-7.16). Other independent predictors of all-cause mortality were- increasing age (HR 1.44, 95% CI: 1.21-1.71 per 10 years), presence of diabetes (HR 1.59, 95% CI: 1.02-2.46), hypertension (HR 1.77, 95% CI: 1.11-2.81), COPD (HR 1.77, 95% CI: 1.03-3.05) and history of current smoking (HR 2.48, 95% CI: 1.30-4.73). For the secondary outcome of deaths due to COVID-19 (Table 3), the results were largely identical. Further, we did not find significant interactions between ALD and decompensated CLD or HCC for overall survival on multivariate analysis (test of interaction P > 0.2) (Table S4).

Next, we performed a subgroup survival analysis in patients with cirrhosis and COVID-19 (Table 4). The liver-specific factors associated with higher all-cause mortality in patients with cirrhosis were prior hepatic decompensation (HR 3.89, 95% CI: 2.18-6.95), HCC (HR 3.66, 95% CI: 1.67-8.01). In the subgroup of patients with non-cirrhotic CLD, ALD was associated with higher all-cause mortality (HR 4.72, 95% CI: 2.05-10.85) and higher COVID-19 related mortality (HR 7.39, 95% CI: 2.96-18.46) (Table S5).

Serial liver related labs were available in a majority of the hospitalized patients, but not in the majority of those managed as outpatient. We performed a subgroup analysis in hospitalized

patients in whom serial lab values were available for analysis. Peak values of AST, bilirubin, alkaline phosphatase and MELD score were observed to predict mortality (Table S6).

Predictors of Severe COVID-19 in Patients with CLD

Overall, 535 patients with CLD met criteria for the composite endpoint of severe COVID-19. As shown in Table 5, multivariate analysis showed that a history of hepatic decompensation (odds ratio [OR] 2.50, 95% CI: 1.20-5.21) predicted severe COVID-19. Other independent predictors were increasing age (OR 1.43, 95% CI: 1.25-1.65), Hispanic ethnicity (OR 2.33, 95% CI: 1.47-3.70), diabetes (OR 1.51, 95% CI: 1.04-2.19), cardiovascular disease (OR 1.85, 95% CI: 1.09-3.13) and COPD (OR 2.26, 95% CI: 1.15-4.45).

DISCUSSION

According to the Center for Disease Control (CDC), patients with CLD might be at increased risk for severe illness with COVID-19 [16]. CLD represents a clinical spectrum ranging from mild asymptomatic disease to severe decompensated cirrhosis. It is not clear which subgroups of patients with CLD are more vulnerable to adverse outcomes with COVID-19. In this multi-center study, we investigated predictors of mortality and COVID-19 disease severity in patients with CLD and SARS-CoV-2 infection. Among the 867 patients with CLD from 21 centers across the US, we observed an all-cause mortality of 14.0%; 60.4% were hospitalized and 23% were admitted to the ICU. New or worsening hepatic decompensation during COVID-19 was noted in 7.7% of patients. We identified the liver-specific factors ALD, hepatic decompensation and HCC as predictors of adverse outcomes from COVID-19, apart from established factors like older age, hypertension, diabetes and COPD. Additionally, we found that patients of Hispanic ethnicity had a higher risk for severe COVID-19. Thus, our large multicenter study identifies specific subgroups of patients with CLD who have higher mortality with COVID-19.

Given that COVID-19 is a novel pandemic, our knowledge of its impact on patients with CLD is still evolving. Singh et al recently identified 250 patients with COVID-19 who had an underlying CLD using a de-identified research network database, and reported a hospitalization rate of 52% and mortality 12%, similar rates to our study [9]. Preliminary data from an international registry of 152 patients with CLD however reported a higher overall mortality rate of 31% and a hospitalization rate of 95% for patients with cirrhosis [11]. The higher mortality rates in this clinician-reported registry study may have been due to selection bias. Around 90% of the

patients with CLD and COVID-19 in our cohort had mild liver disease with either non-cirrhotic stage disease or compensated cirrhosis at baseline, and they had relatively favorable outcomes. Patients with decompensated cirrhosis were disproportionately adversely affected by COVID-19, with an all-cause mortality rate of 31.4% in this subgroup. These findings are in line with the higher morbidity and mortality in patients with decompensated cirrhosis and influenza pneumonia [17,18]. We posit the less favorable outcomes noted in patients with decompensated cirrhosis may be due to cirrhosis-associated immune dysfunction and fragile physiological buffers, likely increasing susceptibility to severe COVID-19 [19]. Our findings highlight the challenges in taking extra precautions to minimize the risk of exposure to SARS-CoV-2 in the vulnerable patients with decompensated cirrhosis, while continuing to optimally manage their decompensating events.

In our study, ALD was independently associated with a higher risk of poor survival and COVID-19 related mortality. This is a novel association and one that has significant implications for patients with CLD. Patients with ALD are known to be at higher risk for infections due to the underlying dysregulation of the immune system [20]. ALD is associated with a sterile inflammatory state induced by damage-associated molecular patterns (DAMPs), which leads to the systemic production of pro-inflammatory cytokines by various immune cells [21,22]. We hypothesize that the superimposed cytokine storm triggered by SARS-CoV-2 could exacerbate the heightened inflammatory state in patients with ALD thus leading to worse outcomes [23]. Moreover, there has been significant concern about increased alcohol use during the COVID-19 pandemic, highlighting the importance of this association [24,25]. In our study, up to a third of

patients with CLD, and an alarming 50% of patients with ALD reported daily alcohol consumption, which was disconcertingly associated with poor outcomes in patients with cirrhosis and COVID-19. These findings emphasize the need to implement an aggressive remote care plan for patients with ALD to manage their alcohol use disorder while simultaneously minimizing the risk of exposure to COVID-19. Future studies will be needed to analyze specific subgroups within the spectrum of alcohol liver disease (ALD) who are at higher risk for adverse outcomes with COVID-19.

Another subgroup that was found in our study to be at significantly high risk for mortality was that of patients with HCC. The all-cause mortality rate in this subgroup was 52.4% (n = 11), almost 7-fold higher than in patients without HCC, however the number of patients is small. Patients with cancer, in general, have worse clinical outcomes after COVID-19 [14,26]. Patients with HCC may be uniquely susceptible to COVID-19 related complications due to a constellation of active malignancy, presence of cirrhosis, as well as the presence of an active underlying liver disease that led to that cirrhosis, all resulting in compromised immune function, which may be further complicated by HCC-directed treatment.

Our cohort includes a racially and ethnically diverse population that is 31% non-Hispanic white, 31% non-Hispanic black and 25% Hispanic. We found that patients of Hispanic ethnicity had a higher risk of developing severe COVID-19 compared to non-Hispanic Whites, even after adjusting for age, comorbidities and hepatic decompensation. These findings are in line with recent reports showing higher age-adjusted rates of hospitalization in Hispanic patients [27,28].

The strengths of our study include large sample size, broad geographical distribution of sites across the US as well as the granularity of the collected data. We have included patients treated both as outpatients or inpatients, and also patients with non-cirrhotic or cirrhotic stage CLD, thus making our findings generalizable. Limitations of our study include the retrospective-prospective timeline which was used mainly because of the rapidly evolving nature of the pandemic. Another limitation of our study is the restriction of SARS-CoV-2 testing during the earlier phase of the pandemic, likely leading to decreased representation of mild COVID-19. Also, we could have enrollment bias since not all patients with CLD have a documented ICD9/10 code in their electronic health records. Also, despite our best efforts, it is possible that not all patients with CLD and COVID19 were identified from the participating centers. Lastly, the majority of the contributing centers are tertiary medical health systems, potentially introducing referral bias. However, our cohort represents an ethnically diverse population with varying stages of liver disease. Larger and longer-term studies will be needed to confirm these findings.

To date, this is the largest study on COVID-19 among patients with CLD in the United States. Our cohort of 867 patients with CLD had substantial rates of all-cause mortality (14.0%), hospitalization (60.4%) and ICU admission (23%). We identify decompensated cirrhosis, ALD, and HCC to be determinants of mortality in patients with CLD, and additionally show that Hispanic ethnicity is independently associated with severe COVID-19. These findings can be used to prospectively design protective measures for these vulnerable populations, such as continuing the emphasis on telemedicine, prioritizing them for future vaccinations, as well as actively including these patients in prospective COVID-19 surveillance studies and drug trials.

REFERENCES

1. Hirode, G., Saab, S. & Wong, R. J. Trends in the Burden of Chronic Liver Disease Among Hospitalized US Adults. *JAMA Netw Open* **3**, e201997 (2020).

2. GBD 2017 Cirrhosis Collaborators. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol* **5**, 245–266 (2020).

3. Asrani, S. K., Devarbhavi, H., Eaton, J. & Kamath, P. S. Burden of liver diseases in the world. *Journal of Hepatology* vol. 70 151–171 (2019).

4. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* **392**, 1789–1858 (2018).

5. Chau, T.-N. *et al.* SARS-associated viral hepatitis caused by a novel coronavirus: report of three cases. *Hepatology* **39**, 302–310 (2004).

6. Alsaad, K. O. *et al.* Histopathology of Middle East respiratory syndrome coronovirus (MERS-CoV) infection - clinicopathological and ultrastructural study. *Histopathology* **72**, 516–524 (2018).

7. Zhang, C., Shi, L. & Wang, F.-S. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol* **5**, 428–430 (2020).

8. Fan, Z. *et al.* Clinical Features of COVID-19-Related Liver Damage. *SSRN Electronic Journal* doi:10.2139/ssrn.3546077.

9. Singh, S. & Khan, A. Clinical Characteristics and Outcomes of COVID-19 Among Patients with Pre-Existing Liver Disease in United States: A Multi-Center Research Network Study. *Gastroenterology* (2020) doi:10.1053/j.gastro.2020.04.064.

10. Iavarone, M. *et al.* High rates of 30-day mortality in patients with cirrhosis and COVID-19. *J.*

Hepatol. (2020) doi:10.1016/j.jhep.2020.06.001.

11. Moon, A. M. *et al.* High Mortality Rates for SARS-CoV-2 Infection in Patients with Pre-existing Chronic Liver Disease and Cirrhosis: Preliminary Results from an International Registry. *J. Hepatol.* (2020) doi:10.1016/j.jhep.2020.05.013.

12. Guidance for certifying deaths due to coronavirus disease 2019 (COVID-19). *National Center for Health Statistics.* https://www.cdc.gov/nchs/data/nvss/vsrg/vsrg03-508.pdf.

13. Zakhari, S. & Li, T.-K. Determinants of alcohol use and abuse: Impact of quantity and frequency patterns on liver disease. *Hepatology* **46**, 2032–2039 (2007).

14. Kuderer, N. M. *et al.* Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. *Lancet* (2020) doi:10.1016/S0140-6736(20)31187-9.

15. Singh, S. & Khan, A. Clinical Characteristics and Outcomes of Coronavirus Disease 2019 Among Patients With Preexisting Liver Disease in the United States: A Multicenter Research Network Study. *Gastroenterology* (2020) doi:10.1053/j.gastro.2020.04.064.

16. Coronavirus Disease 2019- People with Certain Medical Conditions. *CDC* https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fneed-extra-precautions%2Fgroups-at-higher-risk.html.

17. Duchini, A., Viernes, M. E., Nyberg, L. M., Hendry, R. M. & Pockros, P. J. Hepatic decompensation in patients with cirrhosis during infection with influenza A. *Arch. Intern. Med.* **160**, 113–115 (2000).

18. Schütte, A., Ciesek, S., Wedemeyer, H. & Lange, C. M. Influenza virus infection as precipitating event of acute-on-chronic liver failure. *Journal of hepatology* vol. 70 797–799 (2019).

19. Albillos, A., Lario, M. & Álvarez-Mon, M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. *J. Hepatol.* **61**, 1385–1396 (2014).

20. Chan, C. & Levitsky, J. Infection and Alcoholic Liver Disease. *Clinics in Liver Disease* vol. 20 595–606

(2016).

21. Shim, Y.-R. & Jeong, W.-I. Recent advances of sterile inflammation and inter-organ cross-talk in alcoholic liver disease. *Exp. Mol. Med.* **52**, 772–780 (2020).

22. Szabo, G. Gut–Liver Axis in Alcoholic Liver Disease. *Gastroenterology* vol. 148 30–36 (2015).

23. Jose, R. J. & Manuel, A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. *Lancet Respir Med* **8**, e46–e47 (2020).

24. Da, B. L., Im, G. Y. & Schiano, T. D. COVID-19 Hangover: A Rising Tide of Alcohol Use Disorder and Alcohol-Associated Liver Disease. *Hepatology* (2020) doi:10.1002/hep.31307.

25. Clay, J. M. & Parker, M. O. Alcohol use and misuse during the COVID-19 pandemic: a potential public health crisis? *Lancet Public Health* **5**, e259 (2020).

26. Liang, W. *et al.* Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol.* **21**, 335–337 (2020).

27. Tenforde, M. W. *et al.* Characteristics of Adult Outpatients and Inpatients with COVID-19 — 11 Academic Medical Centers, United States, March–May 2020. *MMWR. Morbidity and Mortality Weekly Report* vol. 69 841–846 (2020).

28. Website. CDC. COVID-19 in racial and ethnic minority groups. Atlanta, GA: US Department of Health and Human Services, CDC; 2020. https:// www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/racialethnic-minorities.html.

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FIGURE LEGEND

Figure 1: Liver-specific factors predicting overall survival in patients with CLD and COVID19

a. Overall survival from the time of diagnosis of COVID19 in patients with alcohol related liver disease (ALD) compared to other liver disease etiologies. b. Overall survival in patients with liver disease stratified into those with no cirrhosis vs. compensated cirrhosis vs. decompensated cirrhosis. Significant and hazard ratios are derived from comparison of decompensated cirrhosis vs no cirrhosis. c. Overall survival from the time of diagnosis of COVID19 in patients with underlying hepatocellular carcinoma (HCC).

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Acknowledgements

Table 1. Clinical Characteristics of Patients with Chronic Liver Disease and Clinical Outcome of COVID-19

	Total (n=867)	All-cause Mortality status (n=817)		P value	Severe COVID-19 (n=857)		P value
		Alive (n=696)	Died (n=121)		No (n=322)	Yes (n=535)	
Demographic factors							
Age (years)	56.9 ± 14.5	55.7 ± 14.4	65.4 ± 12.7	**<0.001**	52.1 ± 13.7	59.8 ± 14.3	**<0.001**
<65	596 (68.7)	497 (71.4)	62 (51.2)	**<0.001**	260 (80.8)	330 (61.7)	**<0.001**
≥65	271 (31.3)	199 (28.6)	59 (48.8)		62 (19.3)	205 (38.3)	
Gender (male, %)	473 (54.7)	377 (54.3)	68 (56.2)	0.702	159 (49.5)	308 (57.6)	**0.022**
Race/ethnicity				0.431			**0.020**
Non-Hispanic white	268 (30.9)	204 (29.3)	46 (38.0)		107 (33.2)	156 (29.2)	
Non-Hispanic black	267 (30.8)	217 (31.2)	37 (30.6)		112 (34.8)	152 (28.4)	
Hispanic	219 (25.3)	183 (26.3)	25 (20.7)		69 (21.4)	148 (27.7)	
Non-Hispanic Asian	43 (5.0)	31 (4.5)	6 (5.0)		14 (4.3)	29 (5.7)	
Other	38 (4.4)	32 (4.6)	5 (4.15)		8 (2.5)	30 (5.4)	
Missing	32 (3.6)	29 (4.2)	2 (1.7)		12 (3.7)	20 (3.7)	
Liver-related factors							
Etiology				**<0.001**			**<0.001**
HCV	190 (21.9)	143 (20.6)	34 (28.1)		56 (17.4)	130 (24.3)	
HBV	62 (7.2)	49 (7.0)	5 (4.1)		25 (7.8)	37 (6.9)	
NAFLD	456 (52.6)	394 (56.6)	46 (38.0)		199 (61.8)	256 (47.9)	
ALD	94 (10.8)	58 (8.3)	28 (23.1)		18 (5.6)	72 (13.5)	
Other	65 (7.5)	52 (7.5)	8 (6.6)		24 (7.5)	40 (7.5)	
Missing	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	
Cirrhosis				**<0.001**			**<0.001**
No cirrhosis	620 (71.5)	529 (76.0)	62 (51.2)		254 (78.9)	363 (67.9)	
Compensated cirrhosis	134 (15.4)	107 (15.4)	19 (15.7)		48 (14.9)	83 (15.5)	

Decompensated cirrhosis	93 (10.7)	48 (6.9)	38 (31.4)		14 (4.3)	77 (14.4)	
Missing	20 (2.3)	12 (1.7)	2 (1.7)		6 (1.9)	12 (2.2)	
Hepatocellular carcinoma	22 (2.5)	10 (1.4)	9 (7.4)	**<0.001**	3 (0.9)	18 (3.4)	**0.026**
Comorbidities							
Diabetes	372 (42.9)	294 (42.2)	66 (54.5)	**0.012**	110 (34.2)	259 (48.4)	**<0.001**
Hypertension	492 (56.8)	387 (55.6)	83 (68.6)	**0.008**	165 (51.2)	321 (60.0)	**0.012**
Obesity	365 (42.1)	305 (43.8)	47 (38.8)	0.307	150 (46.6)	213 (39.8)	0.052
Hyperlipidemia	335 (38.6)	273 (39.2)	53 (43.0)	0.419	113 (35.1)	218 (40.8)	0.100
Cardiovascular disease	150 (17.3)	111 (16.0)	33 (27.3)	**0.003**	32 (9.9)	116 (21.7)	**<0.001**
HIV	24 (2.8)	21 (3.0)	1 (0.8)	0.169	8 (2.5)	16 (3.0)	0.664
COPD	77 (8.9)	54 (7.8)	20 (16.5)	**0.002**	15 (4.7)	62 (11.6)	**0.001**
Asthma	91 (10.5)	78 (11.2)	10 (8.3)	0.335	29 (9.0)	61 (11.4)	0.268
Other cancer	68 (7.8)	48 (6.9)	15 (12.4)	**0.036**	21 (6.5)	45 (8.4)	0.315
Behavioral factors							
Alcohol use				**<0.001**			**0.001**
Current daily drinking	107 (12.3)	75 (10.8)	25 (20.7)		34 (10.6)	70 (13.1)	
Social drinking	532 (61.3)	424 (60.9)	81 (66.9)		183 (56.8)	345 (64.5)	
Do not drink currently	172 (19.8)	153 (22.0)	10 (8.3)		85 (26.4)	85 (15.9)	
Missing	56 (6.5)	44 (6.3)	5 (4.1)		20 (6.2)	35 (6.5)	
Smoking							
Current smoker	95 (10.9)	70 (10.1)	19 (15.7)	**<0.001**	35 (10.9)	59 (11.0)	**0.032**
Past smoker	259 (29.8)	195 (28.0)	50 (41.3)		82 (25.5)	175 (32.7)	
Never smoker	482 (55.6)	414 (59.5)	46 (38.0)		199 (61.8)	278 (52.0)	
Missing	31 (3.6)	24 (3.4)	6 (4.9)		6 (1.9)	23 (4.3)	
Opioid use	31 (3.6)	23 (3.3)	2 (1.7)	0.330	8 (2.5)	22 (4.1)	0.209
Marijuana use	24 (2.8)	17 (2.4)	5 (4.1)	0.548	10 (3.1)	13 (2.4)	0.553
Treatment							
Remdesivir	39 (4.5)	31 (4.5)	5 (4.1)	0.874	0 (0.0)	39 (7.3)	**<0.001**

Steroids	54 (6.2)	44 (6.3)	10 (8.3)	0.427	4 (1.2)	50 (9.4)	**<0.001**
Hydroxychloroquine	87 (10.0)	69 (9.9)	12 (9.9)	0.999	4 (1.2)	83 (15.5)	**<0.001**
Azithromycin	101 (11.7)	78 (11.2)	21 (17.4)	0.056	25 (7.8)	76 (14.2)	**0.005**
Hydroxychloroquine + Azithromycin	135 (15.6)	95 (13.7)	38 (31.4)	**<0.001**	4 (1.2)	131 (24.5)	**<0.001**

Abbreviation: COVID-19, coronavirus disease 2019; HCV, hepatitis C virus infection; HBV, hepatitis B virus infection;

NAFLD, nonalcoholic fatty liver disease; ALD, alcoholic liver disease; COPD, chronic obstructive pulmonary disease.

Data are expressed as the mean ± standard deviation or number (proportion).

Table 2. Clinical Presentation of Patients with Chronic Liver Disease and COVID-19 and Clinical Outcomes

	Total (n=867)	All-cause Mortality status (n=817)		P value	Severe COVID-19 (n=857)		P value
		Alive	Died		No	Yes	
General symptom							
Fever (n=810)	561 (69.3)	463 (69.9)	76 (69.1)	0.858	189 (64.3)	371 (72.2)	0.019
Cough (n=801)	620 (77.4)	524 (79.3)	68 (66.7)	0.004	236 (80.0)	383 (76.0)	0.191
Shortness of breath (n=799)	494 (61.8)	388 (59.2)	86 (78.9)	<0.001	122 (42.8)	371 (72.6)	<0.001
Sore throat (n=699)	144 (20.6)	136 (23.0)	7 (8.8)	0.004	71 (27.1)	73 (16.8)	0.001
Runny nose (n=667)	117 (17.5)	105 (18.9)	9 (10.8)	0.073	56 (22.5)	61 (14.7)	0.010
Fatigue (n=684)	341 (49.9)	277 (49.8)	54 (55.7)	0.288	109 (45.6)	231 (52.1)	0.103
Myalgia (n=692)	290 (41.9)	249 (43.4)	28 (31.8)	0.039	106 (43.0)	182 (41.0)	0.592
Chest pain (n=719)	140 (19.5)	118 (19.7)	17 (19.3)	0.933	45 (17.2)	95 (20.8)	0.249
Confusion (n=711)	99 (13.9)	51 (8.8)	44 (43.1)	<0.001	7 (2.7)	92 (20.4)	<0.001
GI symptom							
Diarrhea (n=715)	190 (26.6)	158 (26.7)	23 (25.0)	0.733	48 (19.0)	141 (30.7)	0.001
Nausea/vomiting (n=738)	183 (24.8)	153 (25.0)	22 (23.7)	0.773	47 (17.7)	134 (28.5)	0.001
Anorexia (n=614)	150 (24.4)	120 (23.8)	25 (30.9)	0.169	30 (14.2)	119 (29.7)	<0.001
Anosmia (n=517)	71 (13.7)	62 (14.5)	6 (9.4)	0.269	33 (19.1)	38 (11.1)	0.013

Abbreviation: COVID-19, coronavirus disease 2019. Data are expressed as the number (proportion among patients with reported symptoms).

Table 3. Univariate & Multivariate Analyses: Overall Survival in Patients with Chronic Liver Disease and COVID-

19

	Univariate model for all-cause mortality		Multivariate model for all-cause mortality (events=121)		Multivariate model for mortality due to COVID-19 (events=105)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Demographic factors						
Age (per 10 year)	1.55 (1.35-1.77)	<0.001	1.44 (1.21-1.71)	**<0.001**	1.52 (1.27-1.82)	**<0.001**
Male	1.16 (0.81-1.66)	0.416	1.16 (0.77-1.75)	0.472	1.23 (0.79-1.91)	0.359
Race/ethnicity						
Non-Hispanic white	1		1		1	
Non-Hispanic black	0.75 (0.48-1.15)	0.186	0.81 (0.50-1.32)	0.400	0.84 (0.50-1.43)	0.524
Hispanic	0.73 (0.45-1.20)	0.216	0.94 (0.56-1.60)	0.830	1.20 (0.69-2.09)	0.522
Non-Hispanic Asian	1.03 (0.44-2.42)	0.941	1.60 (0.54-4.70)	0.395	1.93 (0.64-5.77)	0.244
Other	0.77 (0.31-1.94)	0.580	0.60 (0.18-1.96)	0.393	0.80 (0.24-2.66)	0.711
Liver-related factors						
Etiology of liver disease						
HCV	1		1		1	
ALD	1.75 (1.06-2.89)	0.028	2.42 (1.29-4.55)	**0.006**	2.69 (1.44-5.02)	**0.002**
NAFLD	0.48 (0.31-0.75)	0.001	1.05 (0.59-1.87)	0.872	1.08 (0.59-1.97)	0.804
HBV	0.57 (0.22-1.47)	0.247	0.80 (0.23-2.74)	0.718	0.81 (0.23-2.83)	0.746
Other	0.69 (0.32-1.49)	0.344	1.66 (0.72-3.81)	0.236	1.15 (0.42-3.13)	0.782
Presence of cirrhosis						
No	1		1		1	
Compensated cirrhosis	1.45 (0.87-2.42)	0.158	0.83 (0.46-1.49)	0.532	0.90 (0.49-1.65)	0.743
Decompensated cirrhosis	5.26 (3.51-7.89)	<0.001	2.91 (1.70-5.00)	**<0.001**	2.41 (1.34-4.32)	**0.003**
Presence of HCC	4.91 (2.48-9.70)	<0.001	3.31 (1.53-7.16)	**0.002**	3.96 (1.74-8.98)	**0.001**
Comorbidities						

Diabetes	1.49 (1.04-2.13)	0.028	1.59 (1.02-2.46)	**0.040**	1.82 (1.15-2.89)	**0.011**
Hypertension	1.55 (1.05-2.27)	0.003	1.77 (1.11-2.81)	**0.016**	1.69 (1.04-2.76)	**0.034**
Cardiovascular disease	1.70 (1.14-2.53)	0.010	1.10 (0.70-1.74)	0.667	0.86 (0.53-1.42)	0.564
COPD	2.01 (1.25-3.26)	0.004	1.77 (1.03-3.05)	**0.040**	2.29 (1.32-3.96)	**0.003**
Behavioral factors						
Smoking status						
No	1		1		1	
Past smoker	2.18 (1.46-3.25)	<0.001	1.30 (0.82-2.05)	0.263	1.39 (0.86-2.26)	0.179
Current smoker	2.67 (1.56-4.56)	<0.001	2.48 (1.30-4.73)	**0.006**	2.99 (1.56-5.72)	**0.001**
Alcohol consumption						
Do not drink currently	1		1			
Social drinking	0.35 (0.18-0.67)	0.002	0.61 (0.31-1.22)	0.160		
Current daily drinking	1.63 (1.04-2.56)	0.032	1.37 (0.77-2.46)	0.287		

Abbreviations: COVID-19, coronavirus disease 2019; HR, hazard ratio; CI, confidence interval; HCV, hepatitis C virus infection; HBV, hepatitis B virus infection; NAFLD, nonalcoholic fatty liver disease; ALD, alcoholic liver disease; HCC, hepatocellular carcinoma; COPD, chronic obstructive pulmonary disease.

The multivariate model for all-cause mortality was adjusted for adjusted for age, gender, race/ethnicity, etiology of chronic liver disease, cirrhosis, HCC, diabetes, hypertension, cardiovascular disease, COPD, smoking status, and alcohol consumption.

The multivariate model for death due to COVID-19 was adjusted for adjusted for age, gender, race/ethnicity, etiology of chronic liver disease, cirrhosis, HCC, diabetes, hypertension, obesity, cardiovascular disease, COPD, and smoking status.

Table 4. Univariate & Multivariate Analyses of **Risk for Survival** in **Patients with Cirrhosis and COVID-19 (n=212)**

	Univariate model for all-cause mortality		Multivariate model for all-cause mortality (events=57)		Multivariate model for mortality due to COVID-19 (events=45)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Demographic factors						
Age (per 10 year)	1.20 (0.97-1.50)	0.095				
Male	0.77 (0.46-1.30)	0.329				
Race/ethnicity						
Non-Hispanic white	1					
Non-Hispanic black	0.84 (0.46-1.58)	0.609				
Hispanic	0.66 (0.33-1.34)	0.249				
Non-Hispanic Asian	-	-				
Other	1.43 (0.49-4.15)	0.592				
Liver-related factors						
Etiology of liver disease						
HCV	1					
ALD	1.64 (0.85-3.14)	0.138				
NAFLD	1.08 (0.53-2.22)	0.829				
HBV	-	-				
Other	1.22 (0.48-3.12)	0.679				
Decompensated cirrhosis	3.67 (2.11-6.37)	<0.001	3.89 (2.18-6.95)	**<0.001**	3.12 (1.68-5.79)	**<0.001**
Presence of HCC	3.26 (1.52-6.97)	0.002	3.66 (1.67-8.01)	**0.001**	3.61 (1.58-8.25)	**0.002**
Comorbidities						
Diabetes	0.96 (0.57-1.62)	0.888				
Hypertension	0.88 (0.53-1.49)	0.652				

Cardiovascular disease	1.15 (0.64-2.04)	0.646		
COPD	1.60 (0.76-3.38)	0.217	3.12 (1.68-5.79)	**<0.001**
Behavioral factors				
Smoking status				
No	1			
Past smoker	1.42 (0.79-2.58)	0.244		
Current smoker	2.16 (1.03-4.53)	0.042		
Alcohol consumption				
Do not drink currently	1			
Social drinking	0.26 (0.04-1.91)	0.187		
Current daily drinking	2.44 (1.38-4.30)	0.002	2.34 (1.27-4.30)	**0.006**

Abbreviations: COVID-19, coronavirus disease 2019; HR, hazard ratio; CI, confidence interval; HCV, hepatitis C virus infection; HBV, hepatitis B virus infection; NAFLD, nonalcoholic fatty liver disease; ALD, alcoholic liver disease; HCC, hepatocellular carcinoma; COPD, chronic obstructive pulmonary disease.

To identify candidate risk factors of mortality, we performed a stepwise backward logistic regression analysis (probability to enter = 0.05 and probability to remove = 0.1) using all variables in the univariate model.
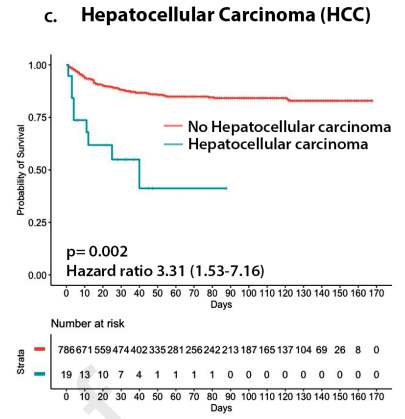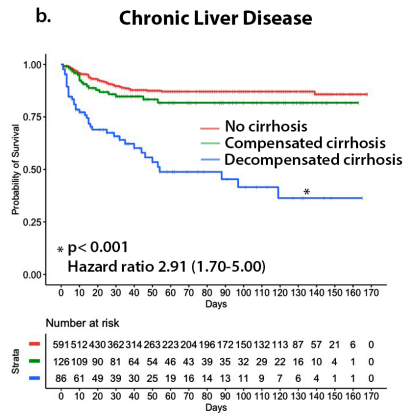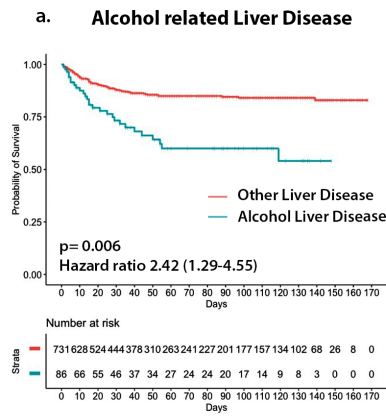
Table 5. Univariate and Multivariate Analyses: Risk of Severe COVID-19 (composite endpoint) among Patients with Chronic Liver Disease and COVID-19

	Univariate model for severe COVID-19		Multivariate model for severe COVID-19	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Demographic factors				
Age (per 10 year)	1.46 (1.32-1.62)	<0.001	1.43 (1.25-1.65)	**<0.001**
Male	1.38 (1.05-1.83)	0.022	1.28 (0.90-1.81)	0.172
Race/ethnicity				
Non-Hispanic white	1		1	
Non-Hispanic black	0.93 (0.66-1.32)	0.685	0.83 (0.54-1.28)	0.406
Hispanic	1.47 (1.01-2.14)	0.045	2.33 (1.47-3.70)	**<0.001**
Non-Hispanic Asian	1.42 (0.72-2.81)	0.314	1.90 (0.85-4.27)	0.124
Other	2.57 (1.14-5.83)	0.024	3.40 (1.31-8.81)	**0.012**
Liver-related factors				
Etiology of liver disease				
HCV	1		1	
ALD	1.72 (0.94-3.15)	0.077	2.08 (0.97-4.45)	0.059
NAFLD	0.55 (0.39-0.80)	0.001	0.68 (0.41-1.13)	0.137
HBV	0.64 (0.35-1.15)	0.139	0.99 (0.46-2.13)	0.973
Other	0.72 (0.40-1.30)	0.275	1.27 (0.60-2.70)	0.536
Presence of cirrhosis				
No	1		1	
Compensated cirrhosis	1.21 (0.82-1.79)	0.338	0.70 (0.43-1.14)	0.152
Decompensated cirrhosis	3.85 (2.13-6.95)	<0.001	2.50 (1.20-5.21)	**0.015**
Presence of HCC	3.70 (1.08-12.67)	0.037	2.99 (0.62-14.36)	0.171
Comorbidities				
Diabetes	1.81 (1.36-2.41)	<0.001	1.51 (1.04-2.19)	**0.029**
Hypertension	1.43 (1.08-1.89)	0.012	1.16 (0.80-1.68)	0.434

Obesity	0.76 (0.57-1.00)	0.052	1.21 (0.84-1.76)	0.302
Cardiovascular disease	2.51 (1.65-3.81)	<0.001	1.85 (1.09-3.13)	**0.022**
COPD	2.68 (1.49-4.80)	0.001	2.26 (1.15-4.45)	**0.019**
Behavioral factors				
Smoking status				
No	1		1	
Past smoker	1.53 (1.11-2.10)	0.009	0.96 (0.65-1.43)	0.855
Current smoker	1.21 (0.76-1.90)	0.419	1.00 (0.54-1.83)	0.990
Alcohol consumption				
Do not drink currently	1		1	
Social drinking	0.53 (0.37-0.75)	<0.001	0.84 (0.55-1.26)	0.390
Current daily drinking	1.09 (0.70-1.71)	0.699	0.98 (0.53-1.83)	0.953

Abbreviations: COVID-19, coronavirus disease 2019; OR, odds ratio; CI, confidence interval; HCV, hepatitis C virus infection; HBV, hepatitis B virus infection; NAFLD, nonalcoholic fatty liver disease; ALD, alcoholic liver disease; HCC, hepatocellular carcinoma; COPD, chronic obstructive pulmonary disease.

The multivariate model for all-cause mortality was adjusted for age, gender, race/ethnicity, etiology of chronic liver disease, cirrhosis, HCC, diabetes, hypertension, obesity, cardiovascular disease, COPD, smoking status, and alcohol consumption.

a. **Alcohol related Liver Disease**

Probability of Survival

Other Liver Disease
Alcohol Liver Disease

p= 0.006
Hazard ratio 2.42 (1.29-4.55)

Days

Number at risk

Strata

| 731 | 628 | 524 | 444 | 378 | 310 | 263 | 241 | 227 | 201 | 177 | 157 | 134 | 102 | 68 | 26 | 8 | 0 |
| 86 | 66 | 55 | 46 | 37 | 34 | 27 | 24 | 24 | 20 | 17 | 14 | 9 | 8 | 3 | 0 | 0 | 0 |

0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170
Days

b. **Chronic Liver Disease**

Probability of Survival

No cirrhosis
Compensated cirrhosis
Decompensated cirrhosis

*

* p< 0.001
Hazard ratio 2.91 (1.70-5.00)

Days

Number at risk

Strata

591	512	430	362	314	263	223	204	196	172	150	132	113	87	57	21	6	0
126	109	90	81	64	54	46	43	39	35	32	29	22	16	10	4	1	0
86	61	49	39	30	25	19	16	14	13	11	9	7	6	4	1	1	0

0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170
Days

c. **Hepatocellular Carcinoma (HCC)**

Probability of Survival

No Hepatocellular carcinoma
Hepatocellular carcinoma

p= 0.002
Hazard ratio 3.31 (1.53-7.16)

Days

Number at risk

Strata

| 786 | 671 | 559 | 474 | 402 | 335 | 281 | 256 | 242 | 213 | 187 | 165 | 137 | 104 | 69 | 26 | 8 | 0 |
| 19 | 13 | 10 | 7 | 4 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170
Days

WHAT YOU NEED TO KNOW

Background and Context

The clinical outcomes of patients with chronic liver disease (CLD) and the novel coronavirus disease-2019 (COVID-19) are not well defined. Also, it is not clear which patients with CLD are most vulnerable to adverse outcomes from COVID-19.

New Findings

In this large study of 867 patients from 21 centers across the US with CLD with COVID-19 we determine that patients with alcohol related liver disease (ALD), decompensated cirrhosis and hepatocellular carcinoma have a high risk for all-cause mortality from COVID-19.

Limitations

Lack of adequate COVID-19 testing during the early phase of the pandemic could have led to decreased representation of patients with CLD and mild COVID-19 in our cohort.

Impact

Our findings will enable risk stratification and personalized management of patients with CLD who acquire COVID-19. Moreover, the association between ALD and poor outcomes with COVID-19 has broad public health implications given recent concerns about increased alcohol consumption during the pandemic.

SUPPLEMENTARY APPENDIX

Predictors of Outcomes of COVID-19 in Patients with Chronic Liver Diseases:

US Multicenter Study
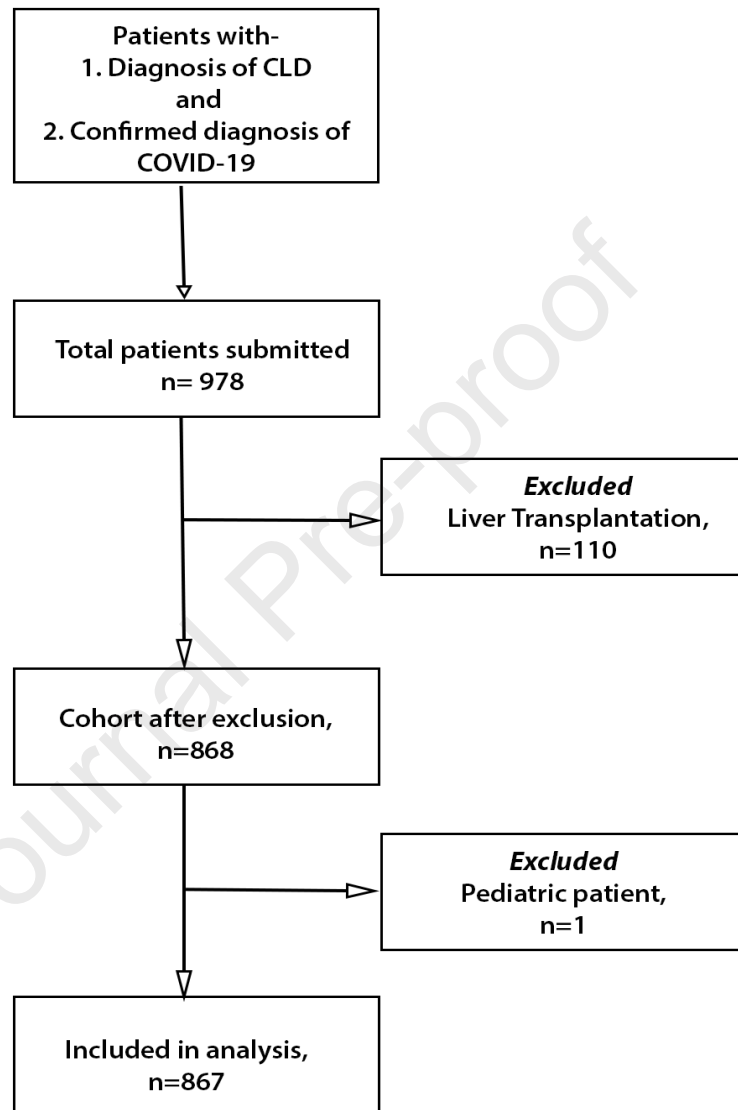
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II. Supplementary Tables

I.   Supplementary Figures

Figure S1: Patient Study Cohort

The flowchart shows how the study cohort was selected.
CLD- Chronic liver disease. COVID-19- Coronavirus disease 2019.

Figure S2: Age at the time of diagnosis of COVID-19 in patients with CLD stratified by overall mortality
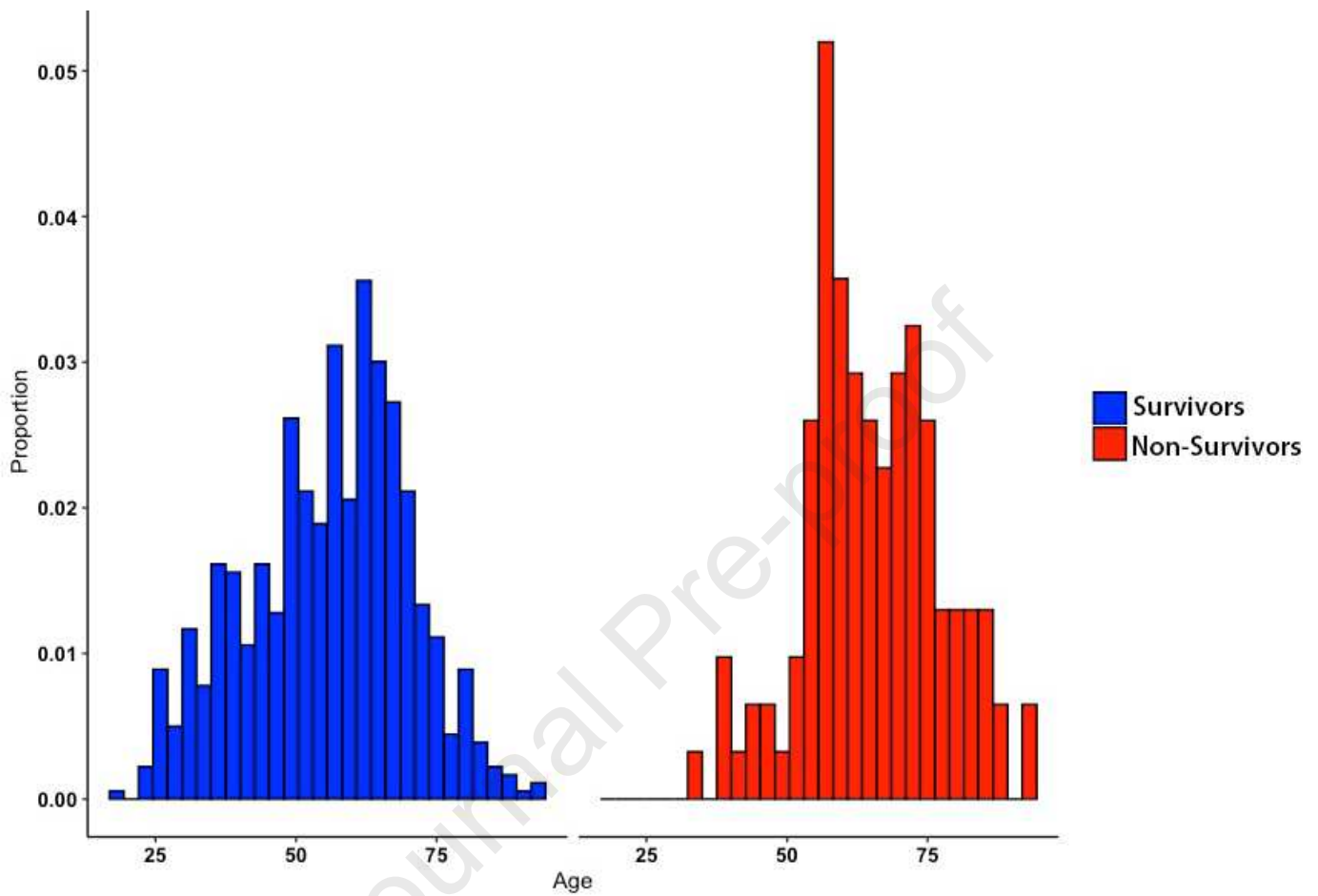
Histogram shows distribution of age (years) in the entire patient cohort compared to deceased patients. *CLD- Chronic liver disease. COVID-19- Coronavirus disease 2019.*

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Figure S3: Patient Demographics Stratified by Clinical Outcomes
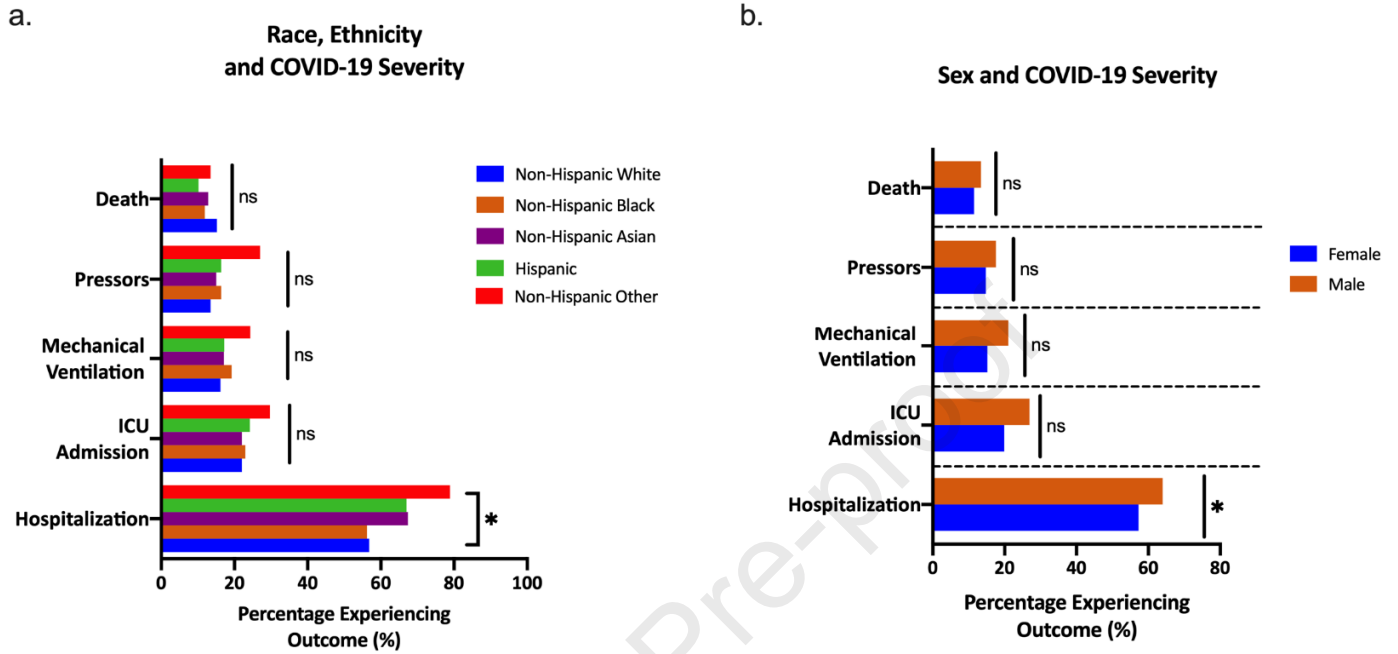
a. Clinical Outcomes of patients with CLD and COVID-19 stratified by race and ethnicity. b. Clinical Outcomes of patients with CLD and COVID-19 stratified by sex
CLD- Chronic liver disease. COVID-19- Coronavirus disease 2019. ICU- Intensive Care Unit. Ns- not significant

Figure S4: Comorbidities in patients with CLD and COVID-19
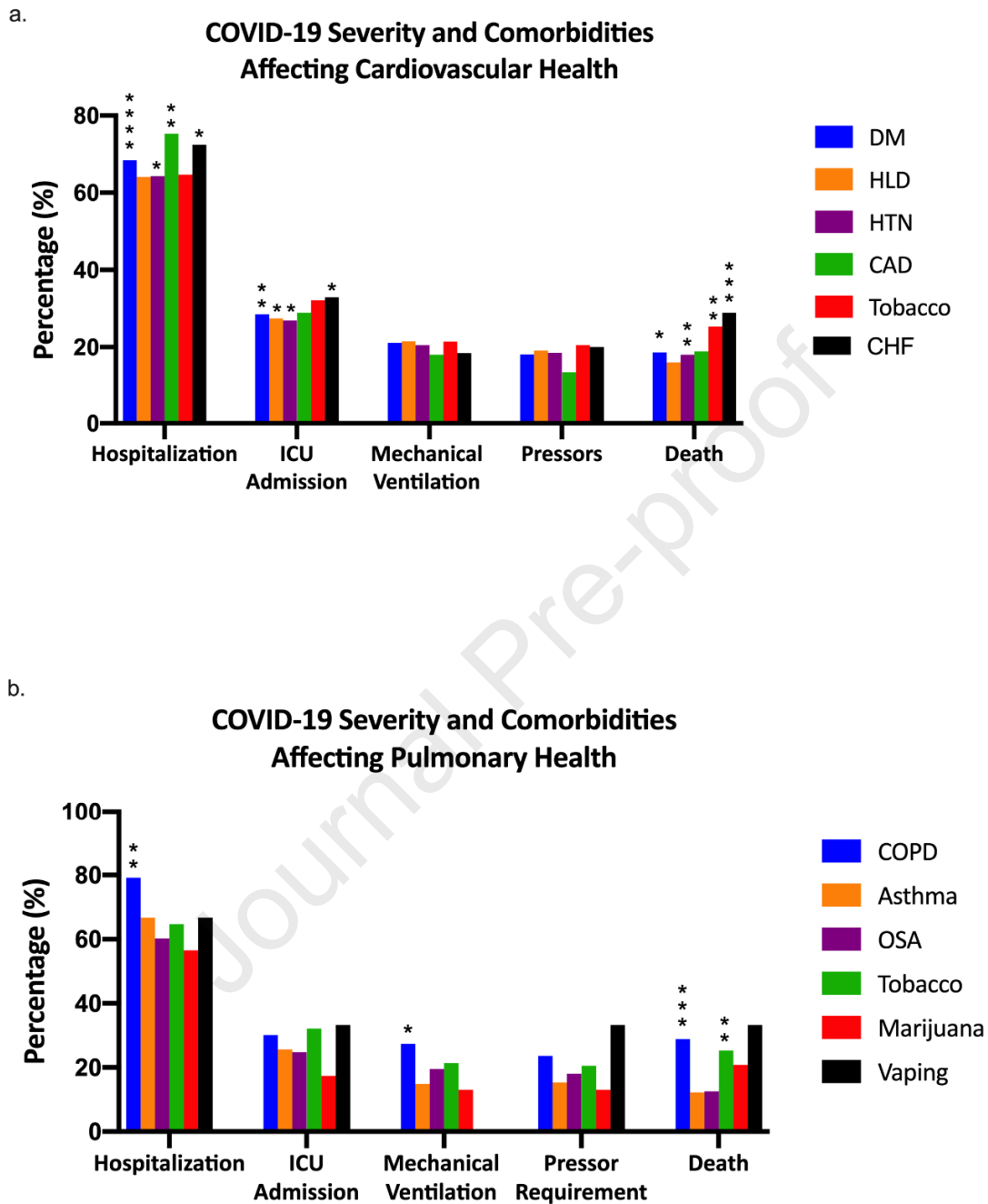
a.

COVID-19 Severity and Comorbidities Affecting Cardiovascular Health

b.

COVID-19 Severity and Comorbidities Affecting Pulmonary Health

a.Clinical Severity of patients with CLD and COVID-19 CLD stratified by comorbidities that affect cardiovascular health b. Clinical Severity of patients with CLD and COVID-19 stratified by comorbidities that affect pulmonary health. The graph shows the percentage of patients with a specific comorbidity who had these outcomes. Significance determined by comparing clinical outcomes in patients with (shown) vs those without (not shown) the specific comorbidity. * indicates a significantly higher proportion. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$, ***** $p < 0.00001$.

CLD- Chronic liver disease. COPD- Chronic obstructive pulmonary disease. COVID-19- Coronavirus disease 2019. ICU- Intensive Care Unit. OSA- Obstructive sleep apnea

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Figure S5: Etiology of CLD among patients with COVID-19

a.

Chronic Liver Disease Etiologies

b.

CLD Etiology Stratified by Liver Disease Severity
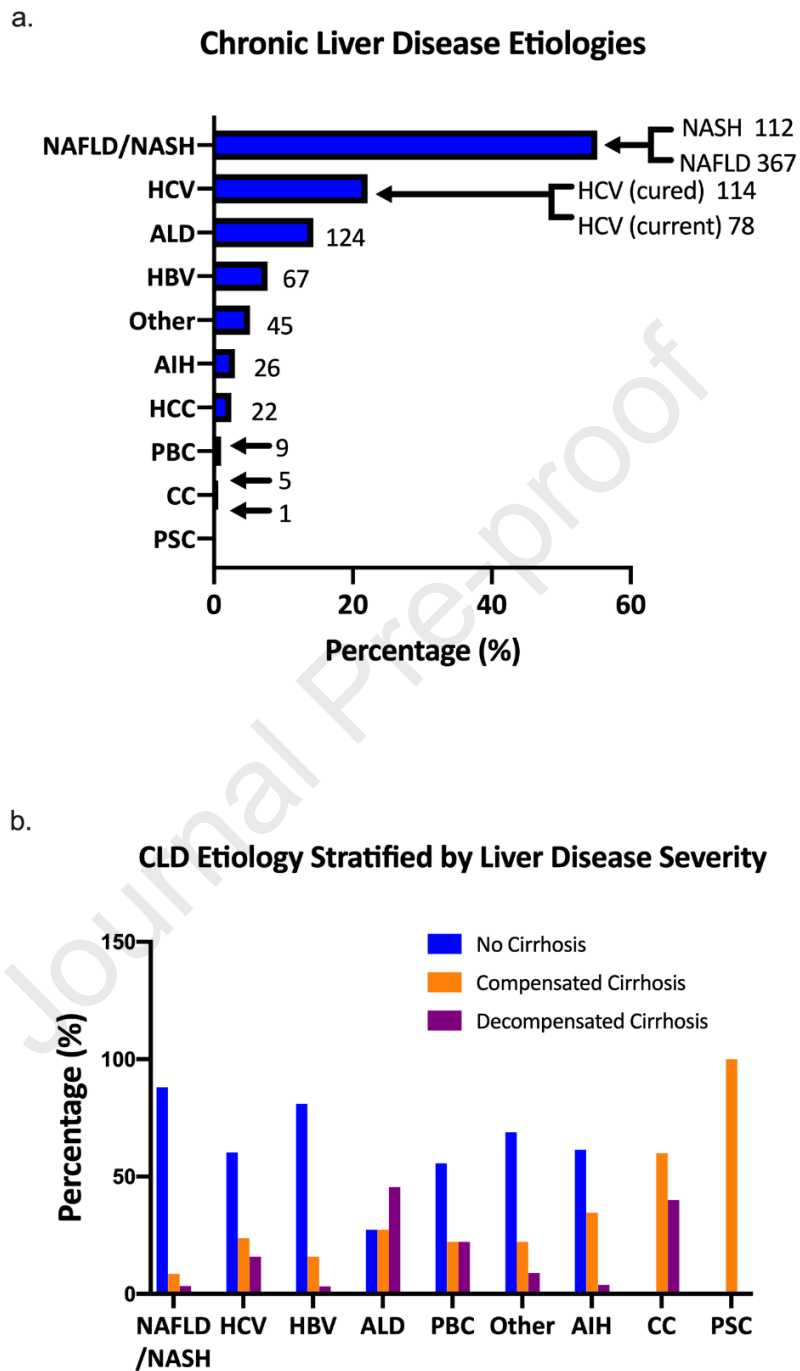
a. Prevalence of different etiologies of CLD in patients with COVID-19.

b. Stage of CLD in patients with COVID-19

AIH- Autoimmune Hepatitis. ALD- Alcoholic liver disease. CC- Cholangiocarcinoma. CLD- Chronic liver disease. COVID-19- Coronavirus disease 2019. HBV- Hepatitis B virus. HCC- Hepatocellular Carcinoma. HCV- Hepatitis C virus. NAFLD- Non-alcoholic fatty liver disease. NASH- Non-alcoholic steatohepatitis. PBC- Primary Biliary Cirrhosis. PSC- Primary Sclerosing Cholangitis.

Figure S6: Etiology of CLD and severity of COVID-19

CLD Etiology and COVID-19 Severity
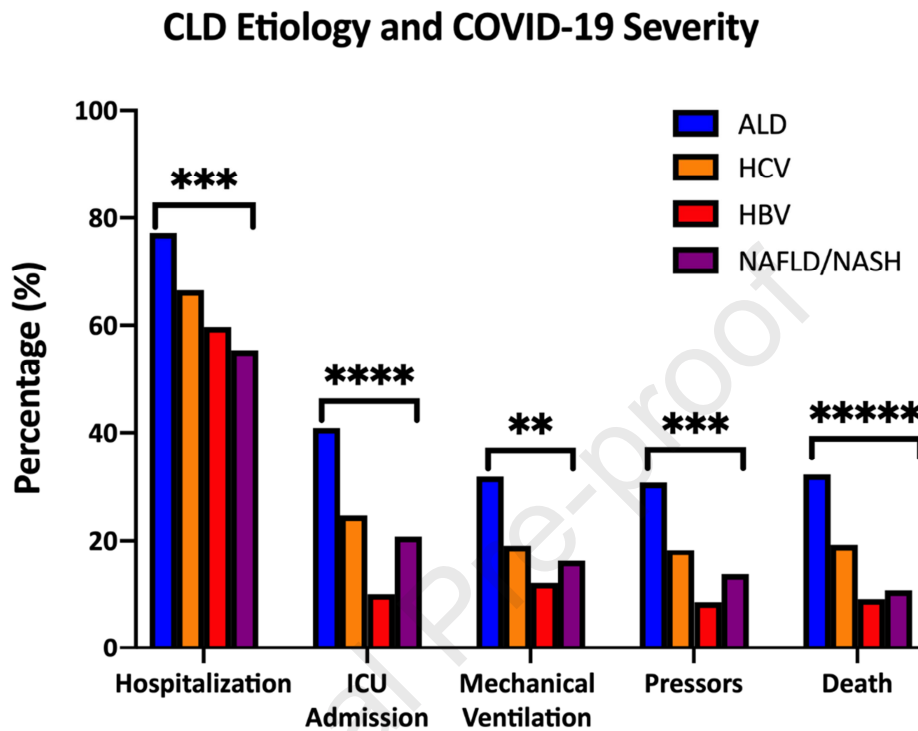
Comparing the proportion of patients with different etiologies of CLD requiring hospitalization, ICU admission, mechanical ventilation, vasopressors or mortality.

** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$, ***** $p < 0.00001$

ALD- Alcoholic liver disease. CLD- Chronic liver disease. COVID-19- Coronavirus disease 2019. HBV- Hepatitis B virus. HCV- Hepatitis C virus. ICU- Intensive care unit. NAFLD- Non-alcoholic fatty liver disease. NASH- Non-alcoholic steatohepatitis.

Figure S7: Indications for testing and risk factors for COVID-19 and in patients with CLD

a.

Indications for COVID-19 Testing

b.

Risk Factors for COVID-19
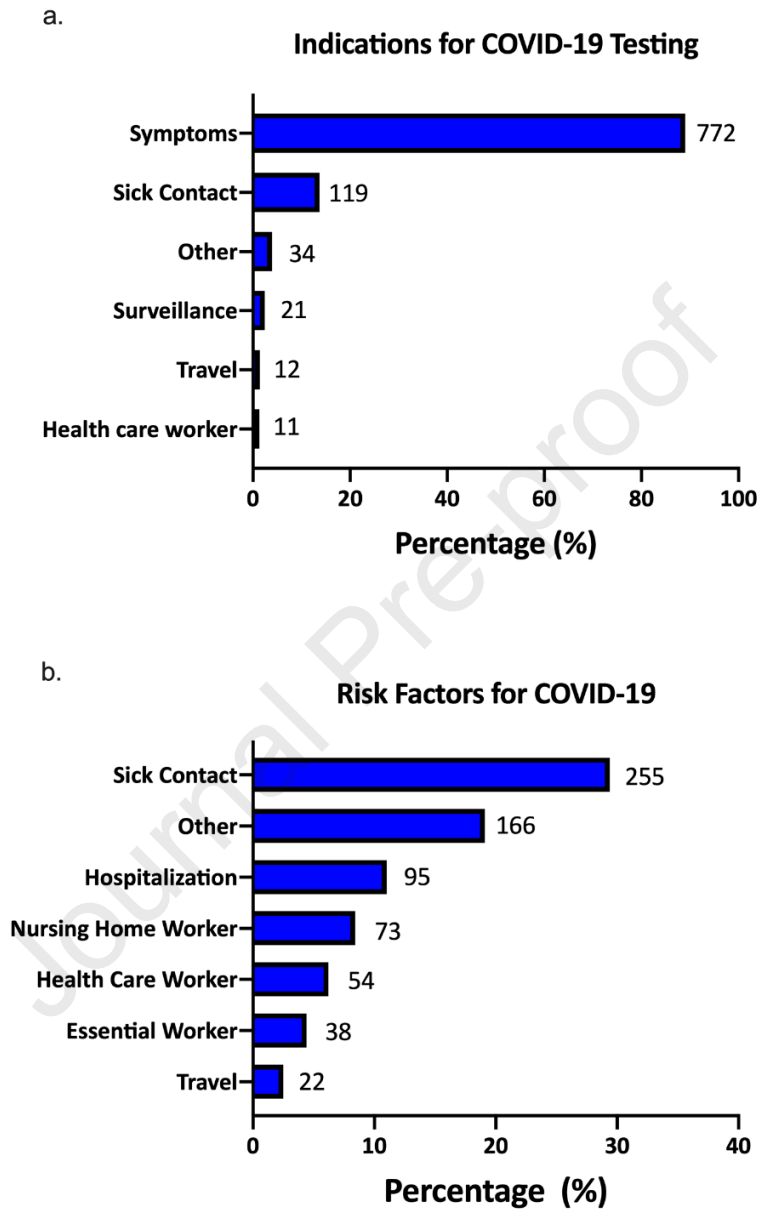
a. Indications of COVID-19 testing in patients with CLD
b. Risk factors for acquiring COVID-19 in patients with CLD
CLD- Chronic liver disease. COVID-19- Coronavirus disease 2019

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Figure S8: Presenting symptoms of COVID-19 among patients with CLD
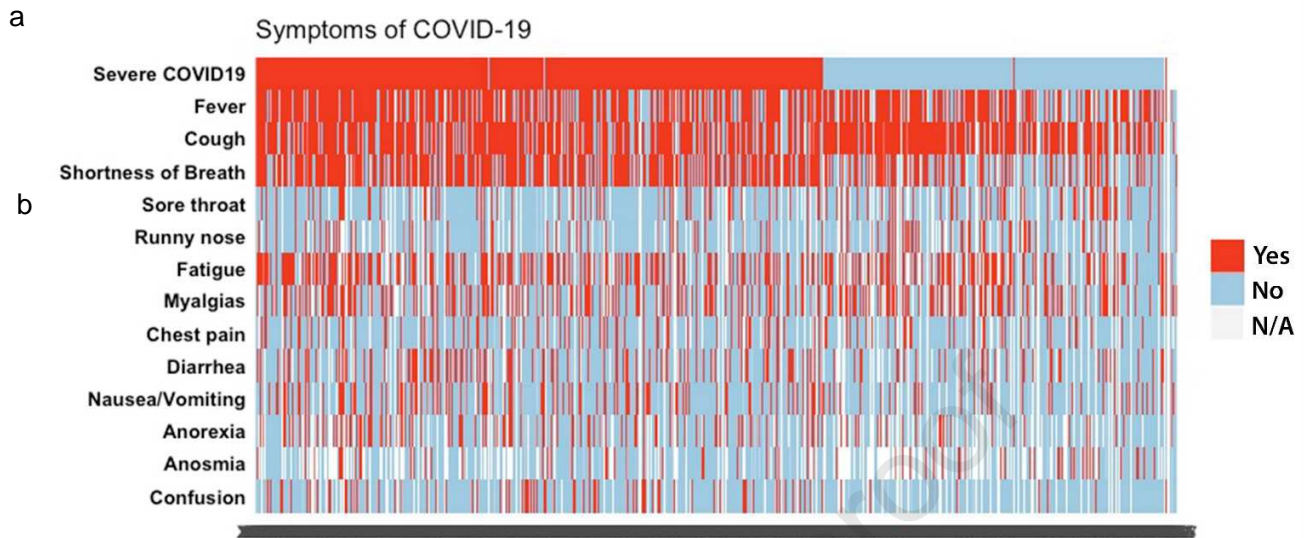
a. Tiled heatmap of symptoms of COVID-19 stratified by severity of COVID-19. Each vertical bar represents a single patient b. Frequency of different COVID-19 symptoms in patients with CLD
CLD- Chronic liver disease. COVID-19- Coronavirus disease 2019

Figure S9 Liver tests during COVID-19

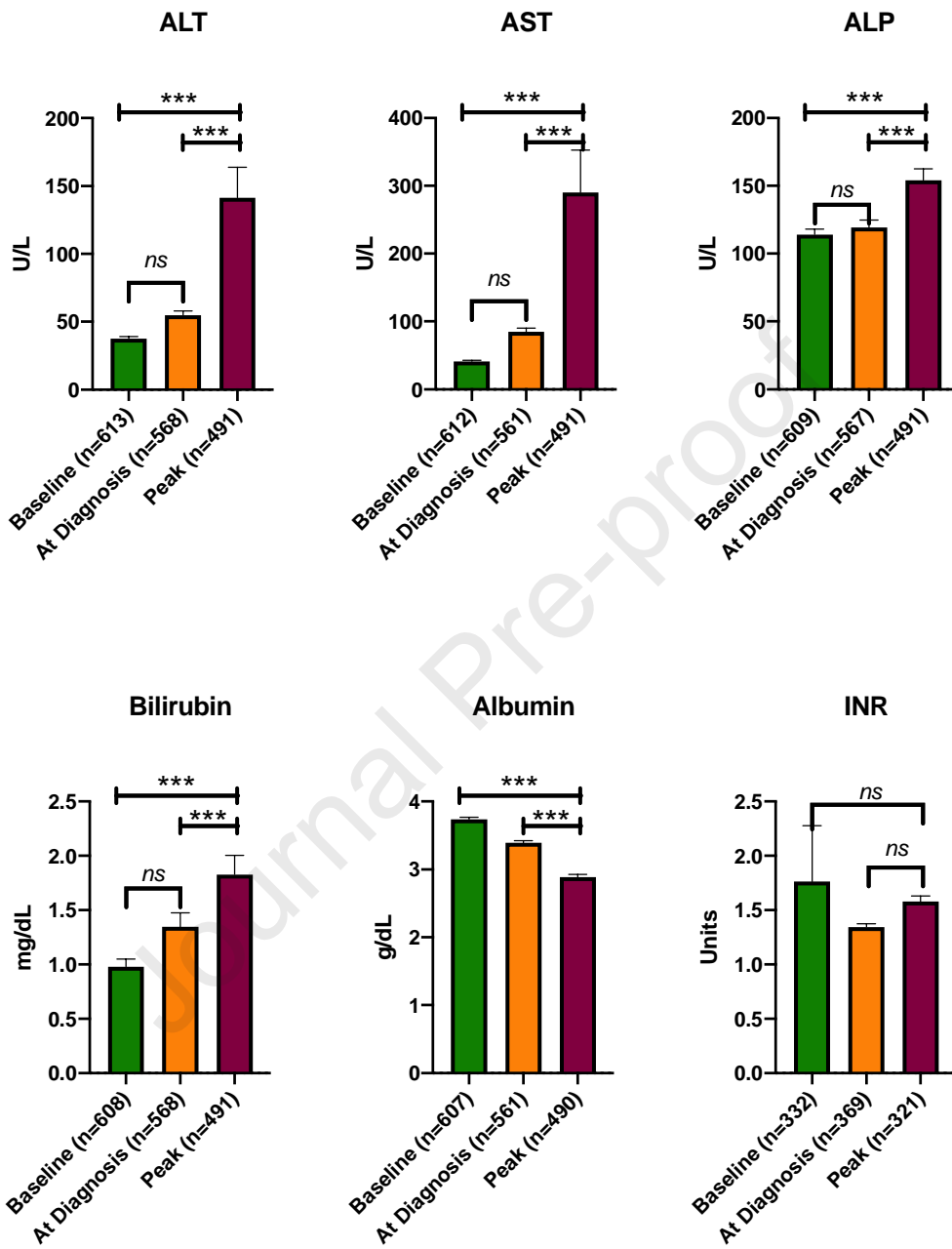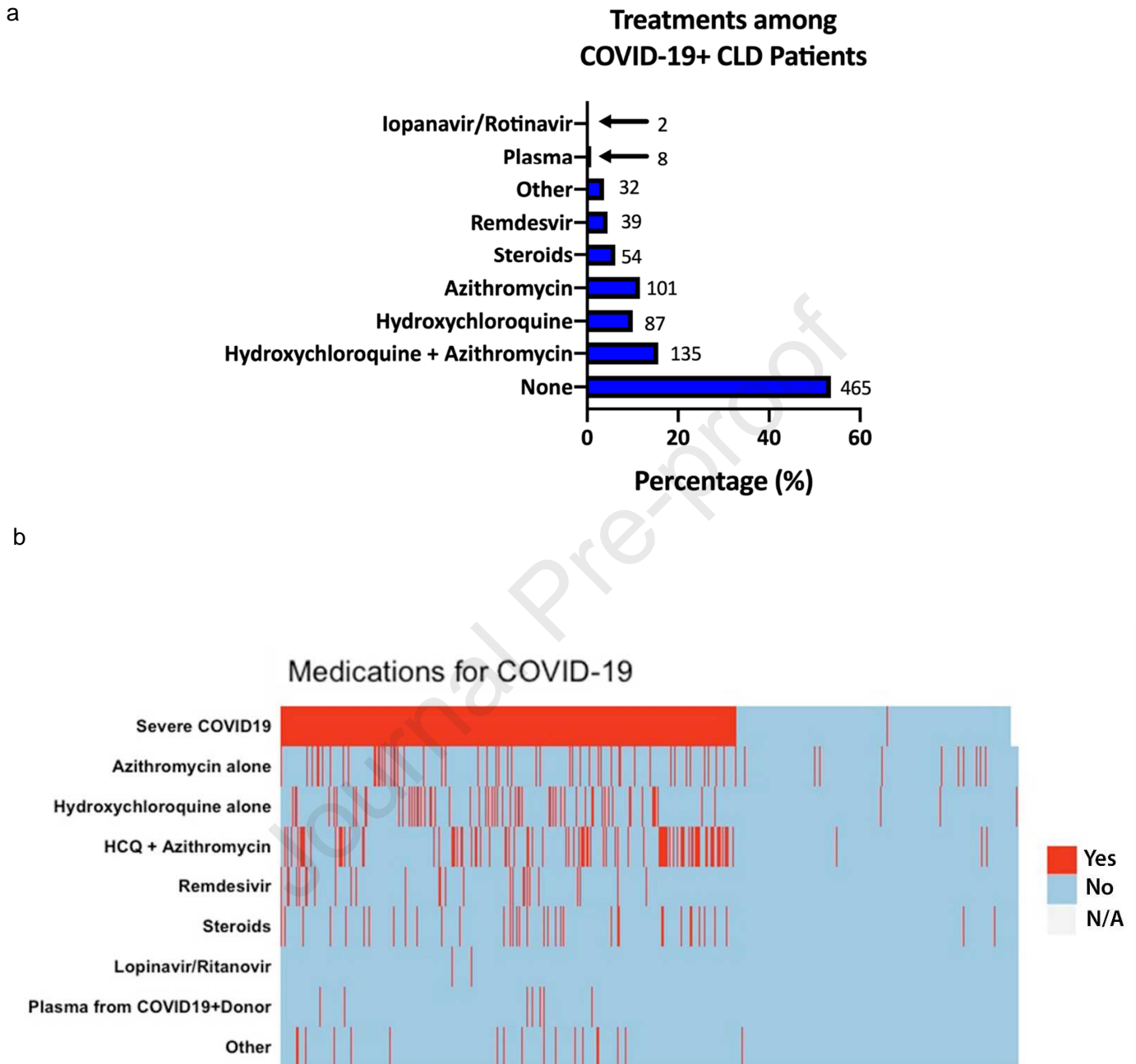**Figure S10: Treatment for COVID-19 among patients with CLD**

a

b

a. Frequency of COVID-19 treatments in patients with CLD b. Tiled heatmap of treatment of COVID-19 stratified by severity of disease. Each horizontal bar represents a single patient.

CLD- Chronic liver disease. COVID-19- Coronavirus disease 2019. HCQ- Hydroxychloroquine

II. Supplementary Tables

Table S1: List of participating institutions and investigators from each site

	Institution	Principal Investigator
1	Ochsner Medical Center, LA	Nyann Latt
2	Massachusetts General Hospital, MA	Patricia P Bloom
3	Mount Sinai School of Medicine, NY	Ponni Perumalswami
4	University of California San Francisco, Fresno, CA	Marina Roytman
5	Hennepin County Medical Center, MN	Elizabeth Aby, Jose Debes
6	Brigham and Women's Hospital, MA	Viveiros, Kathleen, Walter Chan
7	Duke University, NC	Kara Wegermann, Tzu-Hao Lee
8	Beth Israel Deaconess Medical Center, MA	Maria Andreea Catana
9	Stanford University, CA	Donghee Kim, Nia Adeniji, Paul Kwo, Renumathy Dhanasekaran
10	University of Pennsylvania, PA	Rotonya Carr
11	Rush University Medical Center, IL	Costica Aloman
12	University of Michigan, MI	Vincent Chen
13	Veterans Administration (VA) Medical Center, Washington, DC	Atoosa Rabiee
14	University of Minnesota, MN	Elizabeth Aby
15	Georgetown University, Washington DC	Brett Sadowski
16	University of Arizona/Banner Health, AZ	Veronica Nguyen
17	The University of Kansas Medical Center, KS	Winston Dunn
18	University Hospitals Cleveland Medical Center, OH	Kenneth Chavin
19	University of Southern California, CA	Kali Zhou
20	Mayo Clinic, AZ	Blanca Lizaola-Mayo
21	Weill Cornell Medicine, NY	Sonal Kumar

Table S2. List of ICD-10 Codes for Chronic Liver Disease and COVID-19

COVID-19	SARS_CoV2 Lab Code
U07.1 COVID-19	LAB9309
NASH / NAFLD	**Unspecified chronic liver disease**
K75.81 Nonalcoholic steatohepatitis (NASH)	K73 Chronic hepatitis
K76.0 NAFLD (nonalcoholic fatty liver disease)	K73.0 Chronic persistent hepatitis
Alcohol-related liver disease	K73.1 Chronic lobular hepatitis
K70 Alcoholic liver disease	K73.2 Chronic active hepatitis
K70.1 Alcoholic hepatitis	K73.8 Other chronic hepatitis, Recurrent hepatitis
K70.10 …… without ascites	K73.9 Chronic hepatitis, unspecified
K70.11 …… with ascites	K74 Fibrosis and cirrhosis of liver
K70.2 Alcoholic fibrosis and sclerosis of liver	K74.0 Hepatic fibrosis
K70.3 Alcoholic cirrhosis of liver	K74.1 Hepatic sclerosis
K70.30 …… without ascites	K74.2 Hepatic fibrosis with hepatic sclerosis
K70.31 …… with ascites	K74.4 Secondary biliary cirrhosis
K70.4 Alcoholic hepatic failure	K74.5 Biliary cirrhosis, unspecified
K70.40 …… without coma	K74.6 Other and unspecified cirrhosis of liver
K70.41 …… with coma	K74.60 Unspecified cirrhosis of liver
K70.9 Alcoholic liver disease, unspecified	K74.69 Other cirrhosis of liver
Chronic Hep C/Hep B	K71.7 Toxic liver disease with fibrosis and cirrhosis
B18.2 Chronic hepatitis C	K71.3 Toxic liver disease with chronic hepatitis
K74.6 Chronic hepatitis C with cirrhosis	K71.4 Toxic liver disease with chronic lobular hepatitis
K74.69, B19.2 cirrhosis to HCV	K71.5 Toxic liver disease with chronic active hepatitis
B18.1 Chronic hepatitis B	K71.50 …… without ascites
K74.6, B19.1 Chronic hepatitis B with cirrhosis	K71.51 …… with ascites
PBC/PSC/Autoimmune hepatitis	K76.6 Portal hypertension
K74.3 Primary biliary cirrhosis	K76.7 Hepatorenal syndrome
K74.3 Cirrhosis due to primary sclerosing cholangitis	K76.81 Hepatopulmonary syndrome
K83.01 Primary sclerosing cholangitis	**Decompensated cirrhosis**
K75.4 Autoimmune hepatitis	K72.9 Decompensated hepatic cirrhosis
	K74.69 Decompensated liver disease

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Table S3: Data Elements of the COLD Study Data Collection Forms

Variable	Category
Center-Specific Record ID	Identifier
Center Name	
Age (at Diagnosis of COVID)	
Gender	Male Female Other
Race	White African American Asian American Indian Other
Ethnicity	Hispanic or Latino Non-Hispanic
Date of Data Collection	
Home Address Zip Code	
Residence	Home- Apartment Home- Single family home Skilled Nursing Home Long term care facility Assisted Living Facility Other Do not know None/Shelter
Number of people at home	
Insurance	Medicare/Medicaid Private Insurance Uninsured Do not know
Date of COVID-19 Diagnosis	
Mode of diagnosis of COVID-19	Positive PCR test Positive serologic test Not clear Other

Risk Factors for COVID-19	Travel to high risk region Sick Contacts Hospitalization within the past month Healthcare worker Essential worker Nursing home resident Other
Indication of testing	Travel to high risk region Contacts who tested positive for COVID19 Symptoms Healthcare worker surveillance Surveillance Other
Hospitalization for COVID19	Yes No
Use of Supplemental Oxygen	Yes No
Use of Vasopressors	Yes No
Number of pressors used	
ICU admission	Yes No
Mechanical ventilation	Yes No
Non-invasive Positive pressure ventilation	Yes No
Length of Hospital Stay (Days)	
Death related to COVID-19	Yes No
Symptoms	Cough, Shortness of breath, sore throat, runny nose, fatigue, myalgias, chest pain, diarrhea, nausea/vomiting, anorexia, anosmia, confusion
Number of years since the patient has a known diagnosis of chronic liver disease	

Etiology	Hepatitis C- current Hepatitis C- Cured Hepatitis B Nonalcoholic Fatty Liver Disease- Hepatic steatosis alone Nonalcoholic steatohepatitis Alcoholic Liver Disease Cryptogenic Cirrhosis Primary biliary cholangitis Primary sclerosing cholangitis Autoimmune hepatitis Hepatocellular carcinoma (HCC) Other
Cirrhosis	Yes No
Fibroscan	F0-1 F2 F3 F4
FIB4	F0-1 F2 F3 F4
NAFLD fibrosis score	F0-1 F2 F3 F4
MR Elastography	F0-1 F2 F3 F4
US elastography	F0-1 F2 F3 F4
Biopsy	F0-1 F2 F3 F4

Other	F0-1 F2 F3 F4
Comorbidities	Diabetes Hypertension Hyperlipidemia Obesity Tobacco Smoking Coronary artery disease Congestive heart Failure HIV positive COPD Asthma Non- Liver malignancy Opioid use disorder Obstructive sleep apnea Chronic lung disease- Non asthma, non COPD Vaping Marijuana use
Tobacco Smoking status	Never smoker Former smoker (smoked at least 100 cigs in life time)Current smoker
Alcohol use	Do not drink currently Social drinkingDaily drinking
Has the patient received a liver transplantation?	Yes No
Date of transplant	
Type of Immunosuppression at the time of COVID19 diagnosis	Tacrolimus Cyclosporine Prednisone (<20mg/day) Prednisone (>21 mg/day) Mycophenolate Azathioprine mTOR inhibitors (Sirolimus, Everlolimus)
Did the patient receive any of this within 6 months of COVID19 diagnosis?	Intravenous methyprednisolone Anti thymocyte globulin (ATG) Basiliximab

	Rituximab
Other Immunosuppression	
Was immunosuppression modified during COVID19?	Yes No
How was immunosuppression modified?	
Did the patient experience acute rejection during COVID19?	Yes No
Laboratory Data (Prior to COVID-19, At diagnosis of COVID-19, Peak during COVID-19, After COVID-19)	ALT, AST, Alk Phos, GGT, Total Bilirubin, Albumin, Creatinine, Sodium, INR, Platelets, Ferritin, WBC, lymphocytes, Neutrophils, Triglycerides, LDL, HbA1c, CK
Decompensation prior to COVID19	None Ascites Variceal Bleed Hepatic Encephalopathy Other
Did the patient decompensate during COVID-19?	Yes No
Ascites prior to COVID19 (Field Annotation: 1-6 months prior to COVI19)	None Mild-Moderate Severe
Encephalopathy prior to COVID19 (Field Annotation: 1-6 months prior to COVI19)	None Mild-Moderate Severe
Ascites during to COVID19	None Mild-Moderate Severe
Encephalopathy during to COVID19	None Mild-Moderate Severe
Ascites after to COVID19	None Mild-Moderate Severe
Encephalopathy after to COVID19	None Mild-Moderate

	Severe
Did the patient develop variceal bleeding during COVID-19?	Yes No
Were any of the following delayed or cancelled due to diagnosis of COVID-19?	Endoscopy for esophageal varices surveillance Imaging for HCC surveillance Paracentesis for symptomatic ascites Hepatitis C treatment Hepatitis B treatment Liver transplant evaluation Liver transplantation Other
Were ambulatory clinic visits to hepatology delayed or canceled due to COVID-19?	Yes No
Were ambulatory clinic visits to primary care or other specialties delayed or cancelled due to COVID-19?	Yes No
Were medical procedures not related to liver disease delayed or cancelled?	Yes No
Was care impacted not directly by COVID-19 but because of health system overload?	Yes No
Did the patient have a tele-health visit during COVID19?	Yes No
COVID-19 treatment	Remdesivir Chloroquine Hydroxychloroquine Azithromycin Prednisone or Methylprednisolone Lopinavir/ritonavir Donor Plasma Other None

Did the patient receive any of the following antibiotics during COVID-19?	Amoxicillin/Clavulanate Cephalosporins Aminoglycosides Macrolides Minocycline Anti-tuberculosis drugs Fluoroquinolones Azithromycin None
Did the patient receive any of the following hepatotoxic medications for more than 3 days during COVID-19 infection?	Acetaminophen >2 gm per day NSAIDs Anticonvulsants- Phenytoin, Valproic acid, Carbamazepine Azoles Amiodarone Anesthetics- Halothane, Isoflurane Statins Other Hepatotoxic medications None
Was the patient chronically on any of the following medications before acquiring COVID-19 infection?	Proton pump inhibitors ACE inhibitors Angiotensin Receptor blockers
If the patient had HCC, had they received any of the following?	Transarterial therapy Ablative therapy Tyrosine kinase inhibitors Immunotherapy None
Date of Last Follow up	
Status	Alive, fully recovered Alive, still impacted by COVID19 Death from COVID19 Death from other causes

Table S4. Interaction of alcoholic liver disease and decompensated cirrhosis/HCC with the Risk for all-cause mortality/mortality due to COVID-19.

	Univariate model *P* for interaction	Multivariable model *P* for interaction
All-cause mortality		
Alcoholic liver disease*decompensated cirrhosis	0.033	0.278
Alcoholic liver disease*HCC	0.976	0.771
Mortality due to COVID-19		
Alcoholic liver disease*decompensated cirrhosis	0.044	0.225
Alcoholic liver disease*HCC	0.640	0.531

The multivariate model for all-cause mortality was adjusted for age, gender, race/ethnicity, etiology of chronic liver disease, decompensated cirrhosis, HCC, diabetes, hypertension, cardiovascular disease, COPD, smoking status, alcohol consumption, and the interaction term (alcoholic liver disease*decompensated cirrhosis or alcoholic liver disease*HCC).

The multivariate model for mortality due to COVID-19 was adjusted for age, gender, race/ethnicity, etiology of chronic liver disease, decompensated cirrhosis, HCC, diabetes, hypertension, cardiovascular disease, COPD, smoking status, and the interaction term (alcoholic liver disease*decompensated cirrhosis or alcoholic liver disease*HCC).

Table S5. Univariate and Multivariate Survival Analyses in Patients with Non-Cirrhotic Chronic Liver Disease and COVID-19

	Univariate model for all-cause mortality		Multivariate model for all-cause mortality (events=62)		Multivariate model for mortality due to COVID-19 (events=59)	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Demographic factors						
Age (per 10 year)	1.76 (1.46-2.12)	<0.001	1.72 (1.40-2.12)	**<0.001**	1.66 (1.34-2.04)	**<0.001**
Male	1.63 (0.97-2.73)	0.064				
Race/ethnicity						
Non-Hispanic white	1					
Non-Hispanic black	0.73 (0.40-1.34)	0.310				
Hispanic	0.80 (0.41-1.59)	0.532				
Non-Hispanic Asian	1.52 (0.58-4.01)	0.395				
Other	0.29 (0.04-2.16)	0.227				
Liver-related factors						
Etiology of liver disease						
HCV	1					
ALD	1.48 (0.62-3.55)	0.376	4.72 (2.05-10.85)	**<0.001**	7.39 (2.96-18.46)	**<0.001**
NAFLD	0.43 (0.24-0.76)	0.004				
HBV	0.67 (0.23-1.99)	0.472				
Other	0.30 (0.07-1.31)	0.110				
Comorbidities						
Diabetes	2.15 (1.30-3.61)	0.003	1.87 (1.08-3.23)	**0.025**		
Hypertension	3.15 (1.64-6.05)	0.001	2.04 (1.00-4.15)	**0.049**	2.36 (1.14-4.91)	**0.021**
Cardiovascular disease	2.02 (1.16-3.53)	0.014				
COPD	2.20 (1.15-4.22)	0.018			2.01 (1.00-4.04)	0.050
Behavioral factors						
Smoking status						
No	1					

Past smoker	2.30 (1.33-3.97)	0.003				
Current smoker	2.43 (1.10-5.38)	0.028	3.46 (1.52-7.84)	**0.003**	2.97 (1.24-7.13)	**0.014**
Alcohol consumption						
Do not drink currently	1					
Social drinking	0.43 (0.21-0.88)	0.021				
Current daily drinking	0.74 (0.32-1.74)	0.489				

Abbreviations: COVID-19, coronavirus disease 2019; HR, hazard ratio; CI, confidence interval; HCV, hepatitis C virus infection; HBV, hepatitis B virus infection; NAFLD, nonalcoholic fatty liver disease; ALD, alcoholic liver disease; HCC, hepatocellular carcinoma; COPD, chronic obstructive pulmonary disease.

Table S6. Laboratory Characteristics among Hospitalized Patients with Chronic Liver Disease and COVID-19 (n=524).

	All-cause Mortality status		*P* value
	Alive	Died	
ALT			
Before COVID-19 (n=374)	27 (18, 40)	21 (15, 33)	0.075
At COVID-19 diagnosis (n=467)	35 (22, 63)	31.5 (24, 57)	0.220
Peak (n=428)	50 (28, 104)	40.5 (23, 88)	0.307
Delta-ALT (n=410)	0 (0, 27.5)	3 (0, 22.5)	0.278
AST			
Before COVID-19 (n=375)	27 (20, 40)	32 (21, 65)	0.178
At COVID-19 diagnosis (n=463)	50 (30, 81.5)	63.5 (38, 63.5)	0.021
Peak (n=428)	65 (39, 120)	92.5 (51.5, 225)	0.001
Delta-AST (n=406)	5 (0, 35)	22 (0, 123)	0.075
ALP			
Before COVID-19 (n=373)	89 (69, 128)	109 (75, 152)	0.032
At COVID-19 diagnosis (n=467)	83 (63, 119)	91.5 (63, 91.5)	0.374
Peak (n=427)	99 (70, 158.5)	131 (79, 235)	0.001
Delta-ALP (n=413)	8.5 (0, 48)	5.0 (0, 87)	0.330
Bilirubin			
Before COVID-19 (n=372)	0.5 (0.4, 0.8)	0.7 (0.5, 1.7)	0.004
At COVID-19 diagnosis (n=467)	0.6 (0.4, 0.9)	0.8 (0.5, 2.2)	<0.001
Peak (n=428)	0.7 (0.4, 1.2)	1.5 (0.7, 4.0)	<0.001
Delta-bilirubin (n=409)	0.1 (0, 0.5)	0.2 (0, 1.6)	0.037
MELD score			
Before COVID-19 (n=276)	10.0 (7, 14)	11.0 (8, 21)	<0.001
At COVID-19 diagnosis (n=375)	10.5 (7, 18)	16.5 (11, 24)	<0.001
Peak (n=291)	14.0 (8, 21)	21.5 (13, 32)	<0.001
Delta-MELD (n=254)	1.0 (0, 4)	5.0 (0, 12.5)	<0.001

Abbreviation: COVID-19, coronavirus disease 2019; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase.

Data are expressed as the median (interquartile range). Mann-Whitney U test were performed for comparison between groups.