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ORIGINAL ARTICLE

# Hepatic Steatosis Is Associated with Increased Disease Severity and Liver Injury in Coronavirus Disease-19

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## Abstract

**Background** Coronavirus disease-2019 (COVID-19) is a global pandemic. Obesity has been associated with increased disease severity in COVID-19, and obesity is strongly associated with hepatic steatosis (HS). However, how HS alters the natural history of COVID-19 is not well characterized, especially in Western populations.

**Aims** To characterize the impact of HS on disease severity and liver injury in COVID-19.

**Methods** We examined the association between HS and disease severity in a single-center cohort study of hospitalized COVID-19 patients at Michigan Medicine. HS was defined by either hepatic steatosis index > 36 (for Asians) or > 39 (for non-Asians) or liver imaging demonstrating steatosis > 30 days before onset of COVID-19. The primary predictor was HS. The primary outcomes were severity of cardiopulmonary disease, transaminitis, jaundice, and portal hypertensive complications.

**Results** In a cohort of 342 patients, metabolic disease was highly prevalent including nearly 90% overweight. HS was associated with increased transaminitis and need for intubation, dialysis, and vasopressors. There was no association between HS and jaundice or portal hypertensive complications. In a sensitivity analysis including only patients with liver imaging > 30 days before onset of COVID-19, imaging evidence of hepatic steatosis remained associated with disease severity and risk of transaminitis.

**Conclusions** HS was associated with increased disease severity and transaminitis in COVID-19. HS may be relevant in predicting risk of complications related to COVID-19.

**Keywords** SARS-CoV-2 · Acute liver injury · Outcomes · NAFLD

## Abbreviations

| | |
|---|---|
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| BMI | Body mass index |
| COVID-19 | Coronavirus disease-2019 |
| HS | Hepatic steatosis |
| HSI | Hepatic steatosis index |
| IQR | Interquartile range |
| ULN | Upper limit of normal |
| WHO | World Health Organization |

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## Introduction

Coronavirus disease-2019 (COVID-19) is a pandemic responsible for > 25 million cases and > 800,000 deaths worldwide [1]. COVID-19 frequently results in gastrointestinal disease including liver injury [2, 3]. However, whether underlying liver disease influences COVID-19-related disease severity—both severity of respiratory disease and clinically meaningful liver-related outcomes such as jaundice, ascites, and hepatic encephalopathy—is less clear [4]. This question is critical because metabolic dysfunction-associated fatty liver disease, characterized by hepatic steatosis (HS)

and metabolic risk factors including overweight, affects up to 30% of the population [5–8]. Further, metabolic risk factors are strongly associated with increased COVID-19 disease severity [9, 10]. However, the impact of HS on COVID-19-related outcomes is not well understood and has not been reported to our knowledge in the USA [11]. We aimed to evaluate the impact of HS on disease severity and liver injury in COVID-19.

## Methods

This was a retrospective single-center cohort study. Our study included hospitalized adult patients (≥ 18 years old) at Michigan Medicine with COVID-19 diagnosed by polymerase chain reaction between March 10, 2020 (first identified case in the state of Michigan) and May 20, 2020. Patients were followed until death, discharge from the hospital, or September 3, 2020. This study was approved by the University of Michigan Institutional Review Board.

Outcomes were disease severity and liver injury. Disease severity was defined as: death, need for intensive care unit (ICU) admission, intubation, vasopressor requirement, new dialysis requirement, or the World Health Organization (WHO) ordinal scale. Liver injury was defined as peak alanine aminotransferase (ALT) > 2X or 5X the upper limit of normal (ULN) and > 2X or 5X the patient's prior baseline ALT (if known); jaundice (total bilirubin > 2 mg/dL or 4 mg/dL); or new/worsening ascites or encephalopathy. ALT ULN was defined as 19 U/L for women and 30 U/L for men [12, 13].

The primary predictor was HS, defined by either imaging evidence of steatosis > 30 days before COVID-19 diagnosis, or hepatic steatosis index (HSI) > 36 for Asians and > 39 for non-Asians [14], based on ambulatory laboratory values > 30 days before COVID-19 diagnosis. HSI was defined as 8 * ALT/aspartate aminotransferase (AST) + body mass index (BMI) + 2 (if diabetes) + 2 (if female).

Continuous variables were represented as median (interquartile range [IQR]) and categorical variables as percentages. Continuous variables were compared using rank-sum tests and categorical variables using $\chi^2$ tests. Statistical significance was defined as two-tailed $P$ value < 0.05. We used logistic regressions with disease severity/liver injury as dependent variables (except WHO ordinal scale for which linear regression was used) and HS as the main independent variable. The multivariable model was adjusted for age, sex, race, recent healthcare exposure (hospitalization or nursing facility residence < 90 days before COVID-19 diagnosis), hypertension, and dyslipidemia.

All statistical analyses were performed using R version 3.6.1 (Vienna, Austria).

## Results

The cohort included 342 patients, of whom 178 (52%) had HS based on imaging or HSI (Fig. 1). Median follow-up was 113 days after COVID-19 diagnosis. Table 1 shows the characteristics of the cohort. Prevalence of metabolic comorbidities was high: 69% of patients had hypertension, 43% diabetes, 47% dyslipidemia, 85% overweight (BMI > 23 for Asians or > 25 for non-Asians), and 52% obesity. Patients with HS were younger and more often African–American compared to those without HS.

Overall, 19% of patients died and > 50% required ICU admission (Table 1). In unadjusted analyses, patients with HS more often required intubation, dialysis, or vasopressors and had greater odds of transaminitis, but were less likely to die (Tables 1, 2, Fig. 2). There was no difference by HS status in ICU admission or jaundice. In multivariable analyses, HS was associated with increased odds of ICU admission (odds ratio 1.60 [95% confidence interval 1.00–2.57]), intubation (2.51 [1.52–4.16]), vasopressor requirement (1.22 [1.11–1.34]), and ALT > 5x ULN (2.12 [1.03–4.37]). Patients with HS had more severe disease based on higher WHO ordinal scale (Table 2). Rates of new/worsening ascites and encephalopathy were low: 1.3% and 2.5%, respectively, with no difference based on HS status ($P > 0.4$).

We conducted sensitivity analyses where only patients with imaging evidence of hepatic steatosis > 30 days prior to COVID-19 diagnosis. Of 141 patients with prior imaging, 68 (48%) had HS. Imaging evidence of HS was associated with increased adjusted odds of intubation (2.75 [1.21–6.25]), vasopressor requirements (1.22 [1.04–1.43]), and odds of ALT > 5x ULN (7.09 [1.73–28.95]) (Table 3). There was no difference by HS status in ICU admission, death, jaundice, dialysis requirement, or WHO ordinal scale.

## Discussion

We found that in a US cohort of hospitalized patients with COVID-19, HS was associated with increased disease severity and transaminitis, but not with clinically relevant liver complications such as jaundice or new/worsening ascites or hepatic encephalopathy.

Our study adds to a literature on the effects of HS, and chronic liver disease more generally, on COVID-19 severity. Two studies found that HS based on imaging or HSI was associated with increased transaminitis and more severe respiratory disease [11, 15], while in a third it was

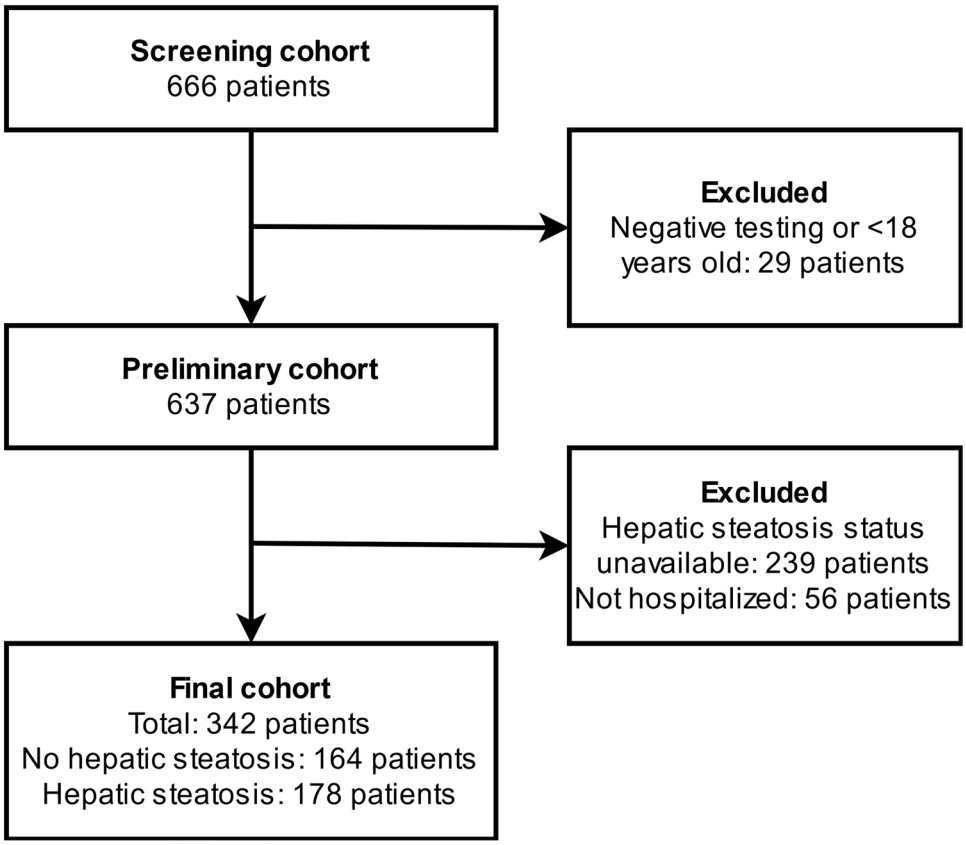


**Fig. 1** Study flowchart

only patients with HS and advanced fibrosis/cirrhosis who suffered poorer outcomes, not those with HS without fibrosis [16]. Notably, all these studies were in cohorts from China, with far lower rates of underlying obesity, diabetes, and other comorbidities than in our cohort. In addition to HS, chronic liver disease generally has also been associated with increased disease severity in COVID-19 [4, 19]. We were unable to evaluate the effect of non-HS chronic liver disease on disease severity as prevalence was low in this cohort.

Transaminitis with ALT > 2x ULN was common in our cohort, and higher in individuals with HS even accounting for baseline ALT. However, severe liver complications such as jaundice, ascites, and encephalopathy were uncommon and unaffected by the presence of HS. This finding is consistent with other literature on high frequency of transaminitis in COVID-19—which is also associated with poorer outcomes severity—but low rates of jaundice [17, 18]. International studies have found that among patients with underlying chronic liver disease with or without cirrhosis, acute liver injury on presentation was > 30% [4, 19]. As our population had a low prevalence of cirrhosis (2%), we lacked power to identify such a trend. However, the low rates of decompensation in a real-world cohort of hospitalized patients not otherwise enriched for liver disease, over half of whom required ICU admission, suggest that in COVID-19 liver disease likely reflects underlying sepsis and is not a primary driver of morbidity.

Limitations of this study include use of a surrogate measure of HS. We addressed this with a sensitivity analysis including only patients with prior imaging and found that HS prevalence based on imaging or HSI was not substantially higher than based on imaging alone. While prevalence of HS was higher than that of the general population in this cohort, this high prevalence likely reflects the metabolic comorbidities including diabetes and obesity among this study population. Strengths include that this is one of the first studies of its kind in the USA and we utilized robust classification through chart review.

In conclusion, the presence of HS is associated with more severe COVID-19 respiratory disease. Liver-related complications were low and had no association with HS.

**Table 1** Clinical characteristics based on hepatic steatosis status

| Characteristic | Overall ($N=342$) | No hepatic steatosis ($n=164$) | Hepatic steatosis ($n=178$) | $P$ value |
|---|---|---|---|---|
| Demographics | | | | |
| Age | 63.0 (52.0–73.0) | 66.5 (54.0–79.2) | 58.5 (49.0–67.0) | < 0.001 |
| % male | 53.5% | 57.3% | 50.0% | 0.19 |
| Race ($n=338$) | | | | < 0.001 |
| White | 44.7% | 54.9% | 35.1% | |
| Black | 44.4% | 35.4% | 52.9% | |
| Other | 10.9% | 9.8% | 12.1% | |
| Comorbidities | | | | |
| Body mass index ($n=337$) | 30.0 (25.9–36.0) | 26.6 (24.8–29.2) | 34.7 (30.3–40.7) | < 0.001 |
| Hypertension ($n=341$) | 69.2% | 67.7% | 70.6% | 0.56 |
| Dyslipidemia ($n=340$) | 47.0% | 47.6% | 46.6% | 0.91 |
| Diabetes | 43.3% | 37.8% | 48.3% | 0.06 |
| Baseline laboratory values | | | | |
| Creatinine (mg/dL) ($n=325$) | 1.0 (0.8–1.3) | 1.0 (0.8–1.5) | 1.0 (0.8–1.2) | 0.11 |
| ALT (U/L) ($n=326$) | 21.0 (15.0–30.0) | 19.0 (14.0–28.0) | 23.0 (16.5–33.0) | < 0.001 |
| Total bilirubin (mg/dL) ($n=322$) | 0.5 (0.4–0.7) | 0.5 (0.4–0.7) | 0.5 (0.4–0.7) | 0.80 |
| Hemoglobin A1c (%) ($n=242$) | 6.2 (5.7–7.3) | 6.0 (5.6–6.8) | 6.3 (5.8–7.6) | 0.01 |
| High-density lipoprotein (mg/dL) ($n=251$) | 46.0 (38.0–56.0) | 46.0 (37.0–56.0) | 45.0 (38.2–55.8) | 0.70 |
| Low-density lipoprotein (mg/dL) ($n=247$) | 91.0 (68.0–120.5) | 88.0 (64.0–114.0) | 92.5 (72.0–125.0) | 0.11 |
| Triglycerides (mg/dL) ($n=251$) | 124.0 (85.5–178.0) | 121.5 (86.2–172.2) | 125.0 (85.0–184.0) | 0.79 |
| Peak laboratory values | | | | |
| Creatinine (mg/dL) ($n=340$) | 1.3 (0.9–2.9) | 1.3 (0.9–2.7) | 1.2 (0.9–3.2) | 0.85 |
| Alanine aminotransferase (U/L) ($n=331$) | 50.0 (31.0–96.5) | 41.0 (26.2–75.0) | 59.0 (36.0–114.0) | < 0.001 |
| Total bilirubin (mg/dL) ($n=331$) | 0.7 (0.5–1.0) | 0.6 (0.4–1.0) | 0.8 (0.5–1.0) | 0.02 |
| Disease severity | | | | |
| Death | 18.7% | 22.6% | 15.2% | 0.01 |
| Intensive care unit | 54.1% | 51.2% | 56.7% | 0.33 |
| Intubation | 34.5% | 25.0% | 43.3% | < 0.001 |
| Dialysis | 12.0% | 8.0% | 15.7% | 0.03 |
| Vasopressors | 24.0% | 14.7% | 32.6% | < 0.001 |
| ALT > 2x ULN | 45.3% | 39.2% | 50.9% | 0.04 |
| ALT > 5x ULN | 13.6% | 8.2% | 18.5% | 0.007 |
| Bilirubin > 2 mg/dL | 8.8% | 8.9% | 8.7% | 1 |
| Bilirubin > 4 mg/dL | 2.1% | 3.2% | 1.2% | 0.27 |
| World Health Organization ordinal scale | 4.0 (4.0–7.0) | 4.0 (3.0–7.0) | 5.0 (4.0–7.0) | 0.34 |
| Treatment | | | | |
| Any treatment | 57.9% | 54.3% | 61.2% | 0.23 |
| Hydroxychloroquine | 34.8% | 32.9% | 36.6% | 0.49 |
| Remdesivir | 5.2% | 5.7% | 4.7% | 0.80 |
| Tocilizumab | 16.7% | 10.8% | 22.1% | 0.01 |
| Corticosteroids | 13.6% | 10.8% | 16.3% | 0.15 |
| Sarilumab (blinded trial) | 5.0% | 4.9% | 5.1% | 1.00 |
| Donor plasma | 0.6% | 0.6% | 0.6% | 1.00 |

*ALT* alanine aminotransferase, *ULN* upper limit of normal, defined as the greater of the patient's prior baseline (if known), 19 U/L for women, or 30 U/L for men

**Table 2** Predictors of disease severity and liver injury based on hepatic steatosis as defined by hepatic steatosis index and imaging

| | Univariable | | Multivariable[a] | |
|---|---|---|---|---|
| Logistic regressions | | | | |
| Outcome | Odds ratio | *P* value | Odds ratio | *P* value |
| Death | 0.61 (0.35, 1.06) | 0.08 | 0.94 (0.49, 1.78) | 0.84 |
| Intensive care unit admission | 1.25 (0.82, 1.91) | 0.31 | **1.60 (1.00, 2.57)** | **0.05** |
| Intubation | **2.29 (1.44, 3.63)** | **< 0.001** | **2.51 (1.52, 4.16)** | **< 0.001** |
| Dialysis | **2.15 (1.07, 4.32)** | **0.03** | 1.72 (0.81, 3.65) | 0.16 |
| Vasopressor use | **2.80 (1.64, 4.78)** | **< 0.001** | **1.22 (1.11, 1.34)** | **< 0.001** |
| ALT > 2x ULN | **1.60 (1.04, 2.48)** | **0.03** | 1.44 (0.90, 2.32) | 0.13 |
| ALT > 5x ULN | **2.53 (1.28, 5.02)** | **0.01** | **2.12 (1.03, 4.37)** | **0.04** |
| Bilirubin > 2 mg/dL | 0.98 (0.46, 2.09) | 0.95 | 0.86 (0.38, 1.95) | 0.72 |
| Bilirubin > 4 mg/dL | 0.36 (0.07, 1.87) | 0.22 | 0.39 (0.07, 2.30) | 0.30 |
| Linear regression | | | | |
| Outcome | Beta | *P* value | Beta | *P* value |
| WHO ordinal scale | 0.21 (−0.19, 0.61) | 0.30 | **0.45 (0.03, 0.86)** | **0.04** |

Bold values indicate statistically-significant association

*ALT* alanine aminotransferase, *ICU* intensive care unit, *ULN* upper limit of normal, defined as the greater of the patient's prior baseline (if known), 19 U/L for women, or 30 U/L for men, *WHO* World Health Organization

[a]Adjusted for age, sex, race (white, black, or other), recent healthcare exposure (hospitalization or residence at an extended care facility or skilled nursing facility < 90 days before COVID-19 diagnosis), presence of hypertension, and presence of dyslipidemia

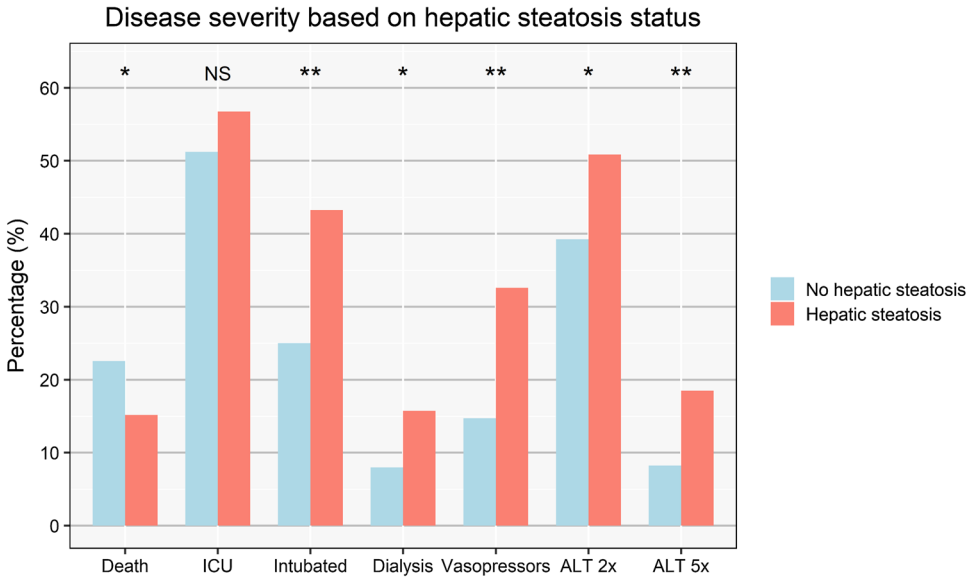


**Fig. 2** Frequency of coronavirus disease-2019 severity and liver injury based on hepatic steatosis status

**Table 3** Predictors of disease severity and liver injury based on hepatic steatosis as defined by imaging alone

| | Univariable | | Multivariable[a] | |
|---|---|---|---|---|
| Logistic regressions | | | | |
| Outcome | Odds ratio | *P* value | Odds ratio | *P* value |
| Death | 0.65 (0.29, 1.49) | 0.31 | 0.83 (0.31, 2.20) | 0.71 |
| Intensive care unit admission | 1.26 (0.64, 2.47) | 0.50 | 1.68 (0.76, 3.71) | 0.20 |
| Intubation | **2.53 (1.25, 5.12)** | **0.01** | **2.75 (1.21, 6.25)** | **0.02** |
| Dialysis | 1.54 (0.58, 4.11) | 0.38 | 1.89 (0.61, 5.86) | 0.27 |
| Vasopressor use | **2.83 (1.25, 6.40)** | **0.01** | **1.22 (1.04, 1.43)** | **0.02** |
| ALT > 2x ULN | **2.28 (1.14, 4.55)** | **0.02** | **3.36 (1.43, 7.87)** | **0.01** |
| ALT > 5x ULN | **7.11 (1.97, 25.71)** | **0.003** | **7.09 (1.73, 28.95)** | **0.01** |
| Bilirubin > 2 mg/dL | 1.79 (0.55, 5.77) | 0.33 | 2.40 (0.61, 9.49) | 0.21 |
| Bilirubin > 4 mg/dL | 0.52 (0.05, 5.90) | 0.60 | 3.63 (0.12, 109.38) | 0.46 |
| Linear regression | | | | |
| Outcome | Beta | *P* value | Beta | *P* value |
| WHO ordinal scale | 0.28 (−0.35, 0.91) | 0.38 | 0.49 (−0.23, 1.21) | 0.18 |

Bold values indicate statistically-significant association

*ALT* alanine aminotransferase, *ICU* intensive care unit, *ULN* upper limit of normal, defined as the greater of the patient's prior baseline (if known), 19 U/L for women, or 30 U/L for men, *WHO* World Health Organization

[a]Adjusted for age, sex, race (white, black, or other), recent healthcare exposure (hospitalization or residence at an extended care facility or skilled nursing facility < 90 days before COVID-19 diagnosis), presence of hypertension, and presence of dyslipidemia

**Author's contributions** Dr. PS and VC are the guarantors of the article and developed the concept, contributed to study design, data analysis, and interpretation, and drafted the manuscript. FH contributed to study design and data analysis and critically reviewed the manuscript. JB contributed to study design, collected the data, and critically reviewed the manuscript. CR, IK, KP, C-YH , CS, and JL collected the data and critically reviewed the manuscript. NG and PS developed the concept, contributed to study design, data analysis, and interpretation, and critically reviewed the manuscript. All authors identified above have critically reviewed the paper and approve the final version of this paper, including the authorship statement.

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## Compliance with Ethical Standards

**Conflict of interest** Vincent Chen, Fadi Hawa, Jeffrey Berinstein, Chanakyaram Reddy, Ihab Kassab, Kevin Platt, Chia-Yang Hsu, Jeremy Louissaint, Calen Steiner, and Pratima Sharma: no financial conflicts of interest to disclose. Naresh Gunaratnam: Co-founder and CMO, Lean Medical, LL. Speaker, Nestle Health Services.

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