

Radiographic Hepatic Steatosis Is Not Associated With Key Clinical Outcomes Among Patients Hospitalized With COVID-19

Hirsh D. Trivedi^{a, b, f, g}, Robert Wilechansky^{c, d, f}, Daniela Goyes^a, Joana Vieira Barbosa^{a, c}, Andrew Canakis^{c, d}, Michelle Lai^{a, b}, Michelle T. Long^{c, d, f}, Zachary Fricker^{a, b, f}

Abstract

Background: Metabolic syndrome increases adverse outcomes in coronavirus disease 2019 (COVID-19) infection. Hepatic steatosis may increase risk of COVID-19 severity. Current studies evaluating steatosis lack reliable definitions. We aimed to evaluate the association of radiographic hepatic steatosis and clinical outcomes of COVID-19 severity in a diverse cohort.

Methods: We retrospectively identified patients with COVID-19 infection admitted to two US academic hospitals. Outcomes were length of stay, intensive care unit use, mechanical ventilation, and in-hospital mortality. We used Mann-Whitney U-test for continuous measures and Chi-square or Fisher's exact test for categorical measures. Multivariable linear and logistic regression analyses were used to adjust for confounders.

Results: Of the 319 patients, 14% had hepatic steatosis. There were no differences in length of stay (6 (4 - 16) vs. 9 (4 - 18) days, $P = 0.6$), intensive care unit (24% vs. 32%, $P = 0.3$), mechanical ventilation (28% vs. 38%, $P = 0.32$), or in-hospital mortality (7% vs. 17%, $P = 0.12$). After adjustment, there was no difference in length of stay (β : -14.37, 95% confidence interval (CI): -30.5 - 1.77, $P = 0.08$), intensive care unit (odds ratio (OR): 0.31, 95% CI: 0.03 - 1.09, $P = 0.06$), mechanical ventilation (OR: 0.13, 95% CI: 0.02 - 1.09, $P = 0.06$), or in-hospital mortality (OR: 0.27, 95% CI: 0.06 - 1.16, $P = 0.08$) among patients with hepatic steatosis.

Conclusion: Radiographic hepatic steatosis was not associated with worse outcomes among patients hospitalized with COVID-19.

Keywords: Fatty liver; Coronavirus; Metabolic syndrome; Steatosis

Introduction

Among patients with the coronavirus disease 2019 (COVID-19), liver disease and metabolic syndrome, along with systemic inflammation, are associated with adverse outcomes [1-5]. Reports suggest 15-50% of patients have hepatic manifestations [6, 7]. Because of its association with metabolic disorders and systemic inflammation [8], hepatic steatosis, from non-alcoholic fatty liver disease (NAFLD), may increase risk of adverse outcomes.

Existing data linking NAFLD with COVID-19 severity are limited. An observational study demonstrates that age, body mass index (BMI), and NAFLD pose increased risk of COVID-19 progression defined by worsening respiratory function. NAFLD may also be associated with incidence of COVID-19, abnormal liver chemistries during infection, and prolonged viral shedding. Estimated hepatic fibrosis also increases risk of COVID-19 severity [9]. However, these reports are limited by small sample size and unique populations which lack generalizability. Additionally, definitions of NAFLD, e.g., hepatic steatosis index (HSI) [9, 10], often incorporate parameters associated with disease severity, such as BMI, which may hinder identification of the unique influence of hepatic steatosis. Studies evaluating NAFLD with COVID-19 severity are scarce.

We evaluated the association of hepatic steatosis and COVID-19 severity in a diverse cohort by identification of radiographic steatosis and key clinical outcomes.

Materials and Methods

We retrospectively identified patients with COVID-19 (by nasopharyngeal polymerase chain reaction) admitted to two United States (US) academic medical centers from March 1 to June 22, 2020 with abdominal imaging (computed tomogra-

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^aDivision of Gastroenterology, Hepatology, & Nutrition, Beth Israel Deaconess Medical Center, Boston, MA, USA

^bHarvard Medical School, Boston, MA, USA

^cEvans Department of Medicine, Section of Gastroenterology, Boston University School of Medicine, Boston, MA, USA

^dBoston University School of Medicine, Boston, MA, USA

^eDivision of Gastroenterology and Hepatology, Lausanne University Hospital and University of Lausanne, Switzerland

^fThese authors contributed equally to this article.

^gCorresponding Author: Hirsh D. Trivedi, Division of Gastroenterology, Hepatology, & Nutrition, Beth Israel Deaconess Medical Center, Boston, MA, USA. Email: htrived1@bidmc.harvard.edu

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phy (CT), magnetic resonance imaging (MRI), or ultrasound) within the last year. We recorded age, sex, race, BMI, history of diabetes or cardiovascular disease (CVD), i.e., hypertension or coronary artery disease, from the medical record; laboratory values at baseline (within 1 year of admission) and admission; and hepatic steatosis as reported by the interpreting radiologist. We chose to include patients with this definition of NAFLD because it is pragmatic, as few patients with NAFLD will have had a liver biopsy. Alcohol use history was not collected due to inability to capture data reliably in the record. Cirrhosis was defined by composite assessment of imaging, histology, and/or elastography. Non-NAFLD chronic liver disease (CLD) was defined by a diagnosis of chronic viral hepatitis, alcohol-related, autoimmune, cholestatic, or cryptogenic liver disease evaluated by problem lists. Outcomes of interest were length of stay (LOS), intensive care unit (ICU) use, mechanical ventilation, and in-hospital mortality. Sensitivity analyses were performed excluding those with CLD and cirrhosis, as well as accounting for imaging modality (CT, MRI or ultrasound). Expedited approval was obtained from the institutional review board (IRB) of each institution to conduct this study. This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Statistical comparisons were made using Mann-Whitney U-test for continuous measures and Chi-square and Fisher's exact test for categorical measures. Stepwise multivariable linear and logistic regression were used for each outcome to adjust for age, sex, race, BMI, diabetes, hemoglobin A1c (HbA1c), CVD, non-NAFLD CLD, cirrhosis, and baseline and admission labs. Statistical analysis was performed using Stata/IC 15.1.

Results

We identified 319 patients (50% women, median age 65 years) admitted with COVID-19 with liver imaging (Table 1). Fourteen percent had hepatic steatosis. In univariable analysis, there were no statistically significant differences among age, sex, race, BMI, or presence of diabetes or CVD, although there was a nearly statistically significant older age among patients without steatosis (66 vs. 58 years old, $P = 0.07$). Baseline alanine aminotransferase (ALT) (28 vs. 17 IU/L, $P = 0.002$) was greater among patients with hepatic steatosis. There was no difference in the prevalence of non-NAFLD CLD (5% vs. 11%, $P = 0.61$) or cirrhosis (12.8% vs. 15.6%, $P = 0.63$) in the two groups. No differences were identified in LOS (6 (4 - 16) vs. 9 (4 - 18) days, $P = 0.6$), use of ICU (24% vs. 32%, $P = 0.3$), use of mechanical ventilation (28% vs. 38%, $P = 0.32$), or in-hospital mortality (7% vs. 17%, $P = 0.12$). After stepwise multivariable adjustment (adjusted covariates shown in Table 2), there was no difference in LOS (β : -14.37, 95% confidence interval (CI): -30.5 - 1.77, $P = 0.08$), use of ICU (odds ratio (OR): 0.31, 95% CI: 0.03 - 3.29, $P = 0.33$), use of mechanical ventilation (OR: 0.13, 95% CI: 0.02 - 1.09, $P = 0.06$), or in-hospital mortality (OR: 0.27, 95% CI: 0.06 - 1.16, $P = 0.08$) among patients with hepatic steatosis compared to those with-

out. Sensitivity analyses after excluding CLD and cirrhosis, as well as accounting for imaging modality, showed similar direction of effect (Supplementary Materials 1 and 2, www.gastrores.org).

Discussion

Metabolic conditions, common among patients with hepatic steatosis, are associated with severity of COVID-19 infection, but it is unknown if there is independent association of hepatic steatosis itself with COVID-19 severity. Prior reports are limited by study of specific populations which may not be generalizable to diverse communities and definitions of NAFLD including potential co-linear conditions, e.g. obesity or diabetes [3, 9, 10], as well as markers of liver disease severity including parameters known to be associated with severity of COVID-19 [11]. A recent meta-analysis reports that NAFLD poses increased risk of COVID-19 severity, but the pooled studies use unreliable definitions [12]. Studies on the association of COVID-19 with reliable definitions of hepatic steatosis and NAFLD are simply lacking.

We identified a diverse cohort of patients and defined hepatic steatosis radiographically, i.e., independently of other conditions. Thus, we improved generalizability of our results and reduced confounding. We found that among hospitalized patients with COVID-19, radiographic hepatic steatosis was not independently associated with longer LOS, increased use of ICU care or mechanical ventilation, or in-hospital mortality. Stepwise multivariable regression yielded relevant covariates that varied slightly with outcome of interest, but essentially all characterized severity of metabolic disease, e.g., BMI, HbA1c, history of CVD, consistent with published experience with COVID-19 [13].

Our study adds more precision to the existing literature describing the relationship between COVID-19 and hepatic steatosis. Importantly, it highlights the need for adequate definitions of metabolic liver disease to draw reliable conclusions. In recent studies, definitions of NAFLD include scores with known independent predictors of COVID-19 disease, potentially overestimating the influence of NAFLD via confounding. For instance, a recent retrospective study from China noted an association of NAFLD with COVID-19 outcomes, but defines NAFLD using the HSI, which consists of BMI and is thus associated with severity of COVID-19 illness [9]. On the other hand, another study found hepatic steatosis, again defined by HSI, was not associated with COVID-19 outcomes [10] proving this definition unreliable. Similarly, another study concludes intermediate or high fibrosis-4 (FIB-4) index, a measure of liver fibrosis that includes age, which is associated with worse outcomes, but it is unclear whether these findings are attributable to liver fibrosis or greater age. Studies with an independent definition of NAFLD are overall lacking. Our data suggest the presence of radiographic hepatic steatosis is not associated with COVID-19-related outcomes.

While novel, use of radiographic steatosis as a measure does have limitations. There may be variability in imaging interpretation or sensitivity between different imaging modali-

Table 1. Baseline Characteristics

Covariate	Steatosis (n = 45)	No steatosis (n = 274)	P-value
Age (IQR)	58 (48 - 75)	66 (55 - 74)	0.07
Female (%)	19 (42.2)	141 (51.5)	0.25
Race (%)			0.14
White/Caucasian	12 (26.7)	97 (35.4)	
Black/African American	9 (20)	74 (27)	
Hispanic	17 (37.8)	59 (21.5)	
Other/not reported	7 (15.6)	44 (16.1)	
BMI (IQR)	31.2 (26 - 35)	28 (24 - 33.1)	0.12
Type 2 diabetes (%)	23 (51.1)	115 (42)	0.26
HbA1c (IQR)	7.1 (6.9 - 9.6)	7.5 (6.4 - 9)	0.69
CVD (%)	23 (51.1)	173 (63.1)	0.12
Non-NAFLD chronic liver disease (%)	5 (11)	31 (11.3)	0.61
Cirrhosis (%)	7 (15.6)	35 (12.8)	0.63
Baseline labs (IQR)			
AST (IU/L)	26 (21 - 41)	22 (17 - 36)	0.14
ALT (IU/L)	28 (17 - 45)	17 (12 - 28)	0.002*
Albumin (g/dL)	4 (3 - 4.4)	3.8 (3.4 - 4.2)	0.91
Total bilirubin (mg/dL)	0.4 (0.2 - 0.5)	0.3 (0.2 - 0.6)	0.86
INR	1.1 (1 - 1.2)	1.1 (1 - 1.3)	0.27
Creatinine (mg/dL)	0.8 (0.77 - 1.1)	1.1 (0.8 - 1.5)	0.003*
Admission labs (IQR)			
AST (IU/L)	51.5 (27.5 - 79.5)	37 (23 - 65)	0.07
ALT (IU/L)	37 (20 - 75.5)	22 (14 - 38)	< 0.001*
Albumin (g/dL)	3.8 (3.3 - 4.2)	3.5 (3 - 3.8)	0.001*
Total bilirubin (mg/dL)	0.4 (0.3 - 0.7)	0.4 (0.3 - 0.6)	0.46
INR	1.1 (1 - 1.3)	1.2 (1.1 - 1.4)	0.016*
Creatinine (mg/dL)	0.9 (0.7 - 1.2)	1.2 (0.9 - 2.1)	< 0.001*
CRP (mg/L)	77.5 (28.3 - 135.6)	81.8 (33.1 - 169)	0.62
Hospital LOS (IQR, days)	6.1 (4 - 16)	9 (4 - 18)	0.59
Need for ICU (%)	11 (24.4)	88 (32.1)	0.3
Days in ICU (IQR)	16 (8 - 22.5)	8 (3 - 23)	0.46
Intubation (%)	9 (20)	62 (22.6)	0.32
Mortality (%)	3 (6.7)	45 (16.4)	0.12

*P-values highlight statistically significant findings. IQR: interquartile range; BMI: body mass index; HbA1c: hemoglobin A1c; CVD: cardiovascular disease (hypertension or coronary artery disease); NAFLD: non-alcoholic fatty liver disease; AST: aspartate aminotransferase; ALT: alanine aminotransferase; INR: international normalized ratio; CRP: C-reactive protein; LOS: length of stay; ICU: intensive care unit.

ties. However, our sensitivity analysis adjusting for the type of imaging shows trend in the same direction as our initial multivariable model suggesting a lack of significant influence. Our cohort of patients only had 14% of patients with steatosis, which is lower than the prevalence of NAFLD in the general public. This may be a result of a previously described under-reporting of radiographic steatosis [14], and poses as a limitation. Despite these limitations, radiographic steatosis still remains a widely used measure of NAFLD and is less subject to

confounding than laboratory tests used elsewhere to evaluate association with COVID-19. Although more precise measures to detect the presence and degree of steatosis exist, the imaging modalities evaluated within this study reflect common diagnostic methods employed in clinical practice and improve generalizability of results.

Our study is limited by its retrospective nature, but the key metrics, i.e., steatosis and admission with COVID-19 are well-captured in the record. The presence of CLD and cir-

Table 2. Multivariable Analysis of Outcomes

Outcome	Beta-coefficient	Odds ratio	95% CI	P-value
LOS	-14.37 ^a		-30.5 - 1.77	0.08
ICU		0.31 ^b	0.03 - 3.29	0.33
Intubation		0.13 ^c	0.02 - 1.09	0.06
Mortality		0.27 ^d	0.06 - 1.16	0.08

^aModel adjusted for HbA1c, CVD, and admission ALT level. ^bModel adjusts for HbA1c, CVD, and admission INR and creatinine. ^cModel adjusts for BMI, diabetes, CVD, non-NAFLD chronic liver disease and admission ALT. ^dModel adjusts for diabetes, admission INR and creatinine. CI: confidence interval; LOS: length of stay; ICU: intensive care unit; BMI: body mass index; HbA1c: hemoglobin A1c; CVD: cardiovascular disease; ALT: alanine aminotransferase; INR: international normalized ratio; NAFLD: non-alcoholic fatty liver disease.

rhosis in the study population may have caused residual confounding, but sensitivity analysis after exclusion continued to show lack of significant difference. Our study has adequate power to detect moderate differences, but a very small difference cannot be excluded. The absence of consistent numerical associations with poor outcomes in those with hepatic steatosis suggests that limited power was not the reason for lack of an observed association. Additionally, the inability to definitively exclude excessive alcohol use limits distinction between etiologies of hepatic steatosis; however, it is unlikely that the presence of alcohol-related liver disease is protective, thus the lack of increased severity of COVID-19 in patients with steatosis is likely true of the subpopulation of true NAFLD patients, as well. Finally, treatment of COVID-19 may have varied across patients and institutions, especially in this early pandemic cohort; however, there has been relatively modest effect of most treatments, especially those used in the early period.

In conclusion, we found that radiographic hepatic steatosis was not independently associated with worse outcomes among patients hospitalized with COVID-19. Further study to clarify what degree of liver disease increases risk of COVID-19 severity it warranted.

Supplementary Material

Suppl 1. Sensitivity Analysis of Outcomes (CLD and Cirrhosis Excluded, N = 258).

Suppl 2. Sensitivity Analysis of Outcomes (Adjustment for Imaging Modality).

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None to declare.

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Conflict of Interest

None to declare.

Informed Consent

Informed consent from the patient was not required for conducting this study since it was a retrospective study that only required chart review.

Author Contributions

HDT, MTL and ZF helped with idea creation. HDT, RW, DG, JVB, and AC performed data acquisition. HDT performed statistical analysis and writing. ML, MTL, and ZF provided critical revision.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

Abbreviations

COVID-19: coronavirus disease 2019; NAFLD: non-alcoholic fatty liver disease; BMI: body mass index; HSI: hepatic steatosis index; US: United States; CT: computed tomography; MRI: magnetic resonance imaging; CVD: cardiovascular disease; CLD: chronic liver disease; LOS: length of stay; ICU: intensive care unit; IRB: institutional review board; HbA1c: hemoglobin A1c; ALT: alanine aminotransferase; β : beta-coefficient; CI: confidence interval; OR: odds ratio; FIB-4: fibrosis-4

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