


# Independent Predictors of Mortality Among Patients With NAFLD Hospitalized With COVID-19 Infection

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The impact of the coronavirus disease 2019 (COVID-19) pandemic among patients with chronic liver disease is unknown. Given the high prevalence of nonalcoholic fatty liver disease (NAFLD), we determined the predictors of mortality and hospital resource use among patients with NAFLD admitted with COVID-19 by using electronic medical records data for adult patients with COVID-19 hospitalized in a multihospital health system who were discharged between March and December 2020. NAFLD was diagnosed by imaging or liver biopsy without other liver diseases. Charlson's comorbidity index (CCI) and Elixhauser comorbidity index (ECI) scores were calculated. In the study sample, among the 4,835 patients hospitalized for COVID-19, 553 had NAFLD (age: 55 ± 16 years, 51% male, 17% White, 11% Black, 58% Hispanic, 8% Asian, 5% from congregated living, 58% obese, 15% morbid obesity [body mass index ≥ 40], 51% type 2 diabetes, 63% hypertension, mean [SD] baseline CCI of 3.9 [3.2], and baseline ECI of 13.4 [11.3]). On admission, patients with NAFLD had more respiratory symptoms, higher body temperature and heart rate, higher alanine aminotransferase and aspartate aminotransferase than non-NAFLD controls (n = 2,736; *P* < 0.05). Of the patients with NAFLD infected with COVID-19, 3.9% experienced acute liver injury. The NAFLD group had significantly longer length of stay, intensive care unit use, and mechanical ventilation, with a crude inpatient mortality rate of 11%. In multivariate analysis, independent predictors of inpatient mortality among patients with NAFLD infected with COVID-19 were older age, morbid obesity, ECI score ≥ 11, higher Fibrosis-4 Index (FIB-4) score, and oxygen saturation <90% (all *P* < 0.05), but not sex, race/ethnicity, or any individual comorbidity (all *P* > 0.05). *Conclusion:* Patients with NAFLD infected with COVID-19 tend to be sicker on admission and require more hospital resource use. Independent predictors of mortality included higher FIB-4 and multimorbidity scores, morbid obesity, older age, and hypoxemia on admission. (*Hepatology Communications* 2022;6:3062-3072).

**N**onalcoholic fatty liver disease (NAFLD) is a highly prevalent cause of chronic liver disease with the global rate of about 25%.<sup>(1)</sup> Closely associated with type 2 diabetes (T2DM) and visceral obesity, NAFLD is a complex liver disease that can be influenced by environmental factors, genetic make-up, the gut microbiota, and personal habits.<sup>(2-5)</sup> Despite the high global burden of NAFLD, awareness of

*Abbreviations:* ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CCI, Charlson's comorbidity index; COVID-19, coronavirus disease 2019; ECI, Elixhauser comorbidity index; EMR, electronic medical record; FIB-4, Fibrosis-4 Index; ICU, intensive care unit; NAFLD, nonalcoholic fatty liver disease; qSOFA, quick Sepsis Organ Failure Assessment; T2DM, type 2 diabetes.

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NAFLD among all stakeholders is quite low, which has led to potential underestimation of the impact of this liver disease.<sup>(6-8)</sup> Nevertheless, NAFLD is rapidly growing in the United States and has already become one of the top indications for liver transplantation and an important cause of liver mortality and liver cancer.<sup>(9-11)</sup> This tremendous burden of NAFLD is compounded by the lack of effective treatment.<sup>(12)</sup>

Since its first appearance in the United States in early 2020, we have learned that COVID-19 does not spare any organ system.<sup>(13-15)</sup> In fact, it has been reported that between 14% and 53% of patients with COVID-19 can develop some form of hepatic dysfunction, which may be associated with poor outcomes.<sup>(13)</sup> Given the very high prevalence of NAFLD in the general population, there is significant interest in assessing the potential implications of the pandemic on NAFLD, especially as several studies have suggested that presence of NAFLD can negatively affect outcomes of patients with COVID-19.<sup>(14,15)</sup> However, because the presence of comorbidities that are common in patients with NAFLD can also negatively affect their outcomes, it is important to control for these comorbidities to understand the effect of COVID-19 on those with NAFLD.<sup>(16)</sup>

The aim of this study was to determine the demographic profile, clinical outcomes, and predictors of inpatient mortality and hospital resource use among patients with NAFLD hospitalized with COVID-19 infection in 2020.

## Patients and Methods

This study used data from our health system's electronic medical records (EMRs) for patients admitted

with COVID-19 who were discharged from March 5 to December 31, 2020. For the purpose of this study, a data collection form with 323 parameters was designed to standardize the data collection. The form included sociodemographic data, medical history, as well as clinical, laboratory, and imaging data available at the time of admission. Given the limitations of the data extracted from EMRs, each case was also reviewed manually by trained research personnel to confirm accuracy and completeness of the data. Only adult patients with COVID-19 (18 years or older at the time of admission) were included in the data set.

In this study, NAFLD was defined as presence of hepatic fat by abdominal imaging, such as magnetic resonance imaging, computer tomography, or ultrasound, in the absence of other chronic liver diseases (e.g., viral hepatitis infection) and excessive alcohol use based on patients' medical history collected from both chart review and 10-year history of International Classification of Diseases codes. In addition, given the very high prevalence of NAFLD among patients with T2DM, only patients without radiologic evidence of fatty liver and without history of T2DM were chosen to be non-NAFLD controls. All patients without an established diagnosis of NAFLD, including those with T2DM, were tested as alternative controls in the sensitivity analysis. To limit bias, no additional exclusion criteria were applied.

Other definitions used in this study were as follows: Race/ethnicity was classified into non-Hispanic White (Whites), non-Hispanic Black (Blacks), Hispanic, Asian, and other/biracial. Obesity was defined as body mass index (BMI)  $\geq 30$ , and morbid obesity as BMI  $\geq 40$ . Living in congregated settings included skilled nursing facilities, residential and other long-term care facilities, or rehabilitation facilities.

### ARTICLE INFORMATION:

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Administrative data extracted from EMRs were used to calculate Charlson's comorbidity index (CCI)<sup>(17)</sup> and Elixhauser comorbidity index (ECI).<sup>(18)</sup> Admission vitals were used to calculate Quick Sequential Organ Failure Assessment (qSOFA) score, which is a semi-quantitative index commonly used for infectious disease states; it ranges from 0 to 3, and a score of 2 or 3 is considered high risk.<sup>(19)</sup> Acute liver injury during the inpatient stay was defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels > 600 U/L at any point.<sup>(20)</sup> Baseline Fibrosis-4 Index (FIB-4) scores were calculated using age, AST, ALT, and platelet count<sup>(21)</sup> collected at admission.

The study outcomes included inpatient mortality and resource use (length of hospital stay, intensive care unit [ICU] admission, and mechanical ventilation use).

## STATISTICAL ANALYSIS

Based on the number of admissions and changes in patient management across the system, the study period was split into three subperiods: March to May 2020, June to October 2020, and November to December 2020; patients were included in these groups based on their admission date. Patients with more than one admission were accounted with their earliest admission only. Comparison groups included NAFLD versus non-NAFLD, patients with NAFLD who died versus discharged alive, and patients with NAFLD admitted during the three periods of the study.

Patients' parameters were summarized as n (%) or mean (SD). Comparison of parameters between groups was done using chi-square or Kruskal-Wallis tests for categorical or continuous parameters, respectively. Logistic regression was used to identify independent association of clinical, demographic, and laboratory factors with inpatient mortality using bidirectional stepwise selection. Unadjusted *P* values were reported, and *P* values < 0.05 were considered statistically significant.

SAS 9.4 (SAS Institute, Cary, NC) was used for all analyses. The study was approved by the Inova Health System's institutional review board.

There was no unique coding used in this study's analysis; however, the coding used can be requested with the submission of a written request.

## Results

Between March 5 and December 31, 2020, there were 4,835 patients with COVID-19 discharged from Inova Health System hospitals. Of those, 553 had NAFLD and 2,736 were chosen to be non-NAFLD controls (Table 1). Similar comparisons to all patients without an established diagnosis of NAFLD regardless of the presence of T2DM (n = 4,279) are given in Supporting Table S1.

In this study, patients with COVID-19 with NAFLD were, on average, 55 ± 16 years of age, 51% male, 17% White, 11% Black, 58% Hispanic, 8% Asian, 5% from congregated living, 58% with obesity, and 15% with morbid obesity. Mean baseline (SD) CCI was 3.92 (3.23), baseline ECI was 13.4 (11.3), with 10% having CCI = 0 and 13% with ECI ≤ 0 (Table 1). In comparison to non-NAFLD controls, patients with COVID-19 with NAFLD were more commonly Hispanic, had higher BMI, higher comorbidity indices, and more cirrhosis, hypertension, and hyperlipidemia (all *P* < 0.05) (Table 1). At the same time, there was no mean age or sex difference (*P* > 0.05) (Table 1). On admission, patients with NAFLD had more respiratory symptoms, higher temperature and heart rate, and higher ALT and AST (*P* < 0.05) (Table 1). Similar observations were made when all patients without an established diagnosis of NAFLD (regardless of T2DM) were used as controls for patients with NAFLD (all *P* < 0.05) (Supporting Table S1). However, unlike controls without T2DM, those controls were now older than patients with NAFLD but still had less T2DM (36% in all patients without NAFLD vs. 51% in NAFLD) (all *P* < 0.05) (Supporting Table S1).

The distribution of patients with COVID-19 with NAFLD over the study periods was as follows: 37% were admitted in March to May 2020, 28% in June to October, and 35% in November to December (Table 2). Of the patients with NAFLD, 3.9% had acute liver injury recorded during their stay (vs. 1.6% in non-NAFLD controls; *P* = 0.0006). The mean length of inpatient stay was 9.6 days, which was longer than in the non-NAFLD controls (mean 7.3 days) (*P* < 0.0001) (Table 2). The use of ICU and mechanical ventilation was also higher in patients with NAFLD, while the proportion of patients switched to hospice care was lower (all *P* < 0.05) (Table 2). Readmission and inpatient mortality rates were not found to be

**TABLE 1. CLINICO-DEMOGRAPHIC CHARACTERISTICS OF PATIENTS WITH NAFLD AND NON-NAFLD CONTROLS WITH COVID-19**

	NAFLD	Non-NAFLD	P
n	553	2,736	
Age, years (mean ± SD)	54.7 ± 15.8	54.0 ± 20.7	0.10
Male	280 (50.6%)	1,340 (49.0%)	0.48
Non-Hispanic White or Caucasian	95 (17.3%)	671 (25.2%)	0.0001
Non-Hispanic Black or African-American	63 (11.5%)	333 (12.5%)	0.50
Hispanic	317 (58.3%)	1,323 (49.7%)	0.0003
Asian	44 (8.0%)	224 (8.4%)	0.76
Other race/ethnicity	32 (5.8%)	141 (5.3%)	0.61
Congregated living	26 (4.7%)	313 (11.4%)	<0.0001
BMI, kg/m <sup>2</sup>	32.6 ± 8.2	29.5 ± 6.8	<0.0001
Obesity (BMI ≥ 30)	305 (57.9%)	1,053 (40.8%)	<0.0001
Morbid obesity (BMI ≥ 40)	81 (15.4%)	176 (6.8%)	<0.0001
Prior medical history:			
CCI	3.92 ± 3.23	2.54 ± 3.08	<0.0001
ECl	13.4 ± 11.3	7.85 ± 10.68	<0.0001
Cirrhosis	23 (4.2%)	28 (1.0%)	<0.0001
T2DM	282 (51.0%)	0 (0.0%)	<0.0001
Hypertension	346 (62.6%)	1,138 (41.6%)	<0.0001
Dyslipidemia	325 (58.8%)	886 (32.4%)	<0.0001
COVID-19 symptoms on admission:			
Fever or chills	319 (58.1%)	1,283 (48.0%)	<0.0001
Cough	318 (57.9%)	1,273 (47.7%)	<0.0001
Shortness of breath	361 (65.8%)	1,519 (56.9%)	0.0001
Fatigue	144 (26.2%)	588 (22.0%)	0.0318
Headache	74 (13.5%)	240 (9.0%)	0.0012
Myalgia	101 (18.4%)	363 (13.6%)	0.0035
Sore throat	22 (4.0%)	64 (2.4%)	0.0330
Nasal congestion	13 (2.4%)	54 (2.0%)	0.60
Nausea, vomiting, or diarrhea	155 (28.2%)	534 (20.0%)	<0.0001
Loss of sense of smell/taste	23 (4.2%)	72 (2.7%)	0.06
Confusion or altered mental status	22 (4.0%)	203 (7.6%)	0.0026
Acute myocardial infarction	43 (7.8%)	142 (5.3%)	0.0210
Stroke/TIA/CVA	2 (0.4%)	28 (1.0%)	0.13
Rash, blue toes, skin findings	3 (0.5%)	5 (0.2%)	0.12
Other symptoms	107 (19.5%)	387 (14.5%)	0.0031
Vital signs at admission:			
Blood pressure diastolic, mmHg	73.0 ± 12.7	73.3 ± 12.6	0.72
Blood pressure systolic, mmHg	127.9 ± 21.7	126.6 ± 21.5	0.07
Temperature, °F	99.1 ± 1.5	98.9 ± 1.5	0.0007
Heart rate per minute	91.9 ± 19.1	88.8 ± 18.9	0.0006
Respiratory rate per minute	22.9 ± 7.4	22.2 ± 8.2	0.0018
Oxygen saturation, %	92.8 ± 7.2	93.6 ± 6.6	0.0015
Low oxygen saturation (≤90%)	128 (23.1%)	509 (18.9%)	0.0225
High risk (qSOFA ≥ 2)	34 (6.2%)	154 (5.8%)	0.70
Laboratory parameters on admission:			
ALT, U/L	60.5 ± 71.3	52.8 ± 73.1	<0.0001
AST, U/L	65.6 ± 87.3	58.0 ± 80.6	0.0018
Bicarbonate, mEq	22.5 ± 3.7	22.8 ± 3.6	0.12
Serum creatinine, mg/dL	1.24 ± 1.29	1.21 ± 1.53	0.19

TABLE 1. *Continued*

	NAFLD	Non-NAFLD	P
C-reactive protein, mg/L	10.8 ± 8.8	11.5 ± 8.7	0.07
D-dimer, mg/L	1.63 ± 2.76	1.99 ± 3.24	0.0011
Ferritin, ng/mL	1,040.7 ± 1,537.2	1,188.0 ± 1,694.2	0.15
Hemoglobin, g/dL	13.3 ± 2.1	13.2 ± 2.3	0.0234
Absolute lymphocyte count	1.33 ± 1.52	2.83 ± 53.05	0.20
Platelet, 10 <sup>9</sup> /L	224.5 ± 90.8	232.8 ± 92.8	0.0371
Total bilirubin, mg/dL	0.663 ± 0.482	0.728 ± 1.161	0.38
White blood count, 10 <sup>9</sup> /L	7.80 ± 4.32	8.85 ± 6.49	<0.0001
FIB-4 score	2.79 ± 5.24	2.67 ± 6.03	0.60

Abbreviations: CVA, cerebrovascular accident; TIA, transient ischemic attack.

TABLE 2. OUTCOMES OF PATIENTS WITH NAFLD INFECTED WITH COVID-19 VERSUS NON-NAFLD CONTROLS

	NAFLD	Non-NAFLD	P
n	553	4,279	
Admission period 1 (March-May 2020)	205 (37.1%)	1,159 (42.4%)	0.0213
Admission period 2 (June-October 2020)	152 (27.5%)	868 (31.7%)	0.0494
Admission period 3 (November-December 2020)	196 (35.4%)	709 (25.9%)	<0.0001
Study outcomes:			
Acute liver injury	21 (3.9%)	38 (1.6%)	0.0006
Length of stay, days	9.60 ± 11.42	7.27 ± 7.55	<0.0001
Admitted to ICU	196 (35.4%)	726 (26.5%)	<0.0001
Received mechanical ventilation	76 (13.7%)	221 (8.1%)	<0.0001
Inpatient hospice care at any point	12 (2.2%)	107 (3.9%)	0.0456
Readmission	25 (4.5%)	95 (3.5%)	0.23
Discharged to:			
Short-term care facility	5 (0.9%)	13 (0.5%)	0.21
Long-term care facility	26 (4.7%)	200 (7.3%)	0.0270
Home	458 (82.8%)	2225 (81.3%)	0.41
Hospice care	4 (0.7%)	59 (2.2%)	0.0249
Died	60 (10.8%)	239 (8.7%)	0.11

significantly different between patients with or without NAFLD (all  $P > 0.05$ ) (Table 2). However, in comparison to all patients without NAFLD diagnosis (including those with T2DM), the difference in resource use became less pronounced (length of stay = 9.6 days in NAFLD vs. 8.7 days without NAFLD [ $P = 0.03$ ]; the differences in ICU and mechanical ventilation use were no longer significant [ $P > 0.05$ ]) (Supporting Table S1). Despite this, the rate of acute liver injury was still higher in diagnosed NAFLD (3.9% vs. 2.4%;  $P = 0.046$ ), whereas readmission and inpatient mortality rates remained similar between NAFLD and non-NAFLD regardless of the choice of controls (Supporting Table S1).

The crude inpatient mortality rate for patients with NAFLD infected with COVID-19 was 10.8%. In comparison to patients with NAFLD who were discharged alive, patients with NAFLD who died were, on average, 15 years older, more commonly White and less Hispanic, with 20% deaths observed in patients coming from congregated living setting (all  $P < 0.05$ ) (Table 3). In addition, patients with NAFLD who died had higher comorbidity scores and more severe respiratory distress on admission, as manifested by higher respiratory rate, lower oxygen saturation, and significantly higher proportion of high-risk patients based on qSOFA score (all  $P < 0.05$ ) (Table 3). From laboratory findings, patients who died had higher baseline

TABLE 3. COMPARISON OF COVID-19 PATIENTS WITH NAFLD WHO DIED AND DISCHARGED ALIVE

	Died	Discharged alive	P	All
n	60	493		553
Period of admission (the year of 2020)				
March-May	28 (46.7%)	177 (35.9%)	0.10	205 (37.1%)
June-October	12 (20.0%)	140 (28.4%)	0.17	152 (27.5%)
November-December	20 (33.3%)	176 (35.7%)	0.72	196 (35.4%)
Age, years	68.0 ± 14.7	53.1 ± 15.2	<0.0001	54.7 ± 15.8
Male	39 (65.0%)	241 (48.9%)	0.0184	280 (50.6%)
Non-Hispanic White or Caucasian	18 (30.0%)	77 (15.7%)	0.0059	95 (17.3%)
Non-Hispanic Black or African-American	8 (13.3%)	55 (11.2%)	0.63	63 (11.5%)
Hispanic	24 (41.4%)	293 (60.3%)	0.0058	317 (58.3%)
Asian	8 (13.3%)	36 (7.4%)	0.11	44 (8.0%)
Other race/ethnicity	2 (3.3%)	30 (6.1%)	0.38	32 (5.8%)
Congregated living	12 (20.0%)	14 (2.8%)	<0.0001	26 (4.7%)
<b>Baseline medical history</b>				
BMI, kg/m <sup>2</sup>	31.5 ± 8.9	32.7 ± 8.1	0.12	32.6 ± 8.2
CCI	6.30 ± 3.38	3.63 ± 3.09	<0.0001	3.92 ± 3.23
CCI = 0	0 (0.0%)	55 (11.2%)	0.0064	55 (9.9%)
CCI = 1	4 (6.7%)	76 (15.4%)	0.07	80 (14.5%)
CCI = 2	0 (0.0%)	89 (18.1%)	0.0003	89 (16.1%)
CCI = 3 or 4	18 (30.0%)	127 (25.8%)	0.48	145 (26.2%)
CCI = 5-8	23 (38.3%)	103 (20.9%)	0.0024	126 (22.8%)
CCI ≥ 9	15 (25.0%)	43 (8.7%)	0.0001	58 (10.5%)
ECI	21.9 ± 9.8	12.3 ± 11.0	<0.0001	13.4 ± 11.3
ECI ≤ 0	0 (0.0%)	71 (14.4%)	0.0016	71 (12.8%)
1 ≤ ECI ≤ 5	0 (0.0%)	86 (17.4%)	0.0004	86 (15.6%)
6 ≤ ECI ≤ 10	6 (10.0%)	80 (16.2%)	0.21	86 (15.6%)
11 ≤ ECI ≤ 17	18 (30.0%)	124 (25.2%)	0.42	142 (25.7%)
18 ≤ ECI ≤ 27	18 (30.0%)	90 (18.3%)	0.0303	108 (19.5%)
ECI ≥ 28	18 (30.0%)	42 (8.5%)	<0.0001	60 (10.8%)
<b>Admission parameters</b>				
Blood pressure diastolic, mmHg	68.9 ± 13.8	73.5 ± 12.5	0.0206	73.0 ± 12.7
Blood pressure systolic, mmHg	126.7 ± 25.8	128.1 ± 21.2	0.84	127.9 ± 21.7
Temperature, °F	99.4 ± 1.8	99.1 ± 1.4	0.0164	99.1 ± 1.5
Heart rate per minute	93.1 ± 25.0	91.7 ± 18.3	0.66	91.9 ± 19.1
Respiratory rate per minute	26.9 ± 8.5	22.4 ± 7.1	<0.0001	22.9 ± 7.4
Oxygen saturation, %	87.9 ± 11.8	93.4 ± 6.2	0.0001	92.8 ± 7.2
Low oxygen saturation (≤90%)	28 (46.7%)	100 (20.3%)	<0.0001	128 (23.1%)
High risk (qSOFA ≥ 2)	10 (16.7%)	24 (4.9%)	0.0004	34 (6.2%)
ALT, U/L	63.1 ± 103.7	60.1 ± 66.4	0.41	60.5 ± 71.3
AST, U/L	100.5 ± 186.6	61.3 ± 64.2	0.0147	65.6 ± 87.3
Bicarbonate, mEq	21.3 ± 5.3	22.6 ± 3.5	0.0199	22.5 ± 3.7
Serum creatinine, mg/dL	1.97 ± 2.11	1.15 ± 1.13	<0.0001	1.24 ± 1.29
C-reactive protein, mg/L	13.1 ± 12.3	10.6 ± 8.2	0.27	10.8 ± 8.8
D-dimer, mg/L	3.04 ± 4.39	1.46 ± 2.45	<0.0001	1.63 ± 2.76
Ferritin, ng/mL	1,212.6 ± 1,116.1	1,020.1 ± 1,580.1	0.0446	1,040.7 ± 1,537.2
Hemoglobin, g/dL	12.9 ± 2.4	13.3 ± 2.0	0.39	13.3 ± 2.1
Absolute lymphocyte count	0.920 ± 0.820	1.39 ± 1.59	<0.0001	1.33 ± 1.52
Platelets, 10 <sup>9</sup> /L	191.2 ± 81.1	228.5 ± 91.2	0.0051	224.5 ± 90.8
Total bilirubin, mg/dL	0.703 ± 0.465	0.658 ± 0.484	0.33	0.663 ± 0.482
White blood count, 10 <sup>9</sup> /L	8.03 ± 6.20	7.77 ± 4.04	0.73	7.80 ± 4.32

TABLE 3. Continued

	Died	Discharged alive	P	All
FIB-4 score	6.59 ± 13.91	2.33 ± 2.33	<0.0001	2.79 ± 5.24
<b>Resource use and disposition</b>				
Acute liver injury	15 (25.4%)	6 (1.2%)	<0.0001	21 (3.9%)
Length of stay, days	17.8 ± 17.5	8.60 ± 10.02	<0.0001	9.60 ± 11.42
Admitted to ICU	50 (83.3%)	146 (29.6%)	<0.0001	196 (35.4%)
Received mechanical ventilation	41 (68.3%)	35 (7.1%)	<0.0001	76 (13.7%)
Discharged to:				
Short-term care facility	0 (0.0%)	5 (1.0%)	0.43	5 (0.9%)
Long-term care facility	0 (0.0%)	26 (5.3%)	0.07	26 (4.7%)
Home	0 (0.0%)	458 (92.9%)	<0.0001	458 (82.8%)
Hospice care	0 (0.0%)	4 (0.8%)	0.48	4 (0.7%)
Died	60 (100.0%)	0 (0.0%)	<0.0001	60 (10.8%)

TABLE 4. INDEPENDENT PREDICTORS OF MORTALITY IN PATIENTS WITH NAFLD INFECTED WITH COVID-19 ACROSS THE ENTIRE STUDY PERIOD ( $P < 0.05$  ONLY)

Predictor	Odds Ratio (95% CI)	P
Age, per 5 years	1.24 (1.09-1.4)	0.0008
Morbid obesity	2.95 (1.16-7.5)	0.0230
11 ≤ ECI ≤ 17 (ref: ECI ≤ 10)	6.35 (2.12-18.98)	0.0009
18 ≤ ECI ≤ 27 (ref: ECI ≤ 10)	5.45 (1.81-16.46)	0.0026
ECI ≥ 28 (ref: ECI ≤ 10)	14.73 (4.66-46.56)	<0.0001
Oxygen saturation ≤ 90%	4.09 (2.07-8.08)	<0.0001
FIB-4 score, per 1 point	1.14 (1.05-1.24)	0.0014

AST, serum creatinine, D-dimer and ferritin, and lower lymphocyte and platelet count; as a result, those patients also had significantly higher FIB-4 scores (all  $P < 0.05$ ) (Table 3). Furthermore, of those who died with NAFLD and COVID-19, 25% had acute liver injury, 83% were admitted to ICU, and 68% received mechanical ventilation (Table 3). Of the patients with NAFLD who were discharged alive, 93% were discharged home (including home healthcare) and 5% to long-term care (Table 3).

Over time, there were some changes in baseline demographic and clinical presentation of patients with NAFLD infected with COVID-19 (Supporting Table S2). In particular, during the most recent period of November to December, patients became older and more commonly White and less Hispanic ( $P < 0.05$ ). At the same time, there were no changes in their comorbidity burden over time ( $P > 0.05$ ). Despite this, there was a substantial decrease in the mean length of inpatient stay, ICU use, and especially the use of

mechanical ventilation, which decreased from 20% in March to May to 12% in June to October to 9% in November to December ( $P = 0.0032$ ). The decrease in mortality was not statistically significant ( $P = 0.21$ ) (Supporting Table S2).

In multiple regression analysis, independent predictors of inpatient mortality in patients with NAFLD infected with COVID-19 included older age, morbid obesity, ECI score ≥ 11, oxygen saturation <90%, and higher FIB-4 score (all  $P < 0.05$ ) (Table 4). At the same time, there was no association of inpatient mortality with the period of admission, sex, race/ethnicity, or any individual comorbidities including T2DM, hypertension or hyperlipidemia (all  $P > 0.05$ ), although the association with diabetes was borderline significant ( $P < 0.10$ ).

Because baseline FIB-4 was found to be highly predictive of mortality even after adjustment for age, we additionally studied patients with COVID-19 with NAFLD based on their FIB-4 score. Furthermore, because FIB-4 has not been validated in the setting of acute COVID-19 infection, we also sought to assess its performance in our data set using available clinical data. As a result, we found that patients with an established diagnosis of cirrhosis had a mean baseline FIB-4 score of 7.4 (SD 5.4) versus 2.6 (SD 5.9) in the rest of the sample including controls ( $P < 0.0001$ ). Because the latter is indeed higher than values typically seen in stable low-risk patients,<sup>(21)</sup> the standard cutoffs for FIB-4 used in clinical practice to rule in and rule out advanced fibrosis could not be applied. Therefore, we used quartiles of the score distribution among patients with NAFLD included in this study to compare patients with low (lowest quartile), moderate

(two mid quartiles), and high (top quartile) FIB-4 scores. As a result, out of all patients with NAFLD, the lowest quartile included patients with FIB-4 < 1.16 and the highest with FIB-4 > 2.91 (Table 5). Patients with higher FIB-4 scores were older, more commonly White and from congregated living setting, had lower BMI but higher comorbidity indices, and lower oxygen saturation on admission ( $P < 0.05$ ) (Table 5). These patients also more commonly experienced acute liver injury during their treatment, and consistent with the findings of our multivariate analysis, these patients also had a substantially higher mortality rate: 28% in patients with the highest FIB-4 scores versus 6% in patients with moderate score versus 3% in patients with low scores ( $P < 0.0001$ ) (Table 5).

## Discussion

As our understanding of COVID-19 expands, it is important to also appreciate its impact among those with chronic diseases. In this study, we assessed the effects of COVID-19 infection among patients with NAFLD by determining the profile and outcomes of patients with NAFLD who were admitted with COVID-19. As such, we found that approximately 11% of patients admitted between March and December 2020 had NAFLD. Similar to previous reports,<sup>(22,23)</sup> patients with COVID-19 with NAFLD tended to be Hispanic, obese, with a substantial comorbidity burden as noted by their high CCI and ECI scores. In comparison to subjects without NAFLD infected with COVID-19, patients with NAFLD infected with COVID-19 were more likely to present with fever or chills, cough, shortness of breath, fatigue, headache, myalgia, nausea, vomiting or diarrhea, and with acute myocardial infarction. They also tended to have higher liver enzymes but lower D-dimer, platelet, and white blood cell count on admission.

The overall mortality of hospitalized patients with COVID-19 with or without NAFLD was not significantly different at the rate of approximately 10%. Although NAFLD was more commonly found in Hispanic patients, the crude mortality rate was higher among those who were White/Caucasian. More importantly, patients with NAFLD who died were older and had significantly higher multimorbidity burden as measured by their CCI and ECI scores. On admission, we found that a few baseline clinical parameters

could predict mortality in patients with COVID-19 with NAFLD; most of them are consistent with prior reports.<sup>(24-27)</sup> In addition, we found that having a higher FIB-4 score on admission was significantly associated with an increased risk of inpatient mortality from COVID-19 even after adjustment for age; this suggests that patients with COVID-19 with more advanced fibrosis could be at a substantially higher risk of adverse outcomes. Additionally, our data show that patients with NAFLD who died were in significant respiratory distress on admission, as noted by an average respiratory rate of 27 and a mean oxygen saturation of 87.9%. Finally, patients with NAFLD who died of COVID-19 had higher qSOFA scores, significantly elevated AST, creatinine, D-dimer and ferritin levels, while their lymphocyte count and platelet count were significantly lower when compared with those who were discharged alive. Notably, the serum creatinine levels could be indicative of renal failure, and 25% of those who died also had acute liver injury as defined by the significant elevation of aminotransferases.

Patients with NAFLD incurred higher hospital use, as noted by their length of stay, which was, on average, 2 days longer than for non-NAFLD controls, a higher rate of admission to the ICU, and a higher rate of mechanical ventilation with a lower rate of inpatient hospice care. This is in line with a recent study in which patients with chronic liver disease also had a higher resource use.<sup>(28)</sup> The trends, however, became less pronounced or disappeared when patients with NAFLD were compared with all patients without an established diagnosis of NAFLD (i.e., including those with T2DM). One plausible explanation is that patients with T2DM are at an increased risk of adverse outcomes, regardless of the presence of NAFLD. However, given the rates of other components of metabolic syndrome (e.g., hypertension, hyperlipidemia) in patients with NAFLD (63% and 59%, respectively) in comparison to the two groups of controls (42% and 32%, respectively, in controls without T2DM; 56% and 47%, respectively, in all patients without diagnosed NAFLD), we believe that it is likely that many patients with T2DM did have undiagnosed NAFLD. The latter could also be indirectly supported by the observation that of all included patients with T2DM, only 16% had an established diagnosis of NAFLD, which is substantially lower than current estimates of at least 50%.<sup>(29)</sup> In addition to these general trends in resource use and outcomes, patients with NAFLD



TABLE 5. COMPARISON OF PATIENTS WITH NAFLD INFECTED WITH COVID-19 BASED ON FIB-4 SCORE

	FIB-4 < 1.16 (Lowest Quartile)	1.16 < FIB-4 < 2.91	FIB-4 > 2.91 (Top Quartile)	P
n	132	266	132	
Period of admission (year 2020)				
March-May	57 (43.2%)	90 (33.8%)	49 (37.1%)	0.19
June-October	36 (27.3%)	73 (27.4%)	40 (30.3%)	0.81
November-December	39 (29.5%)	103 (38.7%)	43 (32.6%)	0.16
Age, years	42.9 ± 13.7	56.1 ± 13.0	64.9 ± 13.9	<0.0001
Male	57 (43.2%)	141 (53.0%)	77 (58.3%)	0.0420
Non-Hispanic White or Caucasian	14 (10.7%)	45 (17.0%)	33 (25.2%)	0.0081
Non-Hispanic Black or African-American	12 (9.2%)	28 (10.6%)	20 (15.3%)	0.25
Hispanic	91 (68.9%)	157 (60.4%)	55 (42.6%)	0.0001
Asian	5 (3.8%)	23 (8.7%)	14 (10.7%)	0.10
Other race/ethnicity	10 (7.6%)	12 (4.5%)	9 (6.9%)	0.41
Congregated living	5 (3.8%)	5 (1.9%)	14 (10.6%)	0.0004
<b>Baseline medical history</b>				
BMI, kg/m <sup>2</sup>	35.1 ± 9.9	32.4 ± 7.8	30.7 ± 6.9	0.0011
CCI	2.57 ± 2.64	3.76 ± 2.96	5.55 ± 3.22	<0.0001
CCI = 0	27 (20.5%)	18 (6.8%)	2 (1.5%)	<0.0001
CCI = 1	36 (27.3%)	37 (13.9%)	4 (3.0%)	<0.0001
CCI = 2	18 (13.6%)	53 (19.9%)	17 (12.9%)	0.12
CCI = 3 or 4	29 (22.0%)	81 (30.5%)	32 (24.2%)	0.15
CCI = 5-8	17 (12.9%)	55 (20.7%)	51 (38.6%)	<0.0001
CCI ≥ 9	5 (3.8%)	22 (8.3%)	26 (19.7%)	<0.0001
ECI	8.88 ± 9.76	13.0 ± 10.4	18.7 ± 11.7	<0.0001
ECI ≤ 0	33 (25.0%)	29 (10.9%)	3 (2.3%)	<0.0001
1 ≤ ECI ≤ 5	24 (18.2%)	47 (17.7%)	11 (8.3%)	0.0323
6 ≤ ECI ≤ 10	20 (15.2%)	43 (16.2%)	22 (16.7%)	0.94
11 ≤ ECI ≤ 17	31 (23.5%)	70 (26.3%)	37 (28.0%)	0.69
18 ≤ ECI ≤ 27	20 (15.2%)	51 (19.2%)	34 (25.8%)	0.09
ECI ≥ 28	4 (3.0%)	26 (9.8%)	25 (18.9%)	0.0001
<b>Admission parameters</b>				
Blood pressure diastolic, mmHg	73.3 ± 11.5	74.1 ± 13.2	70.6 ± 13.0	0.05
Blood pressure systolic, mmHg	126.6 ± 18.8	129.7 ± 22.9	126.5 ± 22.8	0.34
Temperature, °F	98.9 ± 1.4	99.1 ± 1.5	99.2 ± 1.6	0.13
Heart rate per minute	96.6 ± 20.5	91.7 ± 17.6	88.2 ± 20.0	0.0020
Respiratory rate per minute	21.9 ± 5.5	22.7 ± 6.8	24.6 ± 9.7	0.0492
Oxygen saturation, %	94.3 ± 5.6	92.7 ± 6.9	91.1 ± 8.9	0.0006
Low oxygen saturation (≤90%)	20 (15.2%)	62 (23.3%)	43 (32.6%)	0.0038
High risk (qSOFA ≥ 2)	5 (3.8%)	13 (4.9%)	14 (10.8%)	0.0317
ALT, U/L	49.4 ± 39.2	59.8 ± 66.0	72.9 ± 99.5	0.11
AST, U/L	37.6 ± 23.0	57.3 ± 47.7	111.1 ± 150.8	<0.0001
Bicarbonate, mEq	22.4 ± 3.9	22.8 ± 3.7	21.9 ± 3.8	0.0097
Serum creatinine, mg/dL	1.10 ± 1.27	1.20 ± 1.24	1.48 ± 1.44	<0.0001
C-reactive protein, mg/L	10.9 ± 8.6	11.0 ± 8.9	10.3 ± 8.6	0.75
D-dimer, mg/L	1.37 ± 2.20	1.37 ± 2.21	2.45 ± 3.98	<0.0001
Ferritin, ng/mL	648.3 ± 804.6	1,042.8 ± 1,504.8	1,422.6 ± 2,007.2	<0.0001
Hemoglobin, g/dL	13.2 ± 2.0	13.5 ± 1.9	12.9 ± 2.3	0.0056
Absolute lymphocyte count	1.51 ± 0.83	1.45 ± 2.06	0.947 ± 0.680	<0.0001
Platelets, 10 <sup>9</sup> /L	299.6 ± 92.4	222.7 ± 63.1	146.9 ± 56.5	<0.0001
Total bilirubin, mg/dL	0.572 ± 0.483	0.624 ± 0.353	0.832 ± 0.644	<0.0001
White blood count, 10 <sup>9</sup> /L	9.49 ± 4.79	7.68 ± 3.44	6.54 ± 5.14	<0.0001

TABLE 5. Continued

	FIB-4 < 1.16 (Lowest Quartile)	1.16 < FIB-4 < 2.91	FIB-4 > 2.91 (Top Quartile)	P
FIB-4 score	0.794 ± 0.240	1.87 ± 0.49	6.64 ± 9.47	<0.0001
<b>Resource use and disposition</b>				
Acute liver injury	1 (0.8%)	8 (3.0%)	12 (9.1%)	0.0013
Length of stay, days	6.62 ± 6.50	10.3 ± 13.4	12.1 ± 10.9	<0.0001
Admitted to ICU	35 (26.5%)	92 (34.6%)	67 (50.8%)	0.0001
Received mechanical ventilation	6 (4.5%)	34 (12.8%)	35 (26.5%)	<0.0001
Discharged to:				
Short-term care facility	0 (0.0%)	3 (1.1%)	1 (0.8%)	0.47
Long-term care facility	3 (2.3%)	16 (6.0%)	7 (5.3%)	0.26
Home	125 (94.7%)	228 (85.7%)	85 (64.4%)	<0.0001
Hospice care	0 (0.0%)	2 (0.8%)	2 (1.5%)	0.36
Died	4 (3.0%)	17 (6.4%)	37 (28.0%)	<0.0001

who died had significantly increased resource use, such as a twice longer hospital stay with more than 80% being admitted to the ICU and 68% receiving mechanical ventilation.

Our results suggest that the percent of patients with an underlying chronic liver disease is higher than has been recently reported in other studies but is in line with a recent study conducted in the United States.<sup>(15,16,30)</sup> This is most likely due to the low awareness of NAFLD among both practitioners and the lay public, suggesting a high rate of undiagnosed NAFLD.<sup>(31)</sup> In this context, it is important to highlight independent predictors of mortality among patients with NAFLD infected with COVID-19. Contrary to some previously published data, once controlled for multimorbidity scores (ECI or CCI), NAFLD itself as a diagnosis was not found to be independently associated with a higher risk of mortality in patients hospitalized with COVID-19. In addition, no single comorbidity other than morbid obesity, including components of metabolic syndrome (e.g., T2DM, hypertension, hyperlipidemia), was found to be associated with mortality in patients with NAFLD after adjustment for age. Rather, older age and having high multimorbidity scores were found to be independently associated with inpatient mortality along with severe respiratory illness, as documented by low oxygen saturation on admission. For this reason, we suggest that patients who present with NAFLD and morbid obesity and/or high comorbidity scores are at a significant risk of inpatient mortality and must be managed accordingly.

Limitations of the study include its relatively limited sample size and lack of post-discharge data, so no conclusions about COVID-associated morbidity or

post-discharge mortality could be made. In addition, significant underdiagnosis of NAFLD in the general population limited our options to choose proper non-NAFLD controls. Another limitation is the lack of phenotyping and histology data to diagnose patients with advanced NAFLD or nonalcoholic steatohepatitis. It is also important to note that a noninvasive FIB-4 score, which we intended to use to identify patients with more advanced fibrosis, has not been validated in the setting of acute infection, which is known to affect its components (e.g., liver enzymes, platelet count) regardless of the presence of liver disease. On the other hand, significantly higher FIB-4 scores were seen in patients with an established diagnosis of cirrhosis, suggesting that the noninvasive test score could still be correlated with severity of hepatic fibrosis. However, the absolute FIB-4 values could be skewed upward among inpatients with COVID-19; therefore, previously published cutoffs for ruling in and ruling out advanced fibrosis could not be applied. Further studies with histologic staging of fibrosis are needed to reliably confirm the association of baseline liver disease severity with outcomes of COVID-19. Other limitations of data used in this study include lack of serologic tests to exclude alternative forms of liver disease and limited knowledge of alcohol use.

In summary, our study showed that approximately 10% of patients admitted with COVID-19 had an established diagnosis of NAFLD. Although mortality was not affected by NAFLD, resource use was higher among patients with NAFLD infected with COVID-19. Our multivariate model suggested some important predictors of mortality among patients with NAFLD. These included elevated FIB-4 scores as

well as factors associated with more comorbidities and severity of illness on admission. These data can add to the growing body of knowledge about COVID-19 and chronic liver disease.

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## Supporting Information

Additional Supporting Information may be found at [onlinelibrary.wiley.com/doi/10.1002/hep4.1802/supinfo](https://onlinelibrary.wiley.com/doi/10.1002/hep4.1802/supinfo).