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Original article

Metabolic surgery may protect against admission for COVID-19 in persons with nonalcoholic fatty liver disease

Christopher J. Tignanelli, M.D.[a,*], Carolyn T. Bramante, M.D., M.P.H.[b], Nirjhar Dutta, D.O., M.S.[b], Leonardo Tamariz, M.D.[c], Michael G. Usher, M.D., Ph.D.[b], Sayeed Ikramuddin, M.D.[a]

[a]*Department of Surgery, University of Minnesota, Division of Surgical Oncology, Minneapolis, Minnesota*
[b]*Department of Medicine, University of Minnesota, Division of General Internal Medicine, Minneapolis, Minnesota*
[c]*Division of Cardiology, University of Miami, and Miami VA Healthcare Administration, Miami, Florida*

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Abstract

Background: SARS-CoV-2 (COVID-19) disease causes significant morbidity and mortality through increased inflammation and thrombosis. Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are states of chronic inflammation and indicate advanced metabolic disease.
Objective: The purpose of this observational study was to characterize the risk of hospitalization for COVID-19 in patients with NAFLD/NASH and evaluate the mitigating effect of various metabolic treatments.
Setting: Retrospective analysis of electronic medical record data of 26,896 adults from a 12-hospital Midwest healthcare system with a positive COVID-19 polymerase chain reaction (PCR) test from March 1, 2020, to January 26, 2021.
Methods: Variable selection was guided by the least absolute shrinkage and selection operator (LASSO) method, and multiple imputation was used to account for missing data. Multivariable logistic regression and competing risk models were used to assess the odds of being hospitalized within 45 days of a COVID-19 diagnosis. Analysis assessed the risk of hospitalization among patients with a prescription for metformin and statin use within the 3 months prior to the COVID-19 PCR result, history of home glucagon-like peptide 1 receptor agonist (GLP-1 RA) use, and history of metabolic and bariatric surgery (MBS). Interactions were assessed by sex and race.
Results: A history of NAFLD/NASH was associated with increased odds of admission for COVID-19 (odds ratio [OR], 1.88; 95% confidence interval [CI], 1.57–2.26; $P < .001$) and mortality (OR, 1.96; 95% CI, 1.45–2.67; $P < .001$). Each additional year of having NAFLD/NASH was associated with a significant increased risk of being hospitalized for COVID-19 (OR, 1.24; 95% CI, 1.14–1.35; $P < .001$). NAFLD/NASH increased the risk of hospitalization in men, but not women, and increased the risk of hospitalization in all multiracial/multiethnic subgroups. Medication treatments for metabolic syndrome were associated with significantly reduced risk of admission (OR, .81; 95% CI, .67–.99; $P < .001$ for home metformin use; OR, .71; 95% CI, .65–.83; $P < .001$ for home statin use). MBS was associated with a significant decreased risk of admission (OR, .48; 95% CI, .33–.69; $P < .001$).

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*Correspondence: Carolyn T. Bramante, M.D., M.P.H., 420 Delaware Street SE, MMC 276, Minneapolis, MN 55455.
E-mail address: bramante@umn.edu (C.J. Tignanelli).

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Conclusions: NAFLD/NASH is a significant risk factor for hospitalization for COVID-19 and appears to account for risk attributed to obesity. Other significant risks include factors associated with socioeconomic status and other co-morbidities, such as history of venous thromboembolism. Treatments for metabolic disease mitigated risks from NAFLD/NASH. More research is needed to confirm the risk associated with visceral adiposity, and patients should be screened for and informed of treatments for metabolic syndrome. (Surg Obes Relat Dis 2021;17:1780–1786.) © 2021 Published by Elsevier Inc. on behalf of American Society for Bariatric Surgery.

Keywords: metabolic and bariatric surgery; COVID-19; fatty liver disease

Hospitalizations for SARS-CoV-2 (COVID-19) disease continue to disrupt thousands of lives [1]. Obesity and metabolic disease appear to be the most significant modifiable risk factors for poor outcomes from COVID-19 [2,3]. Hepatic steatosis (nonalcoholic fatty liver disease [NAFLD] and nonalcoholic steatohepatitis [NASH]) are evidence of visceral adiposity, advanced metabolic disease, and overt inflammation [4]. Given COVID-19's pathophysiology via inflammation, NAFLD/NASH may put patients at even higher risk of poor outcomes from COVID-19 [5]. Few papers have fully assessed risk for poor outcomes from COVID-19 associated with NAFLD/NASH and factors that might reduce that risk.

We conducted a retrospective analysis of individuals with COVID-19 infection and their likelihood of being admitted for COVID-19 with the following objectives: our primary objective was to quantify the risk for hospitalization for COVID-19 based on a history of NAFLD/NASH. Our secondary objective was to assess whether treatments for metabolic disease modified risk from COVID-19 associated with NAFLD/NASH [6,7]. Third, we were interested in whether NAFLD/NASH was associated with severe COVID-19 (i.e., intubation, mortality). Lastly, because visceral adiposity accumulates at a lower body mass index (BMI) level in men [8] and is more prevalent among certain ethnic groups [9–11], we assessed interactions between sex and race/ethnicity and NAFLD/NASH as drivers of COVID-19 outcomes.

Methods

Design and data source

We conducted a retrospective cohort analysis of electronic medical record (HER) data pooled across 12 hospitals and 56 primary care clinics in the Midwest, the Acute and Chronic Datamart for COVID (ACDC). This COVID-19 data mart includes clinical and administrative data for individuals with a positive COVID-19 polymerase chain reaction (PCR) test. Data were pooled across different EHRs to account for patient transfers and all encounters between systems for each patient, facilitated by generating a master patient index serving as a unique patient identifier. In cases where a patient was seen in two different EHR systems, the most recent EHR co-morbidity and outpatient medication records were used. All patients who opted out of research were excluded from analysis.

Population

The population consisted of 26,896 adults with a positive COVID-19 PCR test result from March 1, 2020, to January 26, 2021 (Fig. 1). Inclusion criteria consisted of patients who opted into research and had a positive COVID-19 PCR test. Patients younger than 18 years were excluded.

Independent variable

Persons with NAFLD/NASH were defined as those with *International Statistical Classification of Diseases and Related Health* (ICD) codes for NAFLD or NASH or a body mass index (BMI) of 30 kg/m^2 or greater and an elevated alanine aminotransferase (ALT) level on 3 separate dates [12]. This laboratory and BMI-based definition was used in addition to ICD coding because NASH and NAFLD are significantly underdiagnosed in the EHR [13,14] and because elevated ALT is more specific for NAFLD/NASH than elevated aspartate aminotransferase (AST) [15].

Dependent variable of interest

An admission to the hospital for COVID-19 disease within 45 days of COVID-19 PCR testing was the dependent variable of interest. Secondary outcomes were assessed for mortality and admission to the intensive care unit (ICU).

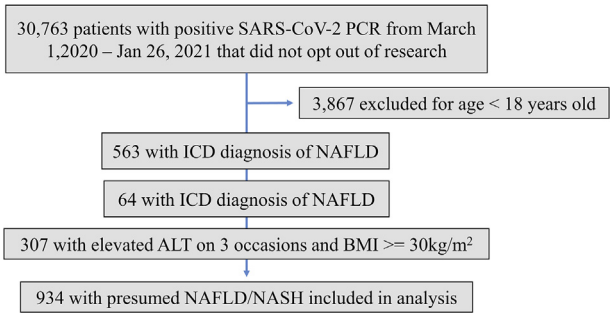

Fig. 1. Diagram outlining the patients included in this study.

Covariates of interest and variable selection for final model

The following variables were hypothesized to be confounders based on clinical experience and medical literature related to COVID-19 and/or NAFLD/NASH: demographics (i.e., age, race, sex, non-English speaking), home medications (i.e., oral steroids, amiodarone, methotrexate, calcium channel blockers, antidementia medications, angiotensin-converting enzyme [ACE] inhibitors/angiotensin II receptor blockers [ARBs], anticoagulants, colchicine, inhaled steroid, statins, glucagon-like peptide 1 receptor agonists [GLP-1RAs], metformin, sodium-glucose co-transporter 2 [SGLT2] inhibitors, dipeptidylpeptidase-4 (DDP4) inhibitors, and albuterol), Elixhauser Comorbidity Index, history of alcohol abuse, obesity, previous bariatric surgery, type 1 diabetes, type 2 diabetes, smoking status, history of venous thromboembolism, and history of asthma. Anticoagulation medications were defined as warfarin, rivaroxaban, enoxaparin, apixaban, and dabigatran.

To reduce the likelihood of overfitting a least absolute shrinkage and selection operator (LASSO) logit model was used to facilitate variable selection, with the tuning parameter determined by the Bayesian information criterion (BIC). LASSO is a penalized regression method that can facilitate variable selection by excluding variables with a minor contribution to the model. After LASSO was completed, the following variables were selected for inclusion in subsequent models: demographics (i.e., age, race, sex, non-English speaking), home medications (i.e., oral steroids, amiodarone, methotrexate, calcium channel blockers, antidementia medications, ACE inhibitors/ARBs, metformin, anticoagulants, colchicine, statins, GLP-1RAs, SGLT2 inhibitors, DDP4 inhibitors, and albuterol), Elixhauser Comorbidity Index, history of alcohol abuse, obesity, previous bariatric surgery, type 1 diabetes, history of venous thromboembolism, and history of asthma.

Missingness

There was an overall low rate of data missingness. A total of 1913 patients (7.1%) were missing co-morbidity data, 4055 patients (15.1%) were missing race data, 58 patients (.2%) were missing age data, and 2 persons (.01%) were missing sex data. There was no missingness in other variables. To account for missing data, we used the multiple imputation (mi) suite of commands with five imputations for each missing value [16].

Analyses

Multivariable logistic regression was used to assess the odds of being hospitalized within 45 days of a positive COVID-19 PCR test. To account for the competing risk that patients may die prior to hospitalization, a competing risk model was also used. The dependent variable in the competing risk model was the time to hospitalization censored at 45 days. Both models were adjusted for variables selected using LASSO. Interactions were assessed by sex and race.

A subgroup analysis of patients with only NAFLD or NASH was also conducted to evaluate the independent association of metformin use, GLP-1RA use, and previous bariatric surgery on hospitalization. In order to account for variables that can worsen NAFLD/NASH, a sensitivity analysis was also done excluding patients with a history of alcohol use disorder and home amiodarone or methotrexate use [17]. Model goodness of fit was assessed using the Hosmer–Lemeshow test ($P > .99$) and area under the curve (AUROC = .86) for the primary multivariable logistic regression model. An analysis using multivariable logistic regression was also conducted for the secondary endpoint of all-cause mortality (defined as in-hospital or out-of hospital death, using state death certificate data). Confounding variables identified from LASSO were included for risk adjustment in the mortality regression model.

Statistical significance was defined with an alpha of .05. Statistical analyses were performed using Stata MP, version 16 (StataCorp, College Station, Texas).

Results

Characteristics of the cohort

A total of 26,896 adults were included in the final analysis, of which 934 (3.5%) had NAFLD/NASH (Fig. 1). The median age was 51 years (interquartile range [IQR], 35–67 yr), and 44% were female. Also, 72.8% of patients identified as white, 11% as black, 7% as Asian, 4.8% as Hispanic, 1.2% as "other," and 3.3% declined. Patients with NAFLD/NASH were more likely to be older (median age, 56.7 versus 51.2 yr) multiracial (69.6% white versus 72.9% white), male (49.4% versus 43.6%) and have a larger BMI (37.5 versus 30.8; Table 1). Patients with NAFLD/NASH were also more likely to have type 1 diabetes (10.9% versus 2.8%), type 2 diabetes (42.0% versus 13.5%). Additional comparisons between those with NAFLD/NASH and those without are provided in Table 1. Additionally, patients with NAFLD/NASH had higher median Elixhauser Comorbidity Indexes (median, 6.0 versus 1.0) (Table 1). On unadjusted univariate analysis (Table 1), patients with NAFLD/NASH had worse clinical outcomes: inpatient admission (45.1% versus 12.7%), intensive care unit admission (18.6% versus 3.4%), in-hospital death (6% versus 1.4%), and in- and out-of hospital death (7.9% versus 2.6%; Table 1).

A history of NAFLD/NASH was associated with increased odds of admission for COVID-19: multivariable logistic regression OR, 1.88 (95% confidence interval [CI], 1.57–2.26, $P < .001$; Table 2 and Fig. 2) and competing risks OR, 1.66 (95% CI, 1.44–1.93; $P < .001$;

Table 1
Characteristics of individuals with positive results from SARS-CoV-2 PCR test and comparing those who have NAFLD/NASH compared with those who do not

Characteristic	Overall cohort	No NAFLD/NASH (n = 25,962)	NAFLD/NASH (n = 934)	*P* value
Age, median (IQR), yr	51.1 (34.6–67.4)	51.2 (34.4–67.3)	56.7 (44.7–66.7)	<.001
Race/ethnicity, n (%)				
White	16,629 (72.8)	16,025 (72.9)	604 (69.6)	<.001
Black	2485 (10.9)	2413 (11.0)	72 (8.3)	
Asian	1603 (7.0)	1517 (6.9)	86 (9.9)	
Hispanic	1096 (4.8)	1024 (4.7)	72 (8.3)	
Declined	759 (3.3)	739 (3.4)	20 (2.3)	
Other	269 (1.2)	255 (1.2)	14 (1.6)	
Male, n (%)	11,773 (56)	11,312 (43.6)	461 (49.4)	<.001
BMI, mean (SD), kg/m^2		30.8 (56.4)	37.5 (72.1)	<.001
Co-morbidities, n (%) unless otherwise specified				
Elixhauser, mean (SD)		2.0 (2.9)	6.3 (4.2)	<.001
Past bariatric surgery		306 (1.3)	37 (4.0)	<.001
Type 1 diabetes		663 (2.8)	100 (10.9)	<.001
Alcohol use disorder		934 (3.9)	147 (16.0)	<.001
Obesity		15,901 (61.2)	743 (79.6)	<.001
History of venous thromboembolism		1029 (4.3)	136 (14.8)	<.001
Asthma		2573 (10.7)	212 (23.0)	<.001
Home medications, n (%)				
Antidementia medications		114 (.4)	6 (.6)	.36
ACE inhibitor/ARB		2868 (11.0)	269 (28.8)	<.001
Metformin		916 (3.5)	141 (15.1)	<.001
Anticoagulants		1068 (4.1)	94 (10.1)	<.001
Colchicine		80 (.3)	11 (1.2)	<.001
Statin		3943 (15.2)	343 (36.7)	<.001
GLP-1RA		284 (1.1)	54 (5.8)	<.001
SGLT2 inhibitors		110 (.4)	21 (2.2)	<.001
DPP4 inhibitors		122 (.5)	17 (1.8)	<.001
Calcium channel blockers		1149 (4.4)	112 (12.0)	<.001
Oral steroids		1157 (4.5)	113 (12.1)	<.001
Amiodarone		75 (.3)	9 (1.0)	<.001
Methotrexate		116 (.4)	13 (1.4)	<.001
Outcomes from COVID-19, n (%)				
Hospitalization		3289 (12.7)	421 (45.1)	<.001
ICU admission		875 (3.4)	174 (18.6)	<.001
Mechanical ventilation		303 (1.2)	113 (12.1)	<.001
In-hospital or out-of-hospital mortality		680 (2.6)	74 (7.9)	<.001
In-hospital mortality		372 (1.4)	56 (6.0)	<.001

PCR = polymerase chain reaction; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; IQR = interquartile range; BMI = body mass index; SD = standard deviation; ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; GLP-1RA = glucagon-like protein 1 receptor agonist; SGLT2 = sodium-glucose co-transporter 2; DPP4 = dipeptidylpeptidase-4; ICU = intensive care unit.

Fig. 3). Each additional year of having NAFLD/NASH was also associated with a 24% increased odds of being hospitalized for COVID-19 (OR, 1.24; 95% CI, 1.14–1.35; $P <$ .001). In subgroup analyses, compared with white individuals without NAFLD/NASH, those with NAFLD/NASH had an increased risk of hospital admission (OR, 1.86; $P <$ .001). Compared with black individuals without NAFLD/NASH, those with NAFLD/NASH had an increased risk of admission (OR, 2.47; $P = .002$); compared with Asian individuals without NAFLD/NASH, those with NAFLD/NASH had an increased risk of hospitalization (OR, 3.57; $P \leq .001$); and compared with Hispanic persons without NAFD/NASH, those with NAFLD/NASH had an increased risk of admission (OR, 3.65; $P <$ .001; Table 2).

Factors independently associated with hospitalization in COVID-19

To evaluate sex-specific interaction, NAFLD/NASH in men was associated with increased odds of admission (OR, 1.4; 95% CI, 1.02–1.96; $P = .04$), but not in women (OR, .71; 95% CI, .51–.98; $P = .04$), suggesting that sex-specific derangements related to NAFLD/NASH may be driving the increased risk of worse outcomes in COVID-19 (Table 2).

Table 2
Odds of admission for COVID-19 among those with positive SARS-CoV-2 PCR test results and odds associated with NAFLD/NASH among demographic subgroups by logistic regression*

Characteristic	Odds ratio (95% confidence interval)		*P* value
Sex			
Female	Ref		
Male	1.2		<.001
Race/ethnicity			
White	Ref		
Black	1.8 (1.55–2.09)		<.001
Asian	2.79 (2.36–3.31)		<.001
Hispanic	2.52 (2.11–3.02)		<.001
Subgroup analysis	**No NAFLD/NASH**	**NAFLD/NASH**	***P* value**
Female	Ref	.71	.04
Male	Ref	1.41	.04
Race/ethnicity			
White	Ref	1.86	<.001
Black	Ref	2.47	.002
Asian	Ref	3.57	<.001
Hispanic	Ref	3.65	<.001

PCR = polymerase chain reaction; Ref = reference group; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis

* Adjusted for home medications (oral steroids, amiodarone, methotrexate, calcium channel blockers, antidementia medications, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, metformin, anticoagulant use, colchicine, statin, glucagon-like peptide 1 receptor agonist, sodium-glucose co-transporter 2 inhibitor, dipeptidylpeptidase-4 inhibitor, albuterol), Elixhauser Comorbidity Index, history of alcohol abuse, obesity, previous bariatric surgery, type 1 diabetes, history of venous thromboembolism, history of asthma.

Metabolic syndrome treatments

Persons who had undergone bariatric surgery (n = 343) had significantly decreased odds of admission for COVID-19 (OR, .46; 95% CI, .33–.68; $P < .001$; Supplemental Table 1 and Fig. 2). Outpatient metformin, GLP-1RA, SGLT2 inhibitor, and DPP4 inhibitor use in the 3 months prior to the COVID-19 diagnosis was not associated with decreased odds of admission. Statin use was associated with decreased odds of admission (Supplemental Table 1 and Fig. 2).

Metabolic syndrome treatments in subgroup of patients with NAFLD/NASH

In a subgroup analysis of the 934 patients with NAFLD/NASH, bariatric surgery (n = 37; OR, .42; 95% CI, .17–.99; $P = .05$), ACE inhibitor/ARB use (n = 269; OR, .45; 95% CI, .3–.66; $P < .001$), and statin use (n = 343; OR, .54; 95% CI, .37–.79; $P = .001$) remained significantly associated with reduced odds of hospitalization.

Sensitivity analysis

A sensitivity analysis was conducted by excluding patients with a history of alcohol abuse (there was a high percentage with this history in the NAFLD/NASH group) and oral steroid, amiodarone, and methotrexate use because these can cause liver disease. In this analysis, NAFLD/NASH remained independently associated with increased odds of hospitalization (OR, 2.8; 95% CI, 2.3–3.4; $P < .001$). The metabolic treatments remained protective for hospitalization: previous bariatric surgery (OR, .48; 95% CI, .33–.69; $P < .001$), metformin use (OR, .81; 95% CI, .67–.98; $P = .03$) and statin use (OR, .73; 95% CI, .65–.82; $P < .001$).

Metabolic syndrome treatments independently associated with all-cause in- and out-of-hospital mortality in COVID-19

A history of NAFLD/NASH was independently associated with increased odds of mortality for patients with COVID-19 (OR, 1.96; 95% CI, 1.45–2.67; $P < .001$). Previous bariatric surgery did not reach statistical significant for reduced mortality in patients with COVID-19 (OR, .54; 95% CI, .25–1.17; $P = .12$). Metformin was associated with reduced mortality in patients with COVID-19 (OR, .52; 9% CI, .35–.77; $P = .001$). Statin use was associated with reduced mortality in patients with COVID-19 (OR, .81; 95% CI, .66–.98; $P = .03$). Nonmetabolic treatment with methotrexate and ACE inhibitor/ARB use was associated with reduced mortality.

Discussion

This is an in-depth assessment of NAFLD/NASH as a risk factor for hospital admission for COVID-19 in a large database in the United States as well as possible treatments for mitigating this risk. We found that NAFLD/NASH was a significant risk factor for hospital admission. This may indicate the significant role of visceral adiposity in the pathophysiology of COVID-19, which appears to amplify the chronic state of inflammation and hypercoagulability created by NAFLD/NASH.

NAFLD/NASH increased the risk of hospitalization in men but not in women. This may point toward sex-specific differences in the accumulation of visceral adiposity [18]. Assessing an interaction with race was done because of significant differences in outcomes in COVID-19 by race and ethnicity [19]. NAFLD/NASH increased the risk of hospitalization in all groups, but controlling for NAFLD/NASH did not eliminate differences in risk between racial/ethnic groups. Of note, persons who had self-identified as black who had NAFLD/NASH had the biggest increased odds of hospitalization. This may be due to lower amounts of visceral adiposity previously reported in black individuals [20].

Promisingly, we found that treatments for metabolic syndrome and NAFLD/NASH greatly mitigated the risk from COVID-19. Bariatric surgery is one of the most effective treatments for metabolic syndrome, and in this analysis, persons who had undergone bariatric surgery had a significant decrease in the odds of hospitalization.

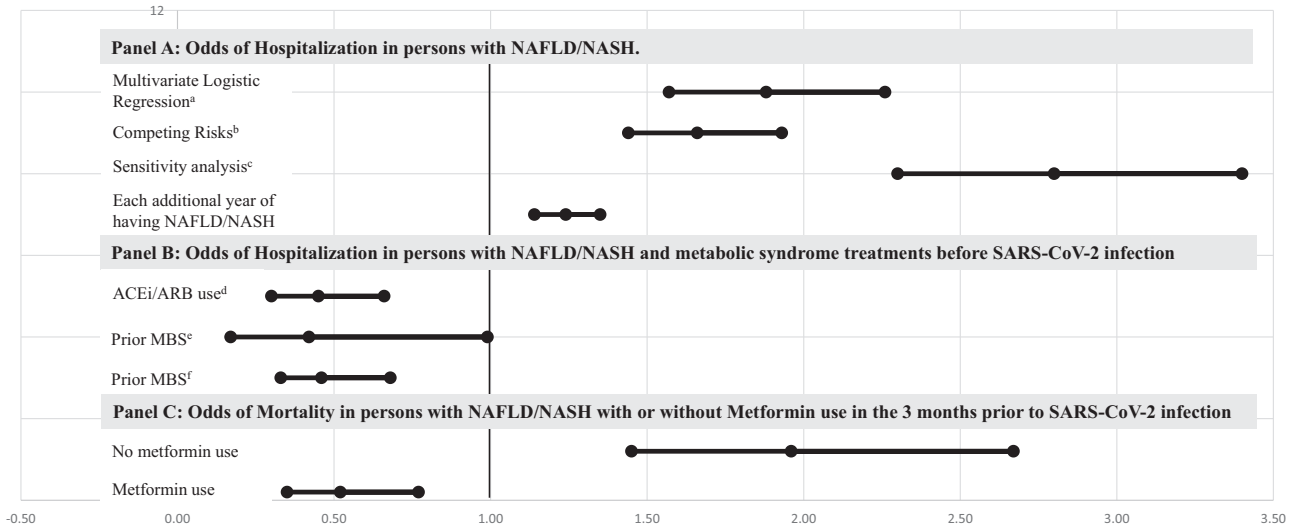

Fig. 2. The bars represent 95% confidence intervals. PCR = polymerase chain reaction; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis. *Logistic regression, adjusted for age, sex, obesity, ethnicity, NAFLD/NASH, alcohol use disorder, Elixhauser Comorbidity Index, and home use of amiodarone, methotrexate, oral steroids, or calcium channel blockers (CCBs), was conducted. [†]Competing risk, adjusted model. [‡]Excluding persons with alcohol use disorder and amiodarone, methotrexate, or CCB use, adjusted model. [§]Odds for admission for each additional year of having NAFLD/NASH. [¶]Among those with home glucagon-like peptide 1 receptor agonist (GLP-1 RA), adjusted model. [‖]Among those with home metformin use in the previous 3 months, adjusted model. [#]Among those with a history of metabolic and bariatric surgery (MBS), adjusted model.

While the protective benefits of metformin, GLP-1RA, and bariatric surgery are promising, more therapies for NAFLD/NASH are urgently needed. The mainstay of treatment for NAFLD/NASH is weight loss, and although advances in obesity medicine have made achieving sustainable weight loss more possible [19], societal forces including the current COVID-19 pandemic continue to create an obesogenic environment because more than 42% of adults in the United States now have obesity [21].

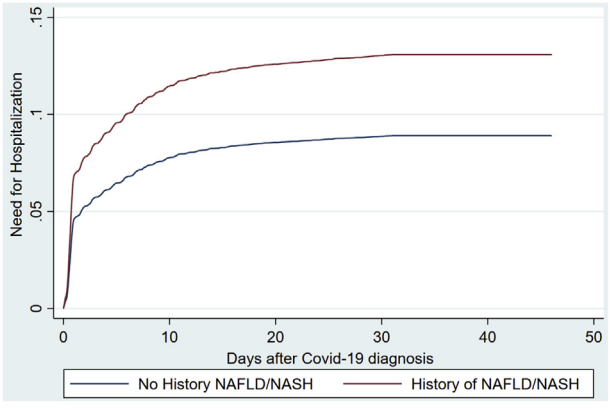

Fig. 3. Outcomes by competing risks comparison between those with nonalcoholic fatty liver disease/nonalcoholic steatohepatitis and those without.

Our study has several limitations. First, there may be unmeasured confounders and residual bias in observational findings. Findings in a sample in the upper Midwest may not be generalizable. Hepatitis B and C were not excluded because they may co-occur with NAFLD/NASH in persons with a BMI $\geq$ 30 kg/m^2, and the prevalence in this region is low: .78% of adults with hepatitis C and .59% of adults with chronic hepatitis B. Further selection bias may be present in that there are likely many more individuals in this population who have NAFLD/NASH but who did not have 3 elevated ALT readings [4]. This selection bias would likely bias findings toward the null.

Conclusions

NAFLD/NASH is a state of chronic inflammation due to visceral adiposity and appears to be a significant risk factor for hospitalization for COVID-19. NAFLD/NASH may account for much of the risk for poor outcomes from COVID-19 attributed to obesity. Bariatric surgery appears to mitigate elevated risk for hospitalization for COVID-19 in persons with NAFLD/NASH. More research is needed to confirm these findings. Patients with elevated BMIs should be screened for NAFLD/NASH and metabolic syndrome and informed of the risks associated with visceral adiposity and COVID-19. Patients also should be informed of treatments for mitigating this risk such as bariatric surgery and some medications [10,19].

Acknowledgments

Dr. Tignanelli is a principal investigator on randomized trials for COVID-19 but not related to metformin. Dr. Bramante has submitted an investigational new drug proposal for a prospective trial for metformin.

Disclosures

The authors have no commercial associations that might be a conflict of interest in relation to this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.soard.2021.05.029.

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