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Observational Study

In-hospital outcomes in COVID-19 patients with non-alcoholic fatty liver disease by severity of obesity: Insights from national inpatient sample 2020

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Abstract

BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) increases the risk of cardiovascular diseases independently of other risk factors. However, data on its effect on cardiovascular outcomes in coronavirus disease 2019 (COVID-19) hospitalizations with varied obesity levels is scarce. Clinical management and patient care depend on understanding COVID-19 admission results in NAFLD patients with varying obesity levels.

AIM

To study the in-hospital outcomes in COVID-19 patients with NAFLD by severity of obesity.

METHODS

COVID-19 hospitalizations with NAFLD were identified using International Classification of Disease -10 CM codes in the 2020 National Inpatient Sample database. Overweight and Obesity Classes I, II, and III (body mass index 30–40) were compared. Major adverse cardiac and cerebrovascular events (MACCE) (all-cause mortality, acute myocardial infarction, cardiac arrest, and stroke) were compared between groups. Multivariable regression analyses adjusted for sociodemographic, hospitalization features, and comorbidities.

RESULTS

Our analysis comprised 13260 hospitalizations, 7.3% of which were overweight, 24.3% Class I, 24.1% Class II, and 44.3% Class III. Class III obesity includes younger patients, blacks, females, diabetics, and hypertensive patients. On multivariable logistic analysis, Class III obese patients had higher risks of MACCE, inpatient mortality, and respiratory failure than Class I obese patients. Class II obesity showed increased risks of MACCE, inpatient mortality, and respiratory failure than Class I, but not significantly. All obesity classes had non-significant risks of MACCE, inpatient mortality, and respiratory failure compared to the overweight group.

CONCLUSION

Class III obese NAFLD COVID-19 patients had a greater risk of adverse outcomes than class I. Using the overweight group as the reference, unfavorable outcomes were not significantly different. Morbid obesity had a greater risk of MACCE regardless of the referent group (overweight or Class I obese) compared to overweight NAFLD patients admitted with COVID-19.

Key Words: Non-alcoholic fatty liver disease; Obesity; Obese; Body mass index; Major adverse cardiac and cerebrovascular events; Mortality; Acute myocardial infarction; Cardiac arrest; Stroke

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Core Tip: Non-alcoholic fatty liver disease (NAFLD) has become a major cause of morbidity and mortality from liver disease and is the most common cause of chronic liver disease, with a global prevalence of 25% and a 50.4% increase in prevalence in the last three decades. To the best of our knowledge, this is the largest study investigating the comorbidities and outcomes of coronavirus disease 2019 hospitalizations with NAFLD and different levels of obesity.

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INTRODUCTION

With the global surge in the obesity pandemic, non-alcoholic fatty liver disease (NAFLD) has become increasingly prevalent and a major contributor to morbidity among liver diseases[1]. There seems to be a bidirectional association between NAFLD and obesity. NAFLD is estimated to have a global prevalence of 25%–30% and up to 90% in morbidly obese individuals[2]. However, these numbers may be underestimated, as NAFLD is usually asymptomatic in the early stages of the disease. Inversely, obese individuals constitute a high proportion of patients with NAFLD[3]. Numerous studies have elucidated the correlation between both coronavirus disease 2019 (COVID-19) and obesity[4] as well as

NAFLD[5], highlighting the adverse outcomes in this patient population. It is widely acknowledged that people falling within the various classes of obesity experience an elevated risk of severe outcomes from COVID-19[6]. The intricate and multifaceted mechanisms linking COVID-19, NAFLD, and obesity encompass systemic inflammation, immune dysregulation, and impaired metabolic pathways. There is a scarcity of data regarding disease progression and prognosis in individuals encompassing all three disease groups. It is crucial to better analyze the outcomes to guide management in this patient population. Given the established relationship between obesity and NAFLD, our study aims to investigate the in-hospital outcomes of NAFLD patients with COVID-19 with varying degrees of obesity categorized by body mass index levels.

MATERIALS AND METHODS

Source of data

The Healthcare Cost and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality, utilizes the National Inpatient Sample (NIS) databases (2020) as its data sources (Table 1). The NIS is the country's largest publicly accessible all-payer inpatient healthcare dataset. With an average of 7 million unweighted discharges annually or more than 35 million weighted countrywide discharges, it comprises discharge data from roughly 20% of United States hospitals in more than 48 states. One primary diagnosis and up to 39 secondary discharge diagnoses are associated with each inpatient admission to the NIS. Since the NIS contains de-identified data, IRB approval was not required. More details regarding the database are available on the HCUP website.

Study population

Using the International Classification of Disease (ICD-10) diagnostic codes and NIS database for the year 2020, hospitalizations with COVID-19 were identified in patients with NAFLD. The NAFLD patients were divided into four groups based on their obesity class: overweight [body mass index (BMI) 25 or higher], Class I (BMI 30–34.9), Class II (BMI 35–39.9), and Class III (BMI 40 or higher). Baseline characteristics, comorbidities, and in-patient outcomes like respiratory failure, mechanical ventilation, and major adverse cardiac and cerebrovascular events (MACCE) [all-cause mortality, acute myocardial infarction (AMI), cardiac arrest, and stroke] were compared between obesity classes. Multivariable regression analyses were adjusted for sociodemographic, hospitalization characteristics, and comorbidities.

Outcomes of interest

The primary outcomes of interest in the study were the in-hospital outcomes of COVID-19 admissions among NAFLD patients stratified by obesity class. These outcomes included respiratory failure, the need for mechanical ventilation, and MACCE. MACCE was defined as the occurrence of all-cause mortality, AMI, cardiac arrest, or stroke. Individual components of MACCE were included as secondary outcomes. Baseline characteristics and comorbidities were also assessed and compared between obesity classes.

Statistical analyses

To compare baseline demographics and hospital characteristics, the Pearson Chi-square test was used to look at categorical variables, and the Mann-Whitney *U* test was used to look at continuous variables, since the distribution of continuous data across obesity classes was not normal. Continuous variables were presented as the median, whereas categorical variables were expressed as percentages. A two-tailed *P* value of less than 0.05 was considered statistically significant. National estimates were generated using complex sample modules, strata or cluster designs, and discharge weights (DISCWT). Multivariable regression analyses were performed to assess the relationship between obesity class and in-hospital outcomes while controlling for confounding factors and keeping overweight and Class I obesity as referent groups individually. This model factored in age, gender, race, elective vs. non-elective admission type, median household income, length of stay, insurance payer, hospital bed size, ownership, location/teaching status of the hospital, as well as clinically relevant comorbid conditions. To report the logistic regression results, adjusted odds ratios (OR), 95% confidence intervals (CI), and *P* values were calculated. IBM SPSS Statistics 25.0 (IBM Corp., Armonk, NY, United States) software was used for all statistical analyses.

RESULTS

There were a total of 13260 admissions for COVID-19 among patients with NAFLD who had a BMI of over 25, and out of those patients, 7.3% were categorized as overweight, 24.3% were categorized as Class I, 24.1% were categorized as Class II, and 44.3% were categorized as Class III. Overall, the entire study group contained more individuals who were white (42.6%) compared to blacks (14%). In total, 6.2% of total admissions died during hospitalization, and 9.1% suffered MACCE events (AMI: 2.5%, Acute ischemic stroke: 0.4%). 77% had routine dispositions; 12.2% required home health care; 8.6% were transferred to a skilled nursing facility; and 2.2% were transferred to a short-term hospital (Table 2).

Class III contained younger individuals than the overweight sub-group (39.0% vs 18.7%); more people were black (14.0% vs 7.9%), fewer Hispanics (35.6% vs 43.8%), and fewer Asians (2.8% vs 5.1%). In terms of comorbidities, Class III had lower hypertension rates compared to the overweight subgroup (58.4 vs 61.1%) and a lower rate of chronic kidney disease (9.3% vs 11.4%), while having higher rates of chronic pulmonary disease (22.3% vs 15.5%). Patients who were

Table 1 Baseline characteristics of coronavirus disease 2019 hospitalizations in non-alcoholic fatty liver disease patients with different levels of obesity: Insights from national inpatient sample 2020

Variables		Overweight, %	Class I, %	Class II, %	Class III, %	P value
Age (yr) at admission	Mean	58	53	52	48	< 0.001
Sex	Male	58.5	59.7	52	43.3	< 0.001
	Female	41.5	40.3	48	56.7	< 0.001
Race	White	42.1	41.6	45	49.5	< 0.001
	Black	7.9	11.8	14.9	15.8	< 0.001
	Hispanic	43.8	41.4	36.3	30.9	< 0.001
	Asian/PI	5.1	4.5	1.8	2.2	< 0.001
	Nat. American	< 0.1	0.8	2	1.6	< 0.001
Payer	Medicare	34.1	26.4	26.6	19.9	< 0.001
	Medicaid	26.7	21.8	15.1	20.7	< 0.001
	Private	33	44.8	49.1	50.9	< 0.001
	Self-pay	5.1	6.7	8.7	8.1	< 0.001
Admission type	Non-elective	99	98.8	98.4	97.7	< 0.001
Comorbidities	Hypertension	61.1	56.4	58.4	59.1	0.024
	Diabetes	46.6	46.7	48.8	50.6	< 0.001
	Hyperlipidemia	45.1	42.5	41.6	32.3	< 0.001
	PVD	3.1	3.6	5.3	2.2	< 0.001
	Tobacco use disorder	19.2	21.6	20.3	17.6	< 0.001
	Prior MI	3.1	2	1.6	1.6	0.007
	Prior TIA/Stroke	3.1	2.8	3	1.7	< 0.001
	Prior VTE	2.6	4	3.6	4.2	0.090
	Cancer	5.2	2.5	1.7	2.5	< 0.001
	CKD	11.4	9.1	9.9	8.7	0.029
	Drug abuse	2.1	1.2	1.7	1.8	0.161
	Cannabis use disorder	< 0.1	0.8	0.6	0.9	0.029
	Depression	7.3	10.1	11.4	13.1	< 0.001
	Chronic pulmonary disease	15.5	18.3	21.4	26.1	< 0.001
	Hypothyroidism	10.9	9.1	10.5	13.9	< 0.001
	Bariatric surgery	< 0.1	0.9	1.9	1.5	< 0.001
Discharge	Routine	66.7	77.4	78.9	77.3	< 0.001
	Transfer to short term Hospital	< 0.1	3	2	2	< 0.001
	Other: SNF, ICF, etc.	16.7	6.9	7.5	9%	< 0.001
	Home health care	15.5	12.7	11.6	11.7	< 0.001
	Length of stay (d)	Median	10	8	8	8

Overweight BMI 25-29.9; Class I Obesity BMI 30-34.9; Class II Obesity BMI 35-39.9; Class III Obesity BMI 40 or higher. PI: Pacific Islander, MI: Myocardial Infarction; PVD: Peripheral vascular disease; VTE: Venous thromboembolism; SNF: Skilled nursing facility; ICF: Intermediate care facility; MACCE: Major adverse cardiovascular and cerebrovascular events.

Table 2 Multivariable odds of in-hospital outcomes in obese coronavirus disease 2019 hospitalizations with non-alcoholic fatty liver disease

	Obesity II vs I	Obesity III vs I	Obesity I vs overweight	
Outcomes	aOR [LL-UL]	aOR [LL-UL]	aOR [LL-UL]	<i>P</i> value
MACCE	1.19 [0.78-1.81]	1.82 [1.22-2.73]	1.66 [0.92-2.98]	0.016
Death during hospitalization	1.10 [0.69-1.76]	1.96 [1.23-3.11]	1.59 [0.84-3.02]	0.015
Acute myocardial infarction	1.91 [0.77-4.72]	2.32 [0.92-5.88]	1.72 [0.53-5.57]	0.346
Cardiac arrest	1.14 [0.49-2.67]	1.25 [0.56-2.80]	0.60 [0.13-2.78]	0.782
Acute ischemic stroke	0.23 [0.04-1.28]	0.36 [0.06-2.02]	5.52 [0.55-55.56]	0.130
Respiratory failure	1.27 [0.99-1.61]	1.35 [1.07-1.70]	0.97 [0.67-1.41]	0.049
Mechanical ventilation	0.90 [0.63-1.31]	1.34 [0.97-1.85]	1.01 [0.58-1.75]	0.095
	I vs overweight	II vs overweight	III vs overweight	
Outcomes	aOR [LL-UL]	aOR[LL-UL]	aOR[LL-UL]	<i>P</i> value
MACCE	0.60 [0.34-1.08]	0.72 [0.39-1.32]	1.10 [0.62-1.95]	0.016
Death during hospitalization	0.63 [0.33-1.19]	0.69 [0.35-1.35]	1.23 [0.66-2.30]	0.015
Respiratory failure	1.04 [0.71-1.51]	1.28 [0.88-1.88]	1.40 [0.96-2.04]	0.057
Mechanical ventilation	0.99 [0.57-1.72]	0.90 [0.51-1.59]	1.33 [0.78-2.27]	0.095

Overweight BMI 25-29.9; Class I Obesity BMI 30-34.9; Class II Obesity BMI 35-39.9; Class III Obesity BMI 40 or higher. Multivariable regression models were adjusted for age at admission, sex, race, income quartile for patient's ZIP code, type of admission, hospital location/teaching status, hypertension, diabetes, hyperlipidemia, peripheral vascular disease, tobacco use disorder, prior MI, prior TIA/Stroke, cancer, CKD and Bariatric surgery status. aOR: Adjusted odds ratio; LL: Lower limit, UL: Upper limit; MACCE: Major adverse cardiac and cerebrovascular events.

overweight had higher rates of MACCE (13% compared to 7.4%, 8.3%, and 9.8%), more inpatient mortality (9.8% vs 5.6%, 5.6%, and 7.4%), and higher rates of mechanical ventilation (13% vs 11%, 9.7%, and 12.9%). Patients who were overweight also had higher rates of inpatient mortality (9.8% vs 5.6%, 5.6%, and 7.4%). This finding, however, did not seem to be significant for MACCE (aOR: 1.66, CI: 0.922-2.98, $P > 0.05$), for inpatient mortality (aOR: 1.59, CI: 0.84-3.02, $P > 0.05$), or mechanical ventilation (aOR: 1.01, CI: 0.58-1.75, $P > 0.05$). The multivariate analysis proved this by showing that there was no significant relationship between these factors and the outcome.

In Class III, more people were younger than there were in Class I (39% against 25.3%), more people were black (15.8% vs 11.8%), more people had hypertension (59.1% versus 56.4%), more diabetics (50.6% vs 46.7%), more people had chronic pulmonary disease (26.1% vs 18.3%), more females (56.7% vs 40.3%), and fewer men (11.2% vs 22.6%). On Multivariable logistic analysis, Class III obese patients, when compared with Class I individuals, had higher odds of MACCE (aOR: 1.82, CI:1.22-2.73, $P = 0.016$), higher odds of inpatient mortality (aOR:1.96, CI: 1.23-3.11, $P = 0.015$), and higher odds of respiratory failure (aOR: 1.35, CI: 1.07-1.70, $P = 0.049$), while for the need for mechanical ventilation, Acute ischemic stroke, AMI, and cardiac arrest, both groups did not differ.

DISCUSSION

To the best of our knowledge, this is the largest study investigating the comorbidities and outcomes of COVID-19 hospitalizations with NAFLD and different levels of obesity. We report the following key points of the study: (1) The overwhelming majority of our study population were whites, even though African Americans have the highest prevalence of obesity; (2) Compared to the overweight and Class I obesity groups, the Class III obesity group were more frequently younger; (3) The overweight group had higher rates of MACCE and in-hospital mortality than all other groups; and (4) Class III obese patients had higher risks of MACCE, inpatient mortality, and respiratory failure than Class I obese patients. However, compared to the overweight group, all other obesity classes had non-significant risks of MACCE, inpatient mortality, and respiratory failure.

In recent times, NAFLD has become a major cause of morbidity and mortality from liver disease. It is the most common cause of chronic liver disease, with a global prevalence of 25% and a 50.4% increase in prevalence in the last three decades[7]. These rates coincide with the increasing pandemic of obesity and type 2 diabetes mellitus (T2DM). Obesity is a global health problem affecting over 2 billion people. BMI is often used to gauge obesity and correlates with cardiovascular diseases, diabetes, hypertension, and certain cancers. The severity of NAFLD also increases with worsening obesity, which is probably why a majority of the patients hospitalized with NAFLD and COVID-19 in our study belonged to the Class III obesity group[8]. There is a rising trend of obesity and overweight in young adults due to increased consumption of calorie-rich foods like fast foods, a lack of exercise, and other socioeconomic and psychological

factors. It was interesting to note that the Class III group had younger individuals but fewer elderly individuals than the overweight group. This is in accordance with the latest NCHS data on obesity[9]. Although the prevalence of obesity among blacks is the highest among any other race, in our study, whites contributed to the majority of the study population. Multiple studies have shown that African American races are protected from NAFLD despite having a higher prevalence of diabetes and obesity, possibly due to fundamental ethnic differences in lipid hemostasis[10]. However, compared to the overweight population, the Class III obesity group more frequently consisted of blacks, coinciding with the most recent national NCHC data on obesity[9].

NAFLD is closely related to metabolic syndrome and hence shares many risk factors with cardiovascular disease (CVD), strengthening the association between the two. There is a strong bidirectional association between the two, which suggests the need for clinical interventions to modify metabolic risk factors like T2DM, dyslipidemia, hypertension, and obesity in this population. NAFLD, obesity, and COVID-19 are highly inflammatory states and are independent risk factors for CVD and associated worse outcomes. NAFLD is associated with a pro-atherogenic lipid profile[11,12] and increased circulating levels of pro-inflammatory cytokines like interleukin (IL)-6[13]. Liver damage is one of the important aspects of COVID-19[14,15]. COVID-19 infection has been linked to elevated levels of serum IL-6, a cytokine with pro-atherogenic properties that can contribute to unfavorable outcomes in individuals with pre-existing coronary artery disease. Furthermore, elevated IL-6 causes a pro-inflammatory state, which has been associated with obesity as well[16]. Logically speaking, patients with worse obesity should have worse outcomes. However, several studies have shown that there is no necessary linear relationship between increasing BMI and worse outcomes. This finding is further highlighted in our study. It was interesting to note that Class III obesity had decreased rates of MACCE, in-patient mortality, and AMI compared to the overweight group but higher rates than the Class I obesity group. Many studies have shown cardiovascular diseases to have better outcomes in overweight and obese patients compared to their leaner counterparts[17], and this phenomenon is termed the “obesity paradox”. This paradox, however, is most likely true for patients with Class 1 obesity[18]. The risk of worse outcomes with increasing obesity follows a U-shaped curve. Class III had worse outcomes than Class I in our study. Although the obesity paradox exists, it may not apply to the morbidly obese[19]. Compared to overweight patients, all other obesity classes had no significant risk for MACCE, inpatient mortality, cardiorespiratory failure. The reasons for this could be multiple. Metabolically “obese” normal-weight individuals (MONW) are those who are on the leaner side but metabolically unhealthy. Current obesity guidelines, which are based on BMI, fail to distinguish between MONW and metabolically healthy obese[20]. This could explain the non-linear relationship between BMI and adverse outcomes. Moreover, leaner individuals have a low pre-test probability and may present at a more advanced stage of the disease, which could lead to an overall worse prognosis.

The NIS helped us achieve nationwide estimates using weighted discharge records. However, there are a few limitations to be considered. These include over- or under-coding errors due to the administrative nature of data collection, no follow-up information, and a lack of medication data. The research uses codes for diagnosis to detect NAFLD, which could result in an estimation of the prevalence of NAFLD, particularly in individuals with less severe forms of the condition. This potential bias in diagnosis might affect how we perceive the severity of NAFLD among obesity categories. Even though multivariable regression analyses have been used to account for factors, there is still a possibility of confounding. There might be unconsidered variables that could affect the reported connections between obesity classes and COVID-19 outcomes. The cross-sectional design of the study makes it challenging to determine a cause-and-effect relationship between NAFLD, different levels of obesity, and COVID-19 outcomes. Moreover, we cannot dismiss the possibility of reverse causation, meaning that COVID-19 impacts outcomes related to obesity. It is important to validate and consider the implications of this study in relation to patient care, taking into account the broader clinical context.

CONCLUSION

In this nationwide analysis, Class III obese NAFLD COVID-19 patients had a greater risk of adverse outcomes than Class I. Using the overweight group as a reference, unfavorable outcomes were not significantly different. Morbid obesity had a greater risk of MACCE regardless of the referent group (overweight or class I obese) compared to overweight NAFLD patients admitted with COVID-19. The presence of morbid obesity consistently amplifies the occurrence of cardiovascular events underscoring the need for personalized care, within this particular high-risk subgroup of COVID-19 population diagnosed with NAFLD.

FOOTNOTES

Author contributions: Srikanth S and Desai R contributed to resources; Srikanth S, Garg V, Subramanian L, Verma J, Klair H, Kavathia S, Teja J, Vasireddy N, Kumar A, Dhanush K, Bodhankar S, Hashmi S, and Desai R contributed to writing-original draft; Garg V, Subramanian L, Verma J, Sharma H, Klair H, Kavathia S, Teja J, Vasireddy N, Kumar A, Dhanush K, Bodhankar S, Hashmi S, Chauhan S, and Desai R contributed to writing - review & editing; Srikanth S and Sharma H, and Desai R contributed to visualization; Sharma H and Chauhan S contributed to supervision; Chauhan S and Desai R contributed to conceptualization, methodology; Desai R contributed to software, formal analysis; All authors have read and approved the final manuscript.

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