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*Retrospective Study*

**Impact of Metabolic Dysfunction-Associated Steatotic Liver Disease on COVID-19 Hospitalizations: A Propensity-Matched Analysis of the United States**

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## Abstract

### BACKGROUND

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Metabolic dysfunction-associated steatotic liver disease (MASLD), formally known as NAFLD (nonalcoholic fatty liver disease), is the most common chronic liver disease in the United States. Patients with MASLD have been reported to be at a higher risk of developing severe Coronavirus Disease 2019 (COVID-19) and death. However, most studies are single-center studies, and nationwide data in the United States is lacking.

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### AIM

We aimed to study the influence of MASLD on COVID-19 hospitalizations during the initial phase of the pandemic.

### METHODS

We retrospectively analyzed the 2020 National Inpatient Sample (NIS) database to identify primary COVID-19 hospitalizations based on an underlying diagnosis of MASLD. A matched comparison cohort of COVID-19 hospitalizations without MASLD was identified from NIS after 1: N propensity score matching based on gender, race, and comorbidities, including hypertension, heart failure, diabetes, and cirrhosis. The

primary outcomes included inpatient mortality, length of stay, and hospitalization costs. Secondary outcomes included the prevalence of systemic complications.

## RESULTS

A total of 2,210 hospitalizations with MASLD were matched to 2,210 hospitalizations without MASLD, with a good comorbidity balance. Overall, there was a higher prevalence of severe disease with more intensive care unit (ICU) admissions (9.5% vs. 7.2%,  $P = 0.007$ ), mechanical ventilation (7.2% vs. 5.7%,  $P = 0.03$ ), and septic shock (5.2% vs. 2.7%,  $P < 0.001$ ) in the MASLD cohort than in the non-MASLD cohort. However, there was no difference in mortality (8.6% vs. 10%,  $P = 0.49$ ), length of stay (5 days vs. 5 days,  $P = 0.25$ ), and hospitalization costs (42,081.5 \$ vs. 38,614\$,  $P = 0.15$ ) between the MASLD and non-MASLD cohorts.

## CONCLUSION

The presence of MAFLD with or without liver cirrhosis was not associated with increased mortality in COVID-19 hospitalizations; however, there was an increased incidence of severe COVID-19 infection. This data (2020) predates the availability of COVID-19 vaccines, and many MASLD patients have since been vaccinated. It will be interesting to see if these trends are present in the subsequent years of the pandemic.

## INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is an ongoing public health emergency with long-term effects on mortality and morbidity. As of November 2023, the World Health Organization has reported over 770 million confirmed cases, resulting in more than 6.9 million deaths worldwide [1]. Although preventive health measures and vaccinations have mitigated the risk of contracting COVID-19 and experiencing adverse outcomes to some extent, individuals with chronic diseases continue to face an elevated likelihood of poor outcomes [2]. Among these, chronic liver disease (CLD), particularly metabolic

dysfunction-associated steatotic liver disease (MASLD), formally known as nonalcoholic fatty liver disease (NAFLD), is presumed to be a high-risk comorbid condition for severe COVID-19 owing to its inherent immune dysregulation [3-5].

MASLD, the hepatic manifestation of metabolic syndrome, comprises a spectrum of diseases ranging from hepatocellular steatosis and steatohepatitis to fibrosis and eventual cirrhosis [6]. MASLD has quickly become the most prevalent etiology of chronic liver disease in the United States [7, 8]. MASLD has been linked to severe infections such as community-acquired pneumonia and a decline in lung function [9, 10].

A recent case-control study revealed that MASLD did not correlate with increased in-hospital mortality rates, ventilatory assistance requirements, ICU admissions, or the total duration of hospital stay [11]. In contrast, other studies have indicated an association between MASLD and severe COVID-19. A recent meta-analysis of 14 studies of 1851 patients with MASLD by Singh *et al* has shed light on the relationship between MASLD and COVID-19, revealing a significantly increased risk of severe COVID-19 outcomes in patients with MASLD. These studies have shown a 1.80-fold increase in the incidence of severe COVID-19 among MASLD patients, although they did not find a significant correlation with COVID-19 mortality [12]. Another meta-analysis by Tao *Et al.* reported an increased risk of severe infection and higher ICU admissions for MASLD patients, with no significant difference in mortality compared with non-MASLD patients [13]. However, these meta-analyses predominantly included studies outside the United States and were often conducted in single-center settings with small sample sizes. These studies also had a high degree of variability owing to differences in the pandemic stage, data availability, sample sizes, study designs, and healthcare settings. This limitation raises concerns about the generalizability of their findings, especially in diverse populations, such as those in the United States.

Considering these contradictions in the literature, utilizing a large national database, our study aimed to provide a more comprehensive and nationally representative analysis of the impact of MASLD on COVID-19 hospitalizations in the United States.

## **MATERIALS AND METHODS**

The present study utilized the National Inpatient Sample (NIS) 2020 database from the United States [14]. Detailed information on NIS's design and sampling methods is available at <https://www.hcup-us.ahrq.gov>. The NIS 2020 utilized the International Classification of Diseases (ICD) 10 coding system to store and report data. We used the "U07.1" ICD 10 code, introduced in March 2020 for COVID-19, to identify hospitalizations with a primary diagnosis (DX1) in the NIS 2020 database [15]. Hospitalizations were excluded if patients were < 18 years old, transferred, or had COVID-19 Listed as a secondary diagnosis. Additionally, hospitalizations were excluded if there was any history of malignant neoplasms or liver and kidney transplant recipients, as these were deemed high-risk conditions that could confound the present analysis.

### **Outcome measures:**

The primary outcomes included inpatient mortality in COVID-19 patients with MASLD (with and without cirrhosis) and resource utilization, including length of stay and hospitalization costs. Secondary outcomes included the prevalence of systemic complications, including acute hypoxic respiratory failure (AHRF), the need for mechanical ventilation (MV), septic shock, and cardiac arrhythmias (including supraventricular tachyarrhythmias (SVT), ventricular tachyarrhythmias (VT), atrial fibrillation/flutter (Afib/Aflutter), and deep venous thromboembolism (DVT).

### **2 Statistical Analysis:**

Statistical analysis was performed using statistical software for data science (STATA 16). We developed matched cohorts (MASLD and non-MASLD) using propensity score matching (PSM) to minimize the effects of hospital- and patient-level confounders. Propensity scores were generated with COVID-19 as the dependent variable and age, sex, cardiac comorbidities (heart failure and valvular dysfunction), hypertension, diabetes mellitus, and compensated and decompensated cirrhosis as independent

variables.<sup>2</sup> A 1:1 matching was performed using the command "clip match" (greedy matching) without replacement. Matched observations had a caliper width of 0.01 for the caliper matching variable (propensity scores). Cases and controls were matched 1:1 on age, sex, and Elixhauser comorbidities, including cardiac comorbidities (heart failure and valvular dysfunction), hypertension, diabetes, and cirrhosis (compensated and decompensated), as previously reported<sup>[16, 17]</sup>.<sup>7</sup> The covariate balance was visualized using the two-way plot shown in Supplementary Figures 1A (before the match) and 1B (after the match).<sup>3</sup> A two-sample Wilcoxon rank-sum (Mann-Whitney) test was used for continuous variables. The Chi-square test was used to compare categorical variables. The significance threshold was set at  $P < 0.05$ . For logistic regression, hierarchical models were designed using unbalanced variables in PSM (none), and outcomes were reported as odds ratios (OR) with 95% confidence intervals (95%CI) and P-values.<sup>3</sup> Patient consent and institutional review were not necessary, as the NIS is a de-identified, hospital-level, third-party database.

## RESULTS

### Baseline characteristics:

Using propensity matching, 2,210<sup>10</sup> hospitalizations with MASLD were matched to 2,210 hospitalizations without MASLD. After matching, there was no significant difference in gender, race, hospital region, or hospital location (Table 1). Additionally, there were no differences in comorbidities, including heart failure ( $P = 1.00$ ), arrhythmias ( $P = 1.00$ ), valvular disease ( $P = 1.00$ ), chronic obstructive pulmonary disease ( $P = 1.00$ ), hypertension ( $P = 1.00$ ), diabetes mellitus type 2 ( $P = 1.00$ ), compensated cirrhosis ( $P = 1.00$ ), and decompensated cirrhosis ( $P = 1.00$ ) (Table 2). The median age at admission was significantly lower in the MASLD group (58 years) than in the non-MASLD group (66 years).<sup>4</sup> The gender distribution was identical in both groups, with the majority of patients being female in both groups. Most patients in both groups were white (58.8%). The regional distribution of hospitalizations showed slight variations that were not statistically significant, and most patients in both groups were admitted to urban



teaching hospitals. Regarding primary payers, Medicare was the most common payer in the non-MASLD group (54.1%), followed by private payers (40.4%) in the MASLD group. In terms of patient disposition, a higher proportion of patients in both groups were discharged to their homes or self-care (66.3% in MASLD and 59.7% in non-MASLD) (Table 1). The list of the remaining comorbid conditions is presented in supplementary table 1.

### **Mortality Outcomes and Subgroup Analyses:**

Overall, there was no difference in mortality between the MASLD and non-MASLD cohorts (8.6% vs. 10%,  $P = 0.49$ ) (OR 0.85, 95%CI 0.53-1.34,  $P = 0.48$ ). Subgroup analysis among patients without liver cirrhosis revealed no difference in mortality between the MASLD and non-MASLD cohorts (7.94% vs. 6.35%,  $P = 0.43$ ) (OR 1.27, 95%CI 0.96-1.67,  $P = 0.08$ ). However, subgroup analysis among patients with liver cirrhosis revealed higher mortality in non-MASLD patients (cirrhosis due to other causes such as alcohol-related liver disease and chronic viral hepatitis) than in the MASLD cohort (18.91% vs. 10.22,  $P = 0.05$ ) (OR 2.03, 95%CI 1.12-4.25,  $P = 0.05$ ).

The prevalence of ICU admission (9.5% vs. 7.2%,  $P = 0.007$ ), mechanical ventilation (7.2% vs. 5.7%,  $P = 0.03$ ), septic shock (5.2% vs. 2.7%,  $P < 0.001$ ), and VT (1.4% vs. 0.5%,  $P < 0.001$ ) was higher in the MASLD cohort than in the non-MASLD cohort. The two cohorts showed no differences in the median hospital stay (5 days vs. 5 days,  $P = 0.25$ ) or hospitalization costs (\$42,081 in the MASLD group and \$38,614 in the non-MASLD group) (Table 1).

## **DISCUSSION**

Our study is among the first in the US to analyze the outcomes of COVID-19 among patients with MASLD at the national level. The results revealed that overall mortality did not significantly differ between the MASLD and non-MASLD cohorts in the initial phase of the pandemic. This trend persisted in subgroup analyses; among patients without liver cirrhosis, mortality rates were similar across both cohorts. However,

among patients with liver cirrhosis, we found higher mortality in the non-MASLD group, which included patients with cirrhosis due to other causes such as chronic viral hepatitis, alcohol, or autoimmune diseases. Notably, the MASLD cohort exhibited a higher prevalence of ICU admission, mechanical ventilation, septic shock, and arrhythmias, indicating more severe disease. However, despite these differences in clinical outcomes, the two cohorts showed no significant differences in median hospital stay or hospitalization costs.

Our results align with those of several previous studies describing the relationship between MASLD and increased severity of COVID-19. Mahmood M. *et al* showed that MASLD was associated with increased severity of COVID-19 pneumonia, irrespective of metabolic syndrome [5]. Another retrospective study by Zheng *et al* showed that obesity is associated with a six-fold higher risk of severe COVID-19 in patients with MASLD. This finding was consistent even after adjusting for factors such as age, gender, smoking habits, diabetes, hypertension, and dyslipidemia. In a study of 202 COVID-19 patients, Ji *et al* discovered a correlation between advanced age, male gender, increased body mass index, the presence of MASLD, and a higher rate of comorbidities with the severity of COVID-19 [18]. There are conflicting reports on whether MAFLD is independently associated with mortality in COVID-19 patients. Kim *et al* performed a retrospective study involving 867 patients and showed that MAFLD was not an independent predictor of mortality in COVID-19 patients (hazard ratio (HR) = 1.08; 95%CI (0.59–1.97);  $P = 0.80$ ) [19]. Lopez-Mendez *et al* reported higher mortality in patients with MASLD and COVID-19 (81.8% vs. 18.2%,  $P = 0.012$ ) [20]. In the initial phase of the COVID-19 pandemic, the available data were predominantly sourced from limited case series and observational studies, offering restricted insights. However, with the escalation of the pandemic, there has been a subsequent emergence of large-scale studies. These studies have contributed to a more robust understanding of the implications of COVID-19 on patients with MASLD. Two recent meta-analyses, Singh *et al* and Tao *et al*, reported increased severity of COVID-19 in patients with MASLD. However, these studies did not find a significant difference in mortality between



MASLD and non-MASLD patients, which is consistent with our results [12, 13]. However, both meta-analyses we examined primarily included studies from outside the United States. They also showed considerable variation because of differences in the pandemic stages, data availability, sample sizes, research methods, and healthcare settings. In contrast, using the largest national-level database in the United States, which encompasses a substantial sample size and diverse demographic coverage, increases the generalizability of our findings. In subgroup analysis, patients without liver cirrhosis showed no significant difference in mortality rates between the MASLD and non-MASLD cohorts. However, among patients with liver cirrhosis in the non-MASLD group (e.g., alcohol-related liver disease and chronic viral hepatitis), there was a higher mortality rate than among those with MASLD-related cirrhosis. This could be explained by previously reported higher rates of complications and mortality among patients with alcohol-related liver diseases in the US during the initial stages of the pandemic [21, 22].

There is ongoing debate regarding the causes of poorer outcomes in certain patients, with various potential factors being studied. One theory suggests that MAFLD aggravates the cytokine storm associated with COVID-19 by promoting the release of inflammatory cytokines from the liver [23, 24]. Conversely, it has been hypothesized that the shift in liver immune cells from pro-inflammatory M1 macrophages to pro-inflammatory M2 macrophages, which are regulatory, weakens innate immunity, thereby worsening the patient's condition [18, 25]. Recent research supports both theories, showing that MAFLD patients exhibit elevated levels of specific inflammatory cytokines, such as interleukin-6 (IL-6), which plays a significant role in severe cases and treatment, and reduced levels of interferon- $\gamma$  (IFN- $\gamma$ ), which is essential for macrophage function [26]. Additionally, the upregulation of proteins facilitating SARS-CoV-2 entry, such as ACE2 and TMPRSS2, particularly in obese patients with MASLD, is another factor [27]. The close association between fatty liver disease and metabolic syndrome suggests that similar harmful pathophysiological processes may contribute [28]. Our results also indicated that COVID-19 patients with MASLD are at a higher risk of cardiac arrhythmias, including VT. Several MASLD-related pathophysiological factors

within the heart result in structural, electrical, and autonomic remodeling, causing arrhythmias [29]. Furthermore, cardiac arrhythmias place patients with COVID-19 at an increased risk of worse outcomes [30].

Regarding resource utilization in US patients with MASLD and COVID-19 hospitalizations, despite a higher total hospitalization cost in the MASLD group than in the non-MASLD group (with costs of \$42,081 and \$38,614, respectively), <sup>16</sup> this difference was not statistically significant ( $P = 0.15$ ). Similarly, the mean length of hospital stay in both groups was similar at 5 days ( $P = 0.25$ ). This apparent lack of significant cost disparity despite the presence of more complications in the MASLD group may be attributed to factors such as standardized treatment protocols and variations in cost calculation methodologies. Moreover, uniform insurance and billing practices and potential unaccounted-for confounding factors may have contributed to the unexpected similarity in hospitalization costs. Further investigations involving larger sample sizes and in-depth analyses are warranted to provide more precise insights. Our findings differ from those of previous studies on MASLD without COVID-19. For instance, Allen *et al* <sup>4</sup> reported annual care costs for MASLD patients with private insurance amounting to \$7,804 for new diagnoses and \$3,789 for long-term management, in contrast to the total annual cost of \$2,298 for matched controls without MASLD, underscoring the economic impact of this condition [31]. Additionally, Adejumo *et al* found differences in length of stay and total healthcare costs between genders, with females experiencing a shorter length of stay (4.55 vs. 4.75 days) and lower total healthcare costs (\$42,848.00 vs. \$47,026.00) compared to males [32]. Unlike these studies, our study provides insights into the economic impact of COVID-19 on patients with MASLD. <sup>9</sup> To the best of our knowledge, this is the first study to provide information on the costs associated with hospitalization for COVID-19 in individuals with MASLD across the US.

While our findings contribute significantly to the current understanding of the relationship between MASLD and COVID-19, they also highlight the need to consider genetic variances as potential modulators of disease severity in patients with MASLD and COVID-19. Research indicates a significant genetic component in the severity of

COVID-19, particularly in patients with MASLD. <sup>4</sup> Genetic polymorphisms, such as PNPLA3 (rs738409), GCKR (rs780094), TM6SF2 (rs58542926), and LYPLAL1 (rs12137855), are associated with increased MAFLD risk and may influence COVID-19 outcomes. These genes are linked to lipid metabolism, glucose regulation, and liver function, which are vital for understanding COVID-19 severity in MAFLD patients with MAFLD. However, studies have reported mixed results regarding the impact of these genetic variants on COVID-19 severity, suggesting a complex relationship between these genetic factors and the disease <sup>[33]</sup>. A bioinformatics and systems biology approach also revealed differentially expressed genes (DEGs) shared between COVID-19 and MAFLD, highlighting the potential common pathogenesis and suggesting therapeutic targets for both conditions <sup>[34]</sup>. Future research should prioritize identifying genetic markers that predict severe COVID-19 in MASLD patients, aiming for more personalized treatment approaches to improve outcomes. Additionally, understanding the genetic interplay between MASLD and COVID-19 will aid in developing public health strategies and novel therapeutics for high-risk groups, ultimately easing healthcare burdens and enhancing patient care.

We acknowledge a few limitations to our study. <sup>5</sup> We utilized the NIS database, which is subject to coding errors due to its dependence on the ICD-10 coding system. Second, the <sup>5</sup> lack of information regarding medications and laboratory and radiological data has limited our ability to determine the specific baseline characteristics of patients with MASLD and individual patient management strategies. However, we used a validated tool for the Chronic Condition Indicator to assess the comorbidity burden of the patients as an essential prognostic factor. We also used PSM to minimize the effects of comorbid conditions in the comparison cohorts <sup>[35]</sup>. <sup>1</sup> Third, the scope of this study was limited to inpatient data and did not include information on the outpatient outcomes of patients with MASLD who had non-severe COVID-19. In addition, the Agency of <sup>5</sup> Healthcare Research and Quality (AHRQ) recommends using an NIS to derive state-level data, owing to the relatively small contribution from several states. If state-level data were obtainable, it could have been helpful for policymakers to make certain

public health efforts in certain states with more patients with MASLD and COVID-19 infection. Instead, we included geographical regions to study the outcome differences across the United States.

<sup>1</sup> Despite some limitations, our study is the first to analyze and summarize national data on the impact of COVID-19-related hospitalizations in patients with MASLD during the early pandemic phase. The broad scope of our study, characterized by a large sample size and diverse range of participants, enhances the generalizability of our results. This diversity is reflected in the data from hospitals of varying sizes (small, medium, and large) and types (both teaching and non-teaching), as well as different settings, including rural and urban areas. Additionally, the variables included in the database allowed us to examine factors such as hospitalization costs, patient income, and other hospital characteristics, which are not often studied in single-center studies.

## CONCLUSION

In conclusion, our study provides valuable insights into the existing and evolving body of evidence on the impact of COVID-19 in patients with MASLD. Our study showed that the presence of MASLD, with or without progression to liver cirrhosis, did not correlate with elevated mortality rates in patients hospitalized due to COVID-19. However, there was a notable increase in the severity of COVID-19 among this demographic group. It is important to note that this data, collected in 2020, predates the widespread distribution of COVID-19 vaccines. Since then, a significant proportion of patients with MASLD have received vaccination. Future analysis is required to determine whether these observed trends persist or are altered in the subsequent phases of the pandemic. This is important since MASLD is the most common cause of Chronic Liver disease in the US. Moreover, to mitigate the impact of COVID-19 on patients with MASLD, it is critical to promote preventive measures, such as vaccination and booster doses, and provide timely treatment with advanced COVID-19 therapies.

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