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Increased Mortality Among Lean Versus Non-Lean Adults With MASLD: A Multicenter Study

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ABSTRACT

Background and Aim: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading cause of chronic liver disease worldwide. Since the adoption of the new terminology from the Delphi Consensus statement, there has not been a large multicenter cohort study of MASLD among lean versus non-lean individuals. This study aims to assess prevalence and incidence outcomes among lean and non-lean individuals with MASLD in a diverse patient cohort.

Methods: We conducted a retrospective multicenter study on patients with MASLD at the Banner and the University of Michigan Health systems from 2012 to 2023. Main outcomes included mortality and incidence of cirrhosis, cardiovascular disease (CVD), major adverse liver outcome (MALO), and cancer.

Results: Seventy-five thousand nine hundred twenty-one patients were included in this cohort with 5% lean individuals. In this cohort, 4.99% were lean, 23.16% were overweight, 28.47% were obesity class I, and 43.39% were obesity class II–III; 58.49% were female; and 66.32% were non-Hispanic White, 22.23% Hispanic, 4.75% Black, 1.71% Native Americans (NAs), and 1.97% Asian/Pacific Islander. After adjusting for confounders, lean individuals had a higher mortality, higher incidence of CVD, and higher incidence of MALO.

Conclusions: Lean individuals have a higher mortality, higher cardiovascular burden, and higher incidence of MALO compared to non-lean individuals. Further studies are warranted to explore lean patients with MASLD, and interventions are needed to decrease mortality in this patient population.

1 | Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) has replaced nonalcoholic fatty liver disease (NAFLD) to include the presence of at least one of five cardiometabolic risk factors after a multi-society Delphi consensus statement [1]. MASLD is the most common cause of chronic liver disease, estimated to impact approximately 30%

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of the global adult population [2] and projected to affect > 50% by 2040 [3], and is a leading cause of liver-related morbidity and mortality [4].

Although MASLD is commonly associated with obesity, it has been increasingly described in individuals with a normal body mass index (BMI) or sometimes referred as "lean MASLD." It is estimated that lean individuals with MASLD is present in up to 20% of individuals with MASLD [5]. Recent studies reported that lean individuals with MASLD may have a higher risk of mortality compared with non-lean individuals [6–8]. In addition, studies have suggested conflicting risks of various comorbidities, such as diabetes mellitus (DM) and cardiovascular disease (CVD), between lean patients with MASLD and non-lean patients with MASLD [6–10]. Unlike NAFLD, MASLD includes cardiometabolic risk factors, and there is limited literature assessing the natural history of MASLD in lean individuals. There lacks a large cohort assessing the incidence of extrahepatic complications of lean compared to non-lean individuals with MASLD [6–10]. The aim of this study is to assess prevalence and incidence of cirrhosis and extrahepatic manifestations among lean vs. non-lean individuals with MASLD in a racially diverse patient population.

2 | Methods

2.1 | Study Population

This retrospective cohort study included individuals diagnosed with MASLD in Banner Health Systems and included primary and tertiary care centers in Arizona, California, Wyoming, Nevada, and Colorado states and individuals diagnosed with MASLD from the University of Michigan Health System from July 2012 to June 2023. Ethical approval for this study was provided by the institutional review board of the Banner University Medical Center – Phoenix and the University of Michigan.

Steatotic liver disease was diagnosed at Banner Health System based on International Classification of Diseases (ICD) codes 9 and 10 (Table S1) and at University of Michigan Health System with natural language processing [8]. We excluded other etiologies of liver diseases ($n = 13\,308$), alcohol use ($n = 12\,341$), age < 18 or age > 80 ($n = 10\,633$), previous history of bariatric surgery ($n = 2672$), baseline cancer diagnosis not including non-melanoma skin cancer ($n = 12\,097$), baseline decompensated cirrhosis including ascites, esophageal varices, or hepatic encephalopathy (HE) ($n = 4020$), missingness of important information obtained before diagnosis of MASLD or within 6 months of index date including race, body mass index (BMI), aspartate aminotransferase, alanine aminotransferase, or platelet ($n = 45\,398$), BMI < 18.5 ($n = 358$), and exclusion of individuals not meeting MASLD criteria ($n = 2078$). MASLD was defined as steatotic liver disease plus 1 out of 5 cardiometabolic risk factors as follows: (1) BMI ≥ 25 kg/m^2 (≥23 kg/m^2 in Asian); (2) presence of type II DM using ICD coding; (3) presence of hypertension by ICD coding; and (4, 5) presence of dyslipidemia [1]. Next, we performed a longitudinal analysis to determine the mortality and incident outcomes in this cohort. Follow-up time was defined as the last clinical encounter date, death, or study end date (June 30, 2023), whichever was earliest. For the longitudinal analysis, we excluded those with a follow-up time of less than 365 days ($n = 19\,797$).

This MASLD cohort was stratified into four subgroups based on average BMI within 6 months of diagnosis. BMI categorization followed World Health Organization guidelines [11, 12], using separate thresholds for Asian and non-Asian populations. Patients were classified as lean, overweight, obesity class I, or obesity class II–III. For non-Asians, the categories were defined as follows: lean (BMI < 25), overweight (BMI 25–29.99), obesity class I (BMI 30–34.99), obesity class II (BMI 35–39.99), and obesity class III (BMI ≥ 40). For Asians, the definitions were as follows: lean (BMI < 23), overweight (BMI 23–27.49), obesity class I (BMI 27.5–32.49), obesity class II (BMI 32.5–37.49), and obesity class III (BMI ≥ 37.5).

2.2 | Statistical Analysis

The baseline characteristics of lean and non-lean groups were compared using the chi-square test for categorical variables and either the *t* test or Mann–Whitney test for continuous variables, as appropriate. Categorical variables, for baseline characteristics, were reported as percentages, while continuous variables were summarized using the median and interquartile range (IQR). To assess the association between disease prevalence and MASLD, multivariable logistic regression was conducted, adjusting for age, sex, ethnicity, smoking status, hypertension, dyslipidemia, and DM. The relationship between MASLD and the prevalence of DM was examined without any adjustment for baseline DM status. The cumulative incidence of death across BMI categories was estimated using Kaplan–Meier survival curves. For this analysis, only patients with follow-up durations exceeding 365 days were included. Time at risk was defined as the period from diagnosis to the event of interest, recorded death, or last follow-up visit. Differences in cumulative incidence of death and events between lean and non-lean individuals were compared using the log-rank test. The impact of BMI category on mortality was further analyzed using Cox proportional hazards models. For other outcomes, the cumulative incidence and the effects of BMI category were evaluated using Fine and Gray competing-risk models, which estimate sub-hazard functions while accounting for competing risks, such as death, that could hinder the occurrence of the primary outcome. In both models, adjustments were made for the same covariates as in the prevalence analysis. Subgroup analyses were performed across different racial groups, as well as among lean versus non-lean individuals, those with no change in BMI category, and smokers versus non-smokers. All analyses were performed using STATA Version 17 (Statacorp, College Station, Texas), and a two-sided *p* value of < 0.05 was considered statistically significant.

3 | Results

3.1 | Cross-Sectional Analysis

Of the 75 921 patients in the cohort, 4.99% were lean, 23.16% were overweight, 28.47% were obesity class I, and 43.39% were obesity class II–III; 58.49% were female. The median age of the cohort was 51 (IQR 38–63). Race was classified as 66.32%

non-Hispanic White, 22.23% Hispanic, 4.75% Black, 1.71% NA, and 1.97% Asian/Pacific Islander. Lean individuals were older, with higher prevalence of CVD including coronary artery disease (CAD), congestive heart failure (CHF), cerebrovascular accident (CVA), and peripheral artery disease (PAD) (Table 1). In multivariable logistic regression analysis, when compared to lean individuals, overweight, obesity class I, and obesity class II–III had a lower prevalence of CVD, CAD, PAD, CVA, CHF, and a higher prevalence of cirrhosis and type II DM (Table 2). The demographic and clinical characteristics of individuals with MASLD at Banner Health and University of Michigan is discussed in Supplementary material and shown in Tables S2 and S3. A subgroup analysis was also completed stratified by racial groups and is discussed in the supplementary table (Table S4).

3.2 | Longitudinal Analysis

Of the 75921 patients in the cohort, 51625 patients had a follow-up time of > 365 days. An analysis was completed for the outcomes of overall mortality, DM, CVD, major adverse cardiac event (MACE), cancer, obesity-related cancer, major adverse liver outcome (MALO), and cirrhosis. The study found that individuals with obesity, particularly those in obesity classes I and II-III, had lower overall mortality compared to lean individuals. However, overweight individuals did not show a significant difference in mortality compared to lean individuals. Overweight and obesity class I individuals had a lower incidence of CVD compared to lean individuals. Overweight and obesity class I individuals had a lower incidence of MACE compared to lean individuals. There was no significant difference in cancer or obesity-related cancer incidence. The incidence of cirrhosis was higher in individuals with obesity class I and obesity class II–III individuals compared to lean individuals. MALO incidence was lower in overweight and obesity class I individuals compared to lean individuals. Individuals with obesity classes I and II–III had a higher incidence of DM compared to lean individuals (Table 3). A subgroup analysis was also completed stratified by racial groups and is discussed in the supplementary table (Table S5).

4 | Discussion

This multicenter cohort of over 75000 individuals with MASLD compared BMI and racial groups followed for up to 10 years, with over 5% of the individuals with normal BMI. The lean individuals had an increased prevalence of any CVD, CAD, PAD, CVA but lower incidence of cirrhosis and DM. Lean individuals with MASLD had significantly higher overall mortality when compared with non-lean individuals.

There are several studies that have shown worse outcomes in lean individuals with MASLD. Wijarnpreecha et al. demonstrated a higher mortality among lean patients with MASLD despite a lower incidence of cirrhosis and DM [8]. Aboona et al. also described a higher incidence of mortality in their cohort, mostly driven by a higher incidence in MALO. Cirrhosis incidence was not significantly different between lean and non-lean individuals [13]. Interestingly, in our study, which defines MASLD according to the new cardiometabolic criteria, lean individuals have increased mortality and increased incidence of CVD, MACE, and MALO with a lower incidence of cirrhosis. It is possible that the driver of mortality in this cohort could be driven by rapid decompensation of liver disease likely secondary to sarcopenia and/or due to worsening cardiovascular outcomes. Despite having fewer metabolic comorbidities, these patients often suffer from more severe liver disease and are more susceptible to MALO, which significantly impacts overall mortality [14]. Our findings align with those from Wakabayashi et al., who conducted a large-scale analysis of over 2.9 million individuals and found that lean MASLD patients had a comparable risk of liver-related events, but a lower risk of cardiovascular events compared to non-lean MASLD patients [15]. This contrasts with our cohort, where lean individuals exhibited a higher incidence of both MALO and CVD. These differences may reflect population heterogeneity, including racial/ethnic variation and differences in healthcare settings, reinforcing the need for individualized risk stratification in MASLD management.

Sarcopenia, characterized by the loss of skeletal muscle mass and function, is prevalent in patients with cirrhosis and is strongly associated with poor clinical outcomes [16–18]. Lean patients with cirrhosis tend to decompensate faster than their non-lean counterparts. This could be due to the "sarcopenic effect," where the presence of sarcopenia exacerbates the clinical course of liver disease [17]. Patients with sarcopenia experience more liver-related complications, including ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, and gastrointestinal varices, which contribute to increased mortality [19]. Sarcopenia also predicts hepatic decompensation, infection risk, and poorer outcomes, including higher waitlist and post-transplant mortality [17]. Malnutrition and frailty, often seen in lean cirrhotic patients, further compromise their ability to withstand the physiological stresses associated with cirrhosis [18]. A recent meta-analysis investigated long-term outcomes in lean versus non-lean individuals with MASLD and showed lean individuals had increased overall mortality compared to non-lean individuals. However, there was no significant difference in MALO between the two groups [20]. The increased mortality exhibited in this cohort can be explained by the sarcopenic effect. Lean individuals had a lower incidence of cirrhosis than non-lean individuals but had a significantly higher risk of MALO. It can be speculated that when lean individuals develop cirrhosis their risk of decompensation is higher than in their non-lean counterparts. Lean patients with MASLD also face a higher risk of liver-related mortality compared to their non-lean counterparts, indicating that lean patients with MASLD is a serious condition that requires vigilant monitoring and management [16]. These individuals often experience more severe liver disease, including advanced fibrosis, and have poorer clinical outcomes with increased MALO and overall mortality, despite having fewer metabolic comorbidities [21]. However, it should be noted that Ha et al. reported increased liver-related mortality among lean individuals but no significant difference in other outcomes [16]. For instance, Danpanichkul et al.'s study was hospital-based, which might include patients with more advanced disease stages, whereas Ha et al.'s systematic review could have encompassed a broader range of studies, including community-based cohorts. The discrepancies between these studies may stem from differences in study design, patient populations, and definitions of outcomes. These variations highlight

TABLE 1 | Baseline characteristics, laboratory values, and prevalence of diseases among persons with MASLD[a].

Characteristics	Lean ($n = 3790$)	Non-lean ($n = 72131$)			p Value (lean vs non-lean)
		Overweight ($n = 17582$)	Obesity class 1 ($n = 21613$)	Obesity class 2–3 ($n = 32936$)	
Age, years (median, IQR)	63 (52–72)	55 (42–67)	53 (40–64)	47 (35–58)	< 0.01
Sex (male, %)	38.28	47.49	45.98	35.76	< 0.01
Race, %					
Asian/Pacific Islander	3.85	2.93	2.12	1.05	< 0.01
Black	5.01	3.77	4.12	5.67	0.443
Non-Hispanic White	72.19	67.93	66.77	64.50	< 0.01
Hispanic	14.30	20.60	22.74	23.67	< 0.01
Native American/Alaskan	1.29	1.33	1.37	2.20	0.04
Other/Unknown	3.35	3.44	2.89	2.91	0.261
Smoking, %					
Never	57.65	65.32	65.75	65.37	< 0.01
Current/former	42.35	34.68	34.25	34.63	
ALT (U/L)	27 (18–49)	34 (22–59)	38 (24–64)	37 (24–63)	< 0.01
AST (U/L)	25 (18–41)	27 (20–42)	28 (20–43)	28 (20–28)	< 0.01
Platelet (K/μL)	240 (192–299)	241 (197–293)	245 (200–295)	256 (210–308)	< 0.01
Cholesterol					
LDL	92 (65–122)	98 (72–124)	98 (73–124)	96 (73–120)	< 0.01
HDL	48 (37–62)	44 (36–54)	35 (42–51)	41 (34–49)	< 0.01
Triglyceride	124 (88–179)	146 (102–213)	155 (110–225)	152 (109–222)	< 0.01
HbA1c	6.1 (5.6–7.8)	6 (5.6–7.3)	6.1 (5.6–7.55)	6.3 (5.7–7.8)	0.19
Cirrhosis	3.67	3.36	3.71	4.14	
Cardiovascular diseases, %					
Coronary artery disease	31.79	20.17	19.95	17.54	< 0.01
Congestive heart failure	17.94	9.63	9.87	12.63	< 0.01
Cerebrovascular accident	16.83	8.43	7.75	6.19	< 0.01
Peripheral arterial disease	17.36	9.96	8.55	6.33	< 0.01
Any cardiovascular disease	43.48	29.74	28.45	26.96	< 0.01
Metabolic diseases, %					
Diabetes mellitus	43.59	29.84	35.87	44.63	< 0.01
Hypertension	52.96	32.74	34.50	37.52	< 0.01
Dyslipidemia	74.64	49.5	50.92	48.01	< 0.01
CKD (stage 3–5), %	13.40	8.88	8.99	8.43	< 0.01

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD, chronic kidney disease; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein.
[a]Data are expressed as median (interquartile range) for continuous variables or number (percentage) for categorical variables.

the importance of considering study settings and population characteristics when interpreting outcomes in MASLD [16, 20]. Emerging evidence suggests that unrecognized body fat accumulation, particularly visceral adiposity, may drive disease progression in lean individuals with MASLD. This is true even in the absence of obesity. For instance, Miwa et al. demonstrated that fat mass index (FMI), rather than BMI alone, was strongly associated with MASLD and NAFLD in non-obese Japanese

TABLE 2 | Logistic regression analysis for factors associated with prevalence of cardiovascular disease, cirrhosis, chronic kidney disease, and type II diabetes mellitus by BMI category[a].

	Any cardiovascular disease		Coronary artery disease		Peripheral artery disease		Cerebrovascular accident		Congestive heart failure		Cirrhosis		Chronic kidney disease stage ≥ 3		Type II DM	
BMI category	OR (95% CI)[a]	*p* Value	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value	OR (95% CI)[b]	*p* Value
Lean	Referent		Referent		Referent		Referent		Referent		Referent		Referent		Referent	
Overweight	0.88 (0.80–0.97)	< 0.01	0.88 (0.80–0.97)	< 0.01	0.82 (0.74–0.91)	< 0.01	0.69 (0.61–0.76)	< 0.01	0.74 (0.67–0.83)	< 0.01	1.22 (1.01–1.47)	< 0.01	0.96 (0.86–1.08)	0.53	0.86 (0.79–0.93)	< 0.01
Obesity class I	0.86 (0.79–0.95)	< 0.01	0.86 (0.79–0.95)	< 0.01	0.72 (0.65–0.80)	< 0.01	0.61 (0.55–0.68)	< 0.01	0.75 (0.67–0.83)	< 0.01	1.35 (1.12–1.63)	< 0.01	1.06 (0.94–1.18)	0.35	1.17 (1.09–1.27)	< 0.01
Obesity class II—III	0.86 (0.78–0.94)	< 0.01	0.86 (0.78–0.94)	< 0.01	0.63 (0.57–0.70)	< 0.01	0.52 (0.55–0.68)	< 0.01	1.14 (1.03–1.26)	0.01	1.58 (1.31–1.89)	< 0.01	1.17 (1.05–1.30)	< 0.01	1.95 (1.81–2.10)	< 0.01
Non-Lean[c]	0.87 (0.81–0.94)	< 0.01	0.87 (0.80–0.94)	< 0.01	0.72 (0.65–0.79)	< 0.01	0.60 (0.54–0.66)	< 0.01	0.89 (0.81–0.98)	0.02	1.40 (1.17–1.67)	< 0.01	1.07 (0.96–1.18)	0.22	1.32 (1.23–1.42)	< 0.01

Abbreviations: CI, confidence interval; OR, odds ratio.
[a]OR adjusted for age, sex, race, smoking status, hypertension, dyslipidemia, DM, and aspirin and statin use.
[b]For type II DM, OR was adjusted with the same confounders excluding DM.
[c]Non-lean analysis was performed using a different model.

TABLE 3 | Competing risk analysis for death and incidence of diseases by BMI category[a].

	Death[b]		Any cardiovascular diseases		Cirrhosis		MALO[c]		Type II diabetes mellitus[d]		Obesity-related cancer		Any cancer		MACE[e]	
BMI category	HR (95% CI)[a]	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Lean	**Referent**		**Referent**		**Referent**		**Referent**		**Referent**		**Referent**		**Referent**		**Referent**	
Overweight	**0.52 (0.42–0.65)**	**<0.01**	**0.85 (0.75–0.97)**	**0.01**	1.15 (0.82–1.61)	0.43	**0.74 (0.56–0.98)**	**0.04**	1.08 (0.93–1.26)	0.31	0.93 (0.73–1.19)	0.58	0.97 (0.81–1.16)	0.76	**0.83 (0.74–0.94)**	**< 0.01**
Obesity class 1	**0.47 (0.38–0.58)**	**< 0.01**	**0.82 (0.73–0.93)**	**< 0.01**	**1.47 (1.05–2.04)**	**0.02**	**0.75 (0.57–0.99)**	**0.045**	**1.65 (1.42–1.91)**	**< 0.01**	0.89 (0.70–1.14)	0.36	0.83 (0.70–1.00)	0.05	**0.82 (0.73–0.92)**	**< 0.01**
Obesity class 2–3	**0.56 (0.46–0.69)**	**< 0.01**	0.94 (0.84–1.07)	0.36	**1.69 (1.22–2.35)**	**< 0.01**	0.84 (0.64–1.11)	0.22	**2.49 (2.15–2.87)**	**< 0.01**	1.08 (0.85–1.36)	0.52	0.92 (0.77–1.10)	0.35	0.93 (0.83–1.05)	0.24

Abbreviations: CI, confidence interval; HR, hazard ratio; MALO, major adverse liver outcome; MACE, major adverse cardiac event.
[a]HR was adjusted for age, sex, race, smoking status, alcohol consumption, type II diabetes mellitus, hypertension, dyslipidemia, and use of aspirin and statin.
[b]Cox proportional hazards model was performed for death analysis.
[c]MALO were defined as the incidence of hepatic encephalopathy, ascites, hepatocellular carcinoma, or variceal bleeding.
[d]For type II diabetes mellitus, HR was adjusted with the same confounders[a] excluding type II diabetes mellitus.
[e]MACE is defined as the incidence of coronary artery disease, all-cause mortality, congestive heart failure, or cerebrovascular accident.

male adults. This partly could be due to an intrinsic limited capacity to store lipids within adipose tissue [22]. This underscores the importance of body composition beyond BMI in assessing risk, as lean individuals may harbor hidden adiposity that contributes to metabolic dysfunction and adverse outcomes.

The increased CVD mortality in lean patients with MASLD could be attributed to several factors. Lean individuals had a higher incidence of CVD. The American Gastroenterological Association stresses the importance of risk stratification for lean patients with MASLD using noninvasive tests to identify those at the highest risk of disease progression [23]. The paradoxical increase in CVD among lean patients with MASLD underscores the need for comprehensive cardiovascular risk assessment and management in this population. Despite having a more benign metabolic profile, lean individuals with MASLD exhibit higher rates of cardiovascular events, suggesting that traditional cardiovascular risk factors may not fully capture the risk in this group [8]. In our study, lean individuals had a significantly higher incidence of MACE compared to non-lean individuals.

This study has several strengths. First, this is the largest multicenter MASLD cohort from West and Midwest region of the United States thus far, with over 75 000 individuals, of which 5% were lean. Second, this is a multicenter study that can be generalizable to the general population due to racially diverse population represented in the database. Lean individuals with MASLD are a unique cohort in which these individuals meet MASLD criteria based on cardiometabolic risk factors per the new nomenclature guidance [1]. This cohort shows the importance of risk stratification in this unique MASLD group. Access to history and laboratory data allows the ability to control for a multitude of confounding factors such as age, sex, race, smoking status, and metabolic risk factors such as hypertension and hyperlipidemia.

This study also has limitations. First, the diagnosis of MASLD, CVD, and metabolic diseases, as well as cirrhosis, MACE, and MALO, were mainly based on ICD codes (except the University of Michigan cohort that has a natural language processing algorithm to confirm MASLD diagnosis) which may not be accurate, although this approach is widely used in other large cohort studies. However, we found that ICD code for MASLD was 99% accurate and other comorbidities were 80–99% accurate in our cohort, with 150 medical records reviewed [8, 13]. Second, this is a retrospective cohort analysis in which data is historical and cannot be confirmed as accurate at the time of the event. Third, we acknowledge that unmeasured confounders can exist in our cohort, such as diet, physical activity, body composition, and genetic variants, which were not available in our study. Lastly, we do not have causes of death data available. Therefore, we cannot determine the specific causes of death and the differences among BMI categories from this study.

In conclusion, this study highlights the complexity of MASLD within lean individuals. Lean patients had an increased mortality likely due to several factors such as sarcopenia, higher incidence of MALO, and higher incidence of CVD compared to non-lean patients. The findings underscore the importance of early identification and management of sarcopenia and CVD risk in lean patients with MASLD to improve their clinical outcomes and emphasize the prevention of MALO to decrease mortality in this population. In addition, NAs had an increased mortality likely driven by increased incidence in MALO and MACE. Hispanics also had a higher incidence of MALO. Further research is needed to elucidate the underlying mechanisms driving these associations and to develop targeted interventions to reduce morbidity and mortality, stratify CVD risk, and understand the pathophysiology in lean patients with MASLD, and recognition of racial disparities is essential to helping improve patient outcomes.

Ethics Statement

Ethical approval for this study was provided by the institutional review board of the Banner University Medical Center – Phoenix and the University of Michigan.

Conflicts of Interest

VLC received research funding from AstraZeneca and KOWA (to University of Michigan).

Data Availability Statement

Data available on request due to privacy/ethical restrictions.

References

1. M. E. Rinella, J. V. Lazarus, V. Ratziu, et al., "A Multisociety Delphi Consensus Statement on New Fatty Liver Disease Nomenclature," *Journal of Hepatology* 79 (2023): 1542–1556.

2. Z. M. Younossi, P. Golabi, J. M. Paik, A. Henry, C. Van Dongen, and L. Henry, "The Global Epidemiology of Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Steatohepatitis (NASH): A Systematic Review," *Hepatology* 77 (2023): 1335–1347.

3. M. H. Le, Y. H. Yeo, B. Zou, et al., "Forecasted 2040 Global Prevalence of Nonalcoholic Fatty Liver Disease Using Hierarchical Bayesian Approach," *Clinical and Molecular Hepatology* 28 (2022): 841–850.

4. W. K. Chan, K. H. Chuah, R. B. Rajaram, L. L. Lim, J. Ratnasingam, and S. R. Vethakkan, "Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): A State-Of-The-Art Review," *Journal of Obesity & Metabolic Syndrome* 32 (2023): 197–213.

5. Q. Ye, B. Zou, Y. H. Yeo, et al., "Global Prevalence, Incidence, and Outcomes of Non-Obese or Lean Non-Alcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis," *Lancet Gastroenterology & Hepatology* 5 (2020): 739–752.

6. S. Huang, Y. Bao, N. Zhang, R. Niu, and L. Tian, "Long-Term Outcomes in Lean and Non-lean NAFLD Patients: A Systematic Review and Meta-Analysis," *Endocrine* 85, no. 1 (2023): 134–141, https://doi.org/10.1007/s12020-023-03351-5.

7. E. M. Weinberg, H. N. Trinh, R. J. Firpi, et al., "Lean Americans With Nonalcoholic Fatty Liver Disease Have Lower Rates of Cirrhosis and Comorbid Diseases," *Clinical Gastroenterology and Hepatology* 19 (2021): 996–1008 e6.

8. K. Wijarnpreecha, F. Li, S. K. Lundin, et al., "Higher Mortality Among Lean Patients With Non-Alcoholic Fatty Liver Disease Despite Fewer Metabolic Comorbidities," *Alimentary Pharmacology & Therapeutics* 57 (2023): 1014–1027.

9. O. T. Ahmed, T. Gidener, K. C. Mara, J. J. Larson, T. M. Therneau, and A. M. Allen, "Natural History of Nonalcoholic Fatty Liver Disease with Normal Body Mass Index: A Population-Based Study," *Clinical Gastroenterology and Hepatology* 20 (2022): 1374–1381, e6.

10. J. C. Leung, T. C. Loong, J. L. Wei, et al., "Histological Severity and Clinical Outcomes of Nonalcoholic Fatty Liver Disease in Nonobese

Patients," *Hepatology* 65, no. 1 (2017): 54–64, https://doi.org/10.1002/hep.28697.

11. Obesity: Preventing and Managing the Global Epidemic. Report of a WHO Consultation. World Health Organization Technical Report Series 2000; 894: i-xii, 1-253.

12. W. H. O. E. Consultation, "Appropriate Body-Mass Index for Asian Populations and Its Implications for Policy and Intervention Strategies," *Lancet* 363 (2004): 157–163.

13. M. B. Aboona, C. Faulkner, P. Rangan, et al., "Disparities Among Ethnic Groups in Mortality and Outcomes Among Adults With MASLD: A Multicenter Study," *Liver International* 44 (2024): 1316–1328.

14. A. L. Fracanzani, S. Petta, R. Lombardi, et al., "Liver and Cardiovascular Damage in Patients With Lean Nonalcoholic Fatty Liver Disease, and Association With Visceral Obesity," *Clinical Gastroenterology and Hepatology* 15 (2017): 1604–1611. e1.

15. S. I. Wakabayashi, N. Tamaki, T. Kimura, T. Umemura, M. Kurosaki, and N. Izumi, "Natural History of Lean and Non-Lean Metabolic Dysfunction-Associated Steatotic Liver Disease," *Journal of Gastroenterology* 59 (2024): 494–503.

16. J. Ha, S. Y. Yim, and R. Karagozian, "Mortality and Liver-Related Events in Lean Versus Non-Lean Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis," *Clinical Gastroenterology and Hepatology* 21 (2023): 2496–2507. e5.

17. J. C. Lai, P. Tandon, W. Bernal, et al., "Malnutrition, Frailty, and Sarcopenia in Patients With Cirrhosis: 2021 Practice Guidance by the American Association for the Study of Liver Diseases," *Hepatology* 74 (2021): 1611–1644.

18. P. Tandon, A. J. Montano-Loza, J. C. Lai, S. Dasarathy, and M. Merli, "Sarcopenia and Frailty in Decompensated Cirrhosis," *Journal of Hepatology* 75, no. Suppl 1 (2021): S147–S162.

19. X. Zeng, Z. W. Shi, J. J. Yu, et al., "Sarcopenia as a Prognostic Predictor of Liver Cirrhosis: A Multicentre Study in China," *Journal of Cachexia, Sarcopenia and Muscle* 12 (2021): 1948–1958.

20. P. Danpanichkul, K. Suparan, V. Prasitsumrit, A. Ahmed, K. Wijarnpreecha, and D. Kim, "Long-Term Outcomes and Risk Modifiers of MASLD Between Lean and Non-Lean Populations," *Clinical and Molecular Hepatology* 31 (2024): 74–89.

21. A. Feldman, B. Wernly, G. Strebinger, et al., "Liver-Related Mortality Is Increased in Lean Subjects With Non-Alcoholic Fatty Liver Disease Compared to Overweight and Obese Subjects," *Journal of Gastrointestinal and Liver Diseases* 30 (2021): 366–373.

22. T. Miwa, C. Francisque, S. Tajirika, et al., "Impact of Body fat Accumulation on Metabolic Dysfunction-Associated Fatty Liver Disease and Nonalcoholic Fatty Liver Disease in Japanese Male Young Adults," *Hepatology Research* 53 (2023): 691–700.

23. M. T. Long, M. Noureddin, and J. K. Lim, "AGA Clinical Practice Update: Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Lean Individuals: Expert Review," *Gastroenterology* 163 (2022): 764–774. e1.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.