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Mortality outcomes in individuals with MASLD *versus* MASLD and increased alcohol intake

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Abstract

Background and Aim: Metabolic dysfunction-associated steatotic liver disease (MASLD) has become a leading cause of chronic liver disease worldwide. A new entity termed MetALD has also been described and is defined as individuals with MASLD and increased alcohol intake. However, the natural history of MetALD compared with MASLD is unknown. We aimed to compare longitudinal outcomes in patients with MASLD *versus* MetALD.

Methods: This study was performed using data from the National Health and Nutrition Examination Survey from 2011 to 2018. MASLD patients (defined by the United States Fatty Liver Index > 30) who met cardiometabolic criteria including body mass index (BMI) > 25 (BMI > 23 in Asians), hypertension, diabetes mellitus, dyslipidemia, and hypertriglyceridemia were included. MetALD was defined as MASLD with increased alcohol intake (3–6 standard drinks per day in males; 2–5 standard drinks per day in females). A comparison of overall, cardiovascular, cancer-related, and other causes of mortality in patients with MASLD *versus* MetALD was performed.

Results: A total of 2838 individuals with MASLD and 2557 individuals with MetALD were included with a median follow-up time of 56 months. MetALD patients were at increased risk of cancer-related mortality compared with patients with MASLD (hazard ratio 1.32; 95% confidence interval 1.14–1.53; $P < 0.01$). However, there was no significant difference in overall, cardiovascular, and other causes of mortality.

Conclusions: Patients with MetALD were at higher risk for cancer-related mortality than MASLD. Close attention to regular cancer surveillance and accurate classification of alcohol consumption in individuals with diagnosed MASLD is warranted to help improve patient care and outcome.

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Introduction

Steatotic liver disease, more specifically metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD), has become a leading cause of chronic liver disease worldwide.[1] MASLD encompasses both steatosis and the presence of one of five cardiometabolic risk factors (increased body mass index [BMI], hypertension, diabetes mellitus (DM), dyslipidemia, or hypertriglyceridemia).[2,3] The global prevalence of MASLD is estimated to be 30% globally,[4] and its prevalence continues to rise rapidly in line with the global obesity epidemic.[5–8]

A new entity termed MetALD has also been described in recent literature and is defined as individuals with MASLD with increased alcohol intake (140–350 g/week or 2–5 standard drinks per day for females and 210–420 g/week or 3–6 standard drinks per day for males).[9] Previous studies in patients with metabolic dysfunction-associated fatty liver disease (MAFLD)[10,11] have shown that alcohol consumption is independently associated with an increased probability of advanced fibrosis and increased mortality risk.[12–14] In addition, there is a trend of increase in the prevalence of alcohol-associated liver disease globally.[15–18] It is known that many chronic liver disease conditions are from the activation of pro-inflammatory cascades within the liver. Studies have concluded that liver fibrosis is characterized by the accumulation of extracellular matrix proteins, which may be due to inflammasome activation.[19] Furthermore, binging of alcohol can promote liver injury and steatosis, especially in individuals with MASH. One proposed mechanism is through the NLRP3 inflammasome activation, described by Babuta et al.[20] However, the effects of alcohol consumption on long-term survival outcomes in patients with MASLD, defined using the new cardiometabolic criteria, have yet to be described in the existing literature. Furthermore, there is limited literature on the effects of alcohol use on patients with steatotic liver disease (SLD). Hence, we aimed to compare the long-term outcomes of patients with MASLD *versus* MetALD using data from a large national cohort.

Methods

Study population. This study was performed within the National Health and Nutrition Examination Survey (NHANES). NHANES was designed to study participants' health in the United States. The NHANES database includes extensive data collected by patient interviews, physical examinations, and clinical tests. Detailed information regarding the procedures used to create the NHANES database is described elsewhere.[21] Data on mortality were obtained by linking the NHANES data to death certificates from the National Death Index. Ethics approval by the Institutional Review Board was exempted due to the anonymous nature of the data made publicly available by the National Centre for Health Statistics. Baseline characteristics including age, gender, ethnicity, BMI, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol, triglyceride, glycated hemoglobin, aspartate aminotransferase, alanine aminotransferase, and past medical history (DM, hypertension, hypertriglyceridemia, dyslipidemia, and smoking) were collected. Information on the outcomes of MASLD and MetALD including all-cause mortality, cardiovascular mortality, cancer-related mortality, and other causes of mortality were also collected. The study was conducted in accordance with the Declaration of Helsinki and is exempt from IRB review as no confidential patient information was involved.

Definitions. Individuals were obtained from the years 2011 to 2018 of the NHANES database. Steatosis was defined according to the United States Fatty Liver Index (US-FLI) of greater than or equal to 30.[22–25] MASLD was defined as the presence of hepatic steatosis with metabolic dysregulation as proposed by experts from the international expert panel.[10] The proposed criteria defined MASLD as the presence of steatosis with one or more of the following cardiometabolic risk factors such as (i) overweight or obesity (i.e., BMI 25 kg/m^2 in non-Asians and BMI 23 kg/m^2 in Asians) or waist circumference $\geq$ 94 cm in non-Asians ($\geq$ 90 cm in Asians) in men and $\geq$ 80 cm in Asian and non-Asian women (central obesity), (ii) type 2 DM or treatment for type 2 DM or increased insulin resistance defined as hemoglobin A1C (HbA1C) $\geq$ 5.7%, fasting serum glucose of $\geq$ 5.6 mmol/L or 2-h post-load glucose levels $\geq$ 7.8 mmol/L, (iii) blood pressure $\geq$ 130/85 mm Hg or receiving antihypertensives, (iv) plasma triglycerides $\geq$ 1.7 mmol/L or receiving specific drug treatment, (v) plasma high-density lipoprotein $<$ 1.03 mmol/L in men, and $<$ 1.29 mmol/L in women. Overweight patients were defined as BMI $\geq$ 25.0 kg/m^2 for Caucasians and BMI $\geq$ 23.0 kg/m^2 for Asians whereas obese patients were defined as BMI $\geq$ 30.0 kg/m^2 for Caucasians and BMI $\geq$ 27.5 kg/m^2 for Asians. The definition for DM was glycohemoglobin $\geq$ 6.5%, fasting plasma glucose $\geq$ 7 mmol/L, self-reported DM or the use of anti-DM medications. Patients with positive Hepatitis B surface antigen, hepatitis C antibody or Hepatitis C RNA were excluded from the cohort. Next, individuals were stratified into pure MASLD or MetALD based on alcohol consumption. Men who have 3–6 drinks per day on average and females who have 2–5 drinks per day on average were defined as MetALD.[26,27] Individuals with significant alcohol consumption defined as alcohol-related liver disease ($>$ 6 drinks per day in males and $>$ 5 drinks per day in females) were excluded from this cohort. Data on mortality were obtained by linking the NHANES data to death certificates from the National Death Index. Cardiovascular disease (CVD)-related mortality was defined as mortality with diseases of the heart as the primary cause using ICD codes I00–I78 while cancer-related mortality was defined as mortality caused by malignant neoplasms using ICD codes C00–C97.

Statistical analysis. Baseline characteristics between MASLD and MetALD groups were compared using the χ^2 test for categorical variables and the Mann–Whitney test for continuous variables. Categorical variables were reported as percentages, and continuous variables were reported as median and interquartile range (IQR). A Cox proportional hazards regression model for hazard ratios (HRs) was utilized to assess overall mortality, while a multivariate competing risk analysis with Fine-Gray subdistribution HR (sHR) was used to evaluate CVD-related mortality, cancer-related mortality, and other causes of mortality. All-cause mortality, cardiovascular mortality, cancer-related mortality, and other causes of mortality were further classified using Kaplan–Meier curve analysis. All multivariate regression models

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adjusted for age, sex, race, BMI status, smoking status, hypertension, hyperlipidemia, insulin resistance, and fibrosis-4 (FIB-4) score. All analyses were performed using STATA® Version 18 (StataCorp, College Station, TX, USA). A two-sided *P* value of < 0.05 was considered statistically significant.

Results

Comparison of baseline characteristics. Of the 5395 individuals in the cohort, 52.60% were MASLD and 47.40% were MetALD, and 56.87% were male. The median age of the cohort was 50 years (IQR: 36–62). Race was classified as 40.74% non-Hispanic White, 27.03% Hispanic, 22.61% Black, 5.71% Asian, and 3.91% other. MASLD patients were older (55 *vs* 45, $P < 0.01$), and had higher prevalence of metabolic components, including hypertension (66% *vs* 57.25%, $P = <0.01$), dyslipidemia (63.64% *vs* 55.92%, $P = <0.01$), hypertriglyceridemia (70.40% *vs* 63.71%, $P = <0.01$), insulin resistance (94.36% *vs* 91.67%, $P = <0.01$) and diabetes mellitus (53.84% *vs* 46.16% $P = <0.01$) than MetALD (Table 1).

Comparison of survival outcomes. The median follow-up time was 56 months (IQR = 34–81). A total of 253 patients died, including 149 MASLD and 94 MetALD with incidence per 1000 person-years 11.21 *versus* 7.61 ($P = <0.01$) for all-cause mortality, 3.69 *versus* 1.94 ($P = <0.01$) for cardiovascular mortality, 2.93 *versus* 1.86 ($P = 0.08$) for cancer-related mortality, and 4.59 *versus* 3.81 ($P = 0.34$) for other causes of mortality, respectively. In univariate analysis, MetALD had a lower risk of all-cause mortality (HR 0.68; 95% confidence interval [CI] 0.52–0.88; $P < 0.01$, cancer-related mortality (HR 0.64; 95% CI 0.54–0.74; $P < 0.01$) and other causes of mortality (HR 0.83; 95% CI 0.73–0.95; $P < 0.01$), but no difference in cardiovascular mortality (HR 0.53; 95% CI 0.30–0.99; $P = 0.05$). However, in multivariable logistic regression analysis after adjusting for confounders including age, sex, race, BMI status, smoking status, hypertension, hyperlipidemia, insulin resistance, and FIB-4 score, patients with MetALD had significantly increased cancer-related mortality compared with patients with MASLD (HR 1.32; 95% CI 1.14–1.53; $P < 0.01$). There was no significant difference between all-cause mortality (HR 1.21; 95% CI 0.91–1.61, $P = 0.19$), CVD (HR 1.09; 95% CI 0.52–2.30, $P = 0.83$), and other causes of mortality (HR 1.27; 95% CI 0.89–1.81, $P = 0.19$) (Fig. 1). Survival analysis of overall mortality and competing risk analysis of cardiovascular mortality, cancer-related mortality, and other causes of mortality stratified by MASLD and MetALD are illustrated in Figure 2.

Subgroup analysis of mortality by FIB-4 score. Subgroup analyses were performed for patients with SLD stratified by FIB-4 score. A subgroup analysis was performed in patients with MASLD and no alcohol use which showed that patients with FIB-4 > 2.67 had a higher risk for all-cause mortality (HR 2.26, 95% CI 1.23–4.18, $P = < 0.01$), cardiovascular mortality (HR 2.10, 95% CI 1.42–3.11, $P = < 0.01$), and other causes of mortality (HR 4.95, 95% CI 2.75–8.90, $P = < 0.01$) compared with those with FIB-4 ≤ 2.67, there was no significant difference cancer-related mortality (HR 0.35, 95% CI 0.06–1.95, $P = 0.23$) compare with MASLD with FIB-4 ≤ 2.67 (Table 2).

Furthermore, a subgroup analysis was performed in patients with MetALD, which showed those with FIB-4 > 2.67 had an increased risk of all-cause mortality (HR 2.95, 95% CI 1.46–6.00, $P = <0.01$), cardiovascular mortality (HR 2.68, 95% CI 1.18–6.07, $P = 0.02$), and cancer-related mortality (HR 5.08, 95% CI 1.08–23.96, $P = 0.04$). There was no significant difference in other causes of mortality (HR 1.97, 95% CI 0.41–9.39, $P = 0.40$) between FIB-4 categories in MetALD (Table 2). Survival analysis of overall mortality and competing risk analysis of cardiovascular mortality, cancer-related mortality, and other causes of mortality stratified by FIB-4 category are illustrated in Figure S1.

Subgroup analysis of mortality by age. Subgroup analyses were performed for patients with SLD by age. Older individuals had a higher risk for all-cause mortality (HR 1.07, 95% CI 1.05–1.08, $P < 0.01$), cardiovascular mortality (HR 1.07, 95% CI 1.05–1.09, $P < 0.01$), cancer-related mortality (HR 1.10, 95% CI 1.09–1.11, $P < 0.01$), and other causes of mortality (HR 1.09, 95% CI 1.08–1.10, $P < 0.01$).

Subgroup analysis of mortality by gender. Subgroup analyses were performed for patients with SLD by gender. There was no significant difference in all-cause mortality (HR 0.92, 95% CI 0.70–1.20, $P = 0.524$), cardiovascular mortality (HR 0.88, 95% CI 0.49–1.56, $P = 0.662$), cancer-related mortality (HR 1.25, 95% CI 0.74–2.10, $P = 0.40$), or other causes of mortality (HR 1.28, 95% CI 0.76–2.16, $P = 0.35$).

Within MASLD patients, there was no significant difference in all-cause mortality (HR 1.06, 95% CI 0.75–1.50, $P = 0.74$), cardiovascular mortality (HR 0.94, 95% CI 0.65–1.36, $P = 0.74$), cancer-related mortality (HR 1.19, 95% CI 0.64–2.22, $P = 0.58$), or other causes of mortality (HR 1.11, 95% CI 0.68–1.82, $P = 0.68$) by gender.

Within MetALD patients, there was no significant difference in all-cause mortality (HR 0.72, 95% CI 0.46–1.10, $P = 0.13$), cardiovascular mortality (HR 0.73, 95% CI 0.30–1.78, $P = 0.49$), cancer-related mortality (HR 1.30, 95% CI 0.65–2.59, $P = 0.46$), or other causes of mortality (HR 0.46, 95% CI 0.0.19–1.15, $P = 0.10$) by gender.

Subgroup analysis of mortality by obesity status. Subgroup analyses were performed for patients with SLD by BMI status. BMI status was defined as BMI > 25 in non-Asians and BMI > 23 in Asians. There was no difference in all-cause mortality (HR 1.84, 95% CI 0.26–13.26, $P = 0.54$) or cardiovascular mortality (HR 0.56, 95% CI 0.15–2.15, $P = 0.40$). Due to limitations in sample size of cancer-related mortality and other cause mortality, stratified by BMI status could not be analyzed.

Sensitivity analysis using hepatic steatosis index. A sensitivity analysis was performed using the hepatic steatosis index (HSI). Steatosis was defined as HSI ≥ 36. Using HSI as a marker of steatosis within this NHANES database showed a sample size of 7255 individuals. When compared with MASLD patients, MetALD did not have a significant difference in all-cause

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Table 1 Baseline characteristics, laboratory values, and prevalence of diseases among persons with metabolic dysfunction-associated steatotic liver disease[†]

Characteristics	MASLD (n = 2838)	MetALD (n = 2557)	P value
Age, years (median, IQR)	55 (41–66)	45 (33–56)	< 0.01
Body Mass Index	32.6 (29.5–36.7)	33.2 (30–37.7)	< 0.01
Sex (male, %)	61.80	51.39	< 0.01
Race, %			
Asian	7.51	3.71	< 0.01
Black	22.90	22.29	
Non-Hispanic White	44.36	36.72	
Hispanic	21.35	33.32	
Other/unknown	3.88	3.95	
Smoking, %			
Never	56.59	45.53	< 0.01
Former smoker	30.15	26.0	
Current smoker	13.26	28.48	
ALT (U/L)	23 (18–32)	24 (18–34)	< 0.01
AST (U/L)	23 (19–28)	23 (19–29)	0.20
Platelet (K/μL)	233 (196–271)	244 (208–289)	< 0.01
Cholesterol	193 (166–220)	196 (169–233)	< 0.01
LDL	115 (89–138)	115 (93–139)	0.16
HDL	45 (38–53)	46 (39–55)	< 0.01
Triglyceride	164 (111–244)	159 (109–235)	0.07
HbA1c	5.7 (5.4–6.2)	5.6 (5.3–6)	< 0.01
FIB-4	1.08 (0.71–1.56)	0.84 (0.57–1.21)	< 0.01
Metabolic diseases, %			
Hypertension	66.0	57.25	< 0.01
Dyslipidemia	63.64	55.92	< 0.01
Hypertriglyceridemia	70.40	63.71	< 0.01
Insulin resistance	94.36	91.67	< 0.01
Diabetes mellitus	53.84	46.16	< 0.01
CAP	302 (267–339)	297 (259–337)	0.08
LSM	5.6 (4.4–7.1)	5.3 (4.3–6.9)	0.03

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; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction-associated steatotic liver disease and increased alcohol intake.

[†]Data are expressed as median (interquartile range) for continuous variables or number (percentage) for categorical variables.

mortality (HR 1.15, 95% CI 0.87–1.52, P = 0.31), cardiovascular mortality (HR 1.03, 95% CI 0.39–2.70, P = 0.95), cancer-related mortality (HR 1.05, 95% CI 0.88–1.26, P = 0.56), or other causes of mortality (HR 1.29, 95% CI 0.90–1.86, P = 0.17).

Discussion

In this longitudinal cohort of over 5000 individuals with SLD followed for 10 years, individuals with MetALD had approximately 30% significantly higher risk of cancer-related mortality despite them being more metabolically healthy than individuals with MASLD. This association between MetALD and cancer-related mortality was independent of potential confounders, including age, sex, race, BMI status, smoking status, hypertension, hyperlipidemia, insulin resistance, and FIB-4 score. In addition, patients with SLD, MASLD, or MetALD with advanced liver fibrosis (FIB-4 > 2.67) had increased all-cause mortality and cardiovascular mortality.

There are several reasons as to why MetALD patients have higher cancer-related mortality. Recent literature has discussed the effects of alcohol consumption on health outcomes.[28,29] An umbrella review concluded that moderate alcohol consumption was associated with an increased risk of colorectal cancer, mortality, and increased esophageal cancer mortality.[30] In the EPIC study, which included 45 studies, alcohol intake, BMI, and abdominal obesity had positive associations with overall cancer mortality.[31] Yet another study concluded that individuals who have more than two drinks per day have an increased risk of total, cardiovascular, and cancer mortality.[32] Furthermore, a study concluded that moderate alcohol consumption was associated with advanced fibrosis, particularly those patients with type 2 DM who had the highest risk of advanced fibrosis.[12] However, the mechanism regarding the relationship between alcohol consumption and hepatic fibrosis outcomes remains unclear.

There are several mechanisms that may explain the increased cancer-related mortality among MetALD patients with more benign metabolic profiles. There are potential mechanisms that may

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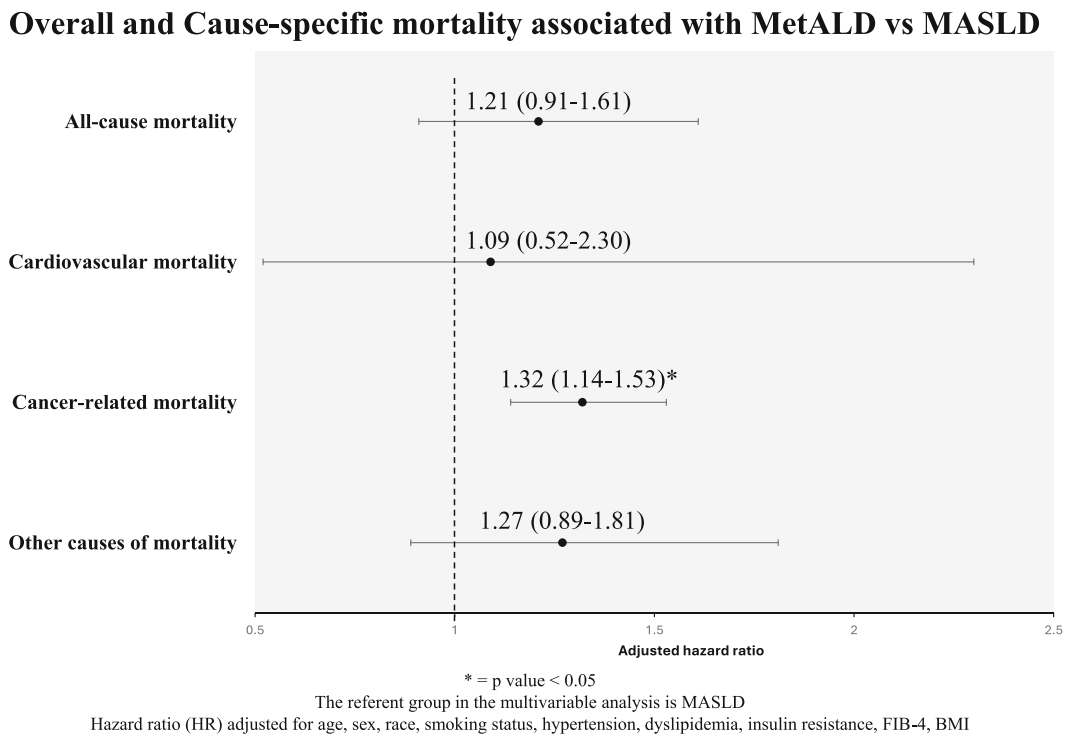


Figure 1 Forest plot diagram of Cox regression analysis for causes of mortality among persons with MASLD *versus* MetALD. MASLD, metabolic dysfunction-associated steatotic liver disease. MetALD, metabolic dysfunction-associated steatotic liver disease and increased alcohol intake.

explain a synergistic relationship that results in worse outcomes in MetALD patients. Greater mitochondrial dysfunction and oxidative stress may explain the combined effect of alcohol and metabolic dysfunction through the release of inflammatory cytokines and activation of the innate immune response.[5,33,34] Oxidative stress and mitochondrial dysfunction have been described in the pathogenesis of malignancy.[35] Literature has discussed that occasional alcohol intake can serve as a "second hit" to individuals with obesity who already have hepatic steatosis.[36] An animal study showed that rats treated with ethanol for 1 day a week for 3 weeks produced massive steatohepatitis in the liver.[36] Moderate alcohol consumption may be associated with rapidly progressive steatohepatitis through upregulation of CYP2E1, resulting in the metabolism of alcohol into acetaldehyde, which creates reactive oxygen species and results in hepatic injury.[36] These findings suggest that individuals with MetALD may have liver disease that progresses more rapidly than individuals with MASLD.

In our cohort, it was shown that MASLD and MetALD patients with advanced liver fibrosis (FIB-4 score $>$ 2.67) was associated with increased mortality. A recent study in the Korean adult population showed that high FIB-4 scores predicted all-cause, cardiovascular and liver-related mortality.[37] Another study showed that FIB-4 scores greater than 2.67 independently predict coronary artery disease.[38,39] It is known that hepatic fibrosis is considered a prognostic factor in advanced liver disease. Furthermore, in our cohort, patients with MetALD and a FIB-4 score $>$ 2.67 had increased overall mortality, increased cardiovascular mortality, and increased cancer-related mortality. This suggests that FIB-4 scores can also be used in MASLD as they have been used in NAFLD as a non-invasive score, which can help determine advanced fibrosis or a higher risk of death. Individuals with advanced fibrosis had an increased overall mortality, increased cardiovascular mortality, and increased other causes of mortality.[40–42]

There was no significant difference in CVD-related mortality between MASLD and MetALD in our cohort. There are several studies that have discussed the effect of alcohol on CVD. Some studies have shown similar conclusions that alcohol consumption does not have an association with cardiovascular death.[43] Other studies have shown that moderate alcohol consumption may promote hepatic fibrosis.[44] Although cardiovascular mortality was not significant among all patients, the subgroup analysis among individuals stratified by FIB-4 showed that individuals with SLD, MASLD, and MetALD with FIB-4 $>$ 2.67 had a higher risk of CVD-related mortality than those with low FIB-4 scores. This may suggest that in SLD individuals with high FIB-4 scores, their risk of CVD-related mortality also increases.

In the sensitivity analysis using HSI $\geq$ 36 as a marker for steatosis, there was no significant difference in all-cause mortality or cause-specific mortality. However, HSI uses gender and diabetes as part of the noninvasive steatosis score, and the sample size using HIS as a marker in this NHANES database would be 7255 individuals. It can be argued that using HSI would be overestimating the number of individuals with steatosis and metabolic risk factors and, therefore, cannot be used in this sample size. The United States Fatty Liver Index has been validated in the NHANES database by Ruhl et al. with 90% specificity and 90% sensitivity[25] and therefore would be the most representative non-invasive method of detecting steatosis in this population.

There are several strengths in this study. This study is the first study utilizing a population-based cohort to describe the

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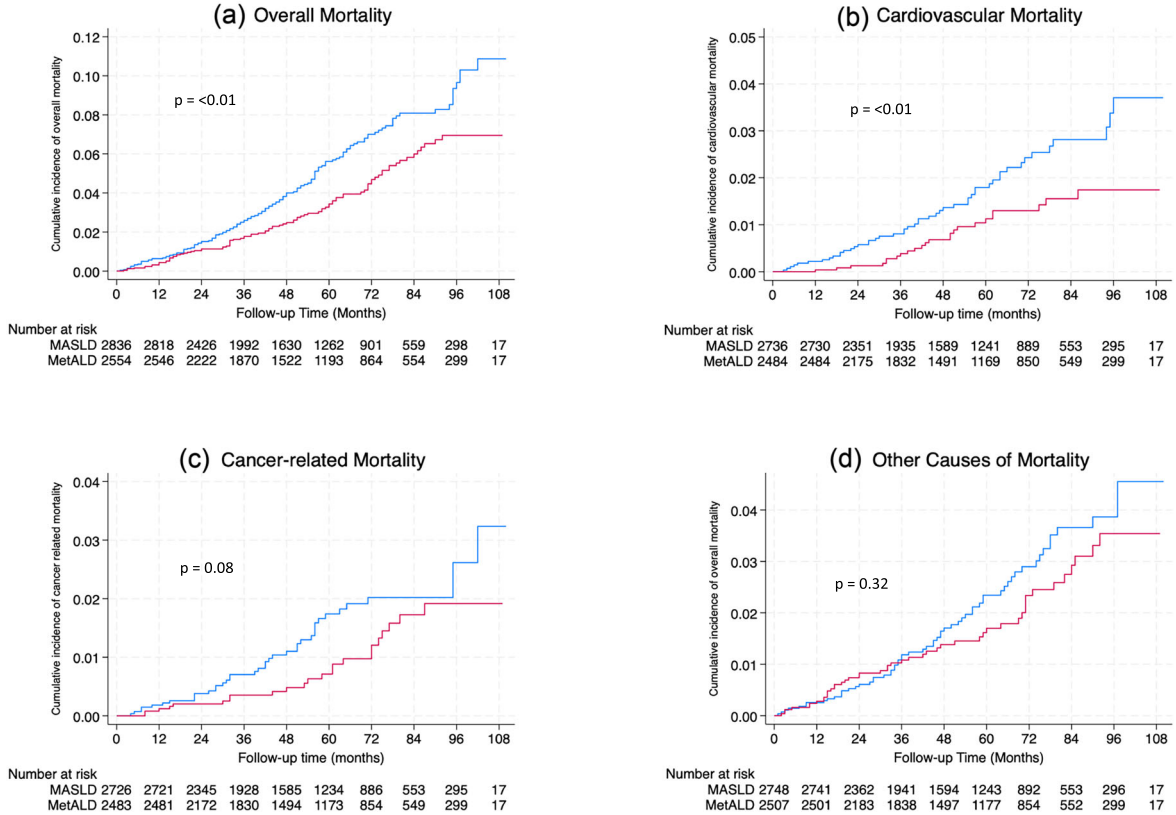


Figure 2 Cumulative incidence of mortality among MASLD *versus* MetALD. (a) Cumulative incidence of overall mortality among MASLD *versus* MetALD. (b) Cumulative incidence of cardiovascular mortality among MASLD *versus* MetALD. (c) Cumulative incidence of cancer related mortality among MASLD *versus* MetALD. (d) Cumulative incidence of other causes of mortality among MASLD *versus* MetALD. MASLD, metabolic dysfunction-associated steatotic liver disease. MetALD, metabolic dysfunction-associated steatotic liver disease and increased alcohol intake. (a) —, MASLD; —, MetALD. (b) —, MASLD; —, MetALD. (c) —, MASLD; —, MetALD. (d) —, MASLD; —, MetALD.

Table 2 Cox regression analysis for causes of mortality stratified by FIB-4 score among persons with steatotic liver disease[†]

	MASLD				MetALD			
	FIB-4 1.3–2.67		FIB-4 > 2.67		FIB-4 1.3–2.67		FIB-4 > 2.67	
Mortality	HR (95% CI)[†]	*P* value	HR (95% CI)[†]	*P* value	HR (95% CI)[†]	*P* value	HR (95% CI)[†]	*P* value
All-cause	1.35 (0.86–2.13)	0.20	2.26 (1.23–4.18)	< 0.01	1.21 (0.71–2.05)	0.48	2.95 (1.46–6.00)	< 0.01
Cardiovascular	0.92 (0.38–2.20)	0.84	2.10 (1.42–3.11)	< 0.01	1.21 (0.33–4.50)	0.77	2.68 (1.18–6.07)	0.02
Cancer-related	0.93 (0.52–1.65)	0.80	0.35 (0.06–1.95)	0.23	2.43 (1.32–4.47)	< 0.01	5.08 (1.08–23.96)	0.04
Other causes	2.29 (1.54–3.40)	< 0.01	4.95 (2.75–8.90)	< 0.01	0.89 (0.33–2.43)	0.82	1.97 (0.41–9.39)	0.40

Abbreviations: CI, confidence interval; HR, hazard ratio; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction-associated steatotic liver disease and increased alcohol intake; SLD, steatotic liver disease.
The referent group in this multivariate analysis is FIB-4 score < 1.3.
[†]HR adjusted for age, sex, race, smoking status, hypertension, dyslipidemia, insulin resistance, and body mass index.

differences between MASLD and MetALD and assess longitudinal outcomes. This study is based on a national database with a sample size of over 5000 individuals. Second, this study is a nationwide cohort with a patient population that can be generalizable to the general population. Third, access to medical history with laboratory studies provided us with valuable information. This allowed us to control for a multitude of confounding factors, including individual characteristics (age, sex, and race), behavioral risk factors (smoking status), and metabolic risk factors (hypertension, dyslipidemia, and insulin resistance).

This study also has limitations. Steatosis was defined using noninvasive measures that may either overestimate or underestimate its prevalence. However, US-FLI has been validated as a non-invasive method of detecting MASLD.[25,45,46] Vibration-controlled transient elastography was not available in this NHANES cohort. Individuals within the NHANES

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2017–2018 cohort with steatosis defined by vibration-controlled transient elastography are too small of a cohort and have inadequate follow-up time to analyze all-cause and specific-cause mortality. Moreover, mortality data are currently unavailable for the 2019–2020 NHANES cohort. Therefore, steatosis was defined using the US-FLI, and the 2011–2018 cohort was utilized. Although the NHANES database is a validated cohort with standardized questions, the definition of MetALD used in this study was based on self-reported alcohol intake, which can be inaccurate. The diagnosis of CVD and metabolic diseases was mainly based on ICD codes, which may not be accurate, although this approach is widely used in other large cohort studies. This is also a retrospective cohort analysis in which data is historical and cannot be confirmed as accurate at the time of the event. There may be individuals with cardiovascular disease or malignant neoplasms who did not have an ICD code, which could introduce selection bias. Due to missing data, we were unable to perform a subgroup analysis for mortality outcomes stratified by liver stiffness measure cutoffs. Another limitation is that there were 253 deaths reported within this cohort and a smaller subset in each cause-specific mortality. The small number of deaths could limit the robustness of the results, particularly in multivariable competing risk analysis. Due to limitations in NHANES data, we were not able to identify, which type of cancer causes higher cancer mortality in MetALD. Furthermore, due to limitations in the NHANES database, there is lack of data on liver-related mortality. Although the NHANES data are representative of the United States population, these results may not be applicable to other countries or ethnic groups that are not adequately represented in this dataset. More studies are necessary to confirm the generalizability of these conclusions to other populations or settings. Lastly, some data acquired were from surveys, which could introduce recall bias from participants.

In conclusion, this study found that patients with MetALD have higher cancer-related mortality than patients with MASLD despite being more metabolically healthy. These findings emphasize the importance of alcohol cessation in patients with SLD. This study also shows that there is a synergistic effect between steatosis and alcohol. In addition, this study showed that high FIB-4 scores in SLD, MASLD, and MetALD are associated with increased overall mortality and CVD-related mortality, suggesting that FIB-4 can be used as a marker to help stratify patients who may be predisposed to worse outcomes. Further studies are warranted to understand the pathophysiology of MASLD and the effect of moderate alcohol consumption on disease progression. Close attention to regular cancer surveillance and accurate classification of alcohol consumption in individuals with diagnosed MASLD is warranted to help improve patient care and outcomes.

Data availability statement. Data available on request due to privacy/ethical restrictions.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1: Cumulative incidence of mortality among steatotic liver disease by FIB-4 score. (A) Cumulative incidence of overall mortality among steatotic liver disease by FIB-4 score. (B) Cumulative incidence of cardiovascular mortality among steatotic liver disease by FIB-4 score. (C) Cumulative incidence of cancer related mortality among steatotic liver disease by FIB-4 score. (D) Cumulative incidence of other causes of mortality among steatotic liver disease by FIB-4 score.

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