Original Article

Prevalence and longitudinal effects on mortality associated with spectrum of alcohol intake in steatotic liver disease: a United States population study

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Background: The recently introduced set of terminologies defining categories of steatotic liver disease (SLD) includes metabolic dysfunction-associated SLD (MASLD), alcohol-associated liver disease (ALD), and metabolic dysfunction associated steatotic liver disease and increased alcohol intake (MetALD). The present retrospective cohort study examines clinical characteristics, prevalence, and mortality risk across alcoholic intake spectrum in SLD individuals.

Methods: Data between 1999 to 2018 were extracted from National Health and Nutrition Examination Survey registries and analysed. Population baseline characteristics were evaluated across classifications of SLD. SLD was confirmed using either fatty liver index (FLI) or United States FLI (US-FLI). Multivariate analyses were used to study mortality-related outcomes.

Results: The 20,510 individuals with SLD included were classified into MASLD predominant (69.00%), MetALD (18.77%), and ALD predominant (12.23%) groups. Temporal analysis revealed significant decreases in MASLD prevalence in the SLD population from 1999–2018 in general [average annual percentage change (AAPC) –4.802%, P=0.001], as well as in females, Mexican Americans, and Non-Hispanic Blacks. MetALD prevalence in the SLD population increased from 1999–2018 in general (AAPC +1.635%, P<0.001), and in males, females, Mexican Americans, Non-Hispanic Blacks and other ethnicities. No significant change in ALD prevalence was found. Compared to MASLD predominant individuals, ALD predominant individuals

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had higher risks of all-cause [hazard ratio (HR): 1.189, 95% confidence interval (CI): 1.026 to 1.378, P=0.02] and cancer-related mortality (subdistribution HR: 1.277, 95% CI: 1.032 to 1.579, P=0.02). No significant difference was observed for all-cause, cancer-related, or cardiovascular disease (CVD)-related mortality in MetALD and CVD-related mortality in ALD predominant individuals, relative to MASLD predominant individuals.

Conclusions: ALD predominant patients have higher all-cause and cancer-related mortality risks than MASLD predominant patients but not CVD-related mortality. SLD is highly heterogeneous in clinical characteristics, prevalence, and mortality risks which healthcare professionals must account for to avert adverse health outcomes.

Keywords: Steatotic liver disease (SLD); mortality; metabolic-dysfunction-associated steatotic liver disease (MASLD); metabolic dysfunction associated steatotic liver disease and increased alcohol intake (MetALD); alcohol-associated liver disease (ALD)

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Introduction

Steatotic liver disease (SLD) refers to a category of fatty liver conditions that vary by etiology (1). Metabolic dysfunction-associated SLD (MASLD) is the commonest cause of chronic liver disease worldwide (2) while alcohol-associated liver disease (ALD) accounts for 5.1% of global disease and injury (3). ALD represents a range of liver conditions such as hepatic steatosis that arise due to excessive chronic alcohol use (4-6) and an intermediate named metabolic dysfunction associated steatotic liver disease and increased alcohol intake (MetALD) exists that represents SLD in the presence of only moderate alcohol intake and one or more cardiometabolic factors (1). Despite their similarities in terms of being different types of SLD, marked differences have been observed in the outcomes of MASLD and ALD. Previous studies have shown that ALD patients have a higher risk of hepatocellular carcinoma than MASLD patients while patients with metabolic associated steatohepatitis (MASH) related cirrhosis were more likely to have extrahepatic events compared to ALD patients (7).

However, while numerous studies have been centred around MASLD and ALD, limited literature is available on MetALD, a newly defined category of SLD influenced by a mix of cardiometabolic and alcoholic factors (8). Existing studies on hepatic steatosis-related mortality typically explore metabolic and alcoholic drivers as separate aetiologies with MASLD juxtaposed against ALD as clinically distinct conditions (9). Outcomes are likely to vary along the spectrum of SLD, from MASLD to MetALD to ALD. Moon *et al.* found that MetALD patients had a higher incidence of cardiovascular disease than MASLD (10). As such, studies to explore characteristics associated with MetALD and assess differences across subtypes of SLD as driven by variable alcohol consumption are justified and necessary. Thus, we sought to comparatively examine the clinical characteristics, prevalence and risks of mortality in MASLD, MetALD and ALD using patients from the United States (US) National

Highlight box

Key findings

- Alcohol-associated liver disease (ALD) predominant patients are at an increased risk of all-cause and cancer-related mortality as compared to metabolic dysfunction-associated steatotic liver disease (MASLD) predominant patients except for cardiovascular disease (CVD)-related mortality.

What is known and what is new?

- Previous studies have revealed that ALD patients are at a higher risk of hepatocellular carcinoma than MASLD patients while patients with metabolic associated steatohepatitis (MASH) related cirrhosis were more likely to have extrahepatic events in comparison to ALD patients.
- Although there have been a number of studies centred around MASLD and ALD, literature on metabolic dysfunction associated steatotic liver disease and increased alcohol intake (MetALD), a newly defined category of SLD caused by a combination of cardiometabolic and alcoholic factors, remains limited.

What is the implication, and what should change now?

- SLD is a highly heterogeneous disease in clinical characteristics, prevalence and mortality risks which must be taken into account by the care team in order to prevent adverse health outcomes.

Health and Nutrition Examination Survey (NHANES) between 1999–2018. We present this article in accordance with the STROBE reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-24-51/rc).

Methods

Study population

Data for the study period of 1999–2018 were extracted from registries of NHANES, a National Centre for Health Statistics (NCHS) program focused on cross-sectional studies on nationally representative samples of the United States population through medical examinations and interviews (11). Data include participants' demographic details, medical information such as blood test results and FIB-4 measurements, behavioural information such as smoking habits and alcohol intake, amongst other characteristic details. Mortality follow-up data up till 2018 were obtained through linkage with National Death Index (NDI) records using NCHS public-use mortality files (12). Our study population included participants aged between 18 and 85 years. Hepatic steatosis was confirmed using either fatty liver index (FLI) or United States FLI (US-FLI), with a cut-off of ≥60 and ≥30 respectively (13,14). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical review and informed consent are not required in this article as no confidential patient information was involved.

Definitions

Participants with hepatic steatosis were classified into MASLD-predominant, MetALD and ALD-predominant groups based on the diagnosis criteria previously defined in the 2023 Multisociety Delphi Consensus Statement (15). Baseline data were used for classification as longitudinal data was largely not available. The MASLD-predominant group was defined based on the presence of at least one in five of the following cardiometabolic risk factors: obesity (BMI ≥25 or 23 kg/m^2 in Asians or waist circumference >94 cm in males or 80 cm in females), high blood glucose (fasting serum glucose ≥100 mg/dL or 2 hour post-load glucose levels ≥140 mg/dL or HbA1c ≥5.7% or type 2 diabetes diagnosis or treatment for type 2 diabetes), hypertension (≥130/85 mmHg or antihypertensive drug treatment), hypertriglyceridemia (plasma triglycerides ≥150 mg/dL in plasma or lipid lowering treatment), or hypoalphalipoproteinemia (plasma HDL-cholesterol ≤40 mg/dL in males and ≤50 mg/dL in females or lipid lowering treatment). Of these individuals, those whose weekly alcohol intake additionally fell between 140–350 g in females or 210–420 g in males were instead considered as part of the MetALD group. Regardless of the presence of cardiometabolic risk factors, participants whose weekly alcohol intake exceeded 350 g in females or 420 g in males were classified as ALD-predominant. Finally, participants with hepatic steatosis despite alcohol consumption below the defined threshold for MetALD and ALD, as well as an absence of cardiometabolic risk factors, were classified under other aetiologies of SLD and were hence excluded from the study population. FIB-4 index values were calculated for each participant based on their age, platelet count (PLT), aspartate aminotransferase (AST) levels and alanine aminotransferase (ALT) levels using the following formula: age (years) × AST (U/L)/[PLT (10^9/L) × ALT1/2 (U/L)]. Where applicable, cause of mortality was ascertained accordingly based on ICD-10 diagnostic codes: participant mortality associated with ICD-10 codes I00-I99 was considered cardiovascular disease (CVD)-related mortality, while association with ICD-10 codes of C00-C97 was considered cancer-related mortality (16,17).

Statistical analysis

Population baseline characteristics were comparatively analysed across MASLD, MetALD and ALD groups—the Wilcoxon ranked sum test and Kruskal-Wallis analysis of variance were used to examine continuous variables, while Pearson's chi-squared test and Fisher's exact test were conducted to analyse binary variables. A temporal analysis of the prevalence of MASLD, MetALD and ALD in the SLD population over 1999 to 2018 was performed, and average annual percentage change (AAPC) was calculated. Prevalence data was stratified by gender and race. Mortality-related outcomes were examined with regression analysis, using MASLD-predominant participants as the reference group. A multivariate Cox proportional-hazards models was used to estimate the hazard ratio (HR) for mortality-related outcomes, controlling for potential confounders: smoking status, gender, age and ethnicity. A separate competing risk analysis was performed to examine preclusion due to CVD-related mortality and cancer-related mortality, using Fine-Gray models to estimate subdistribution hazard ratio (sHR). Point estimates with 95% confidence intervals were reported, and P values ≤0.05 were considered suggestions of

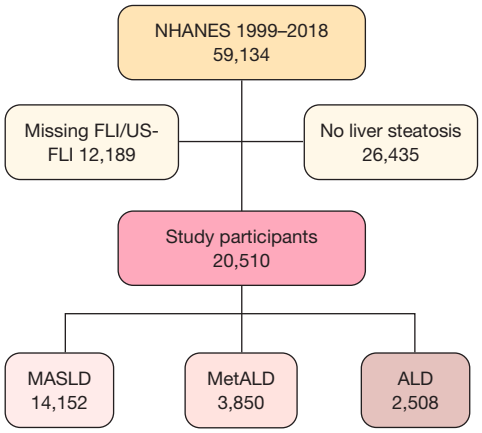

Figure 1 Flowchart of included study population. NHANES, National Health and Nutrition Examination Survey; FLI, fatty liver index; US-FLI, United States FLI; MASLD, metabolic-dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction associated steatotic liver disease and increased alcohol intake; ALD, alcohol-associated liver disease.

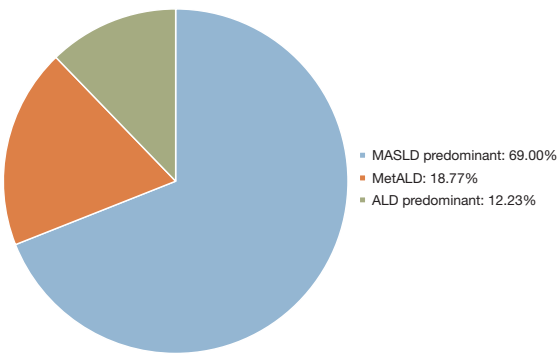

Figure 2 Prevalence of MASLD, MetALD, and ALD in study population. MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction associated steatotic liver disease and increased alcohol intake; ALD, alcohol-associated liver disease.

statistical significance. All statistical analysis was performed in STATA 17.0 (StataCorp, College Station, TX, USA).

Results

The final study population included a total of 20,510 individuals with SLD for analysis and a breakdown of the study population that was included can be found in *Figure 1*. A total of 14,152 patients were MASLD predominant (69.00%, 95% CI: 68.36% to 69.63%; *Figure 2*), 3,850 had MetALD (18.77%, 95% CI: 18.24% to 19.31%; *Figure 2*), and 2,508 were ALD predominant (12.23%, 95% CI: 11.79% to 12.68%; *Figure 2*). A summary of the clinical characteristics of MASLD predominant, MetALD and ALD predominant patients can be found in *Table 1*. Across all baseline characteristics evaluated, there were significant differences between all three groups of individuals with SLD. Amongst all the patients, participants with MASLD predominant were the oldest with a median age of 55.00 years (95% CI: 40.00 to 67.00). There was also a larger proportion of male patients in ALD predominant individuals (95% CI: 69.45% to 72.99%) compared to those with MASLD predominant and MetALD. There were significant differences between the three groups for baseline characteristics such as age, total cholesterol, HDL-cholesterol and triglyceride levels. In terms of ethnicity, most patients across all 3 types of SLD were Non-Hispanic White. The highest proportion of the MASLD (25.14%, 95% CI: 24.19% to 26.12%) and ALD predominant (27.06%, 95% CI: 24.81% to 29.42%) cohorts was in the $25,000–49,999 annual household income bracket, while the highest proportion of the MetALD cohort was in the $75,000 and over bracket (28.82%, 95% CI: 27.01% to 30.70%). MASLD Predominant patients had the highest median FIB-4 (1.01, IQR: 0.66 to 1.47), followed by MetALD (0.83, IQR: 0.56 to 1.20) and then ALD predominant (0.73, IQR: 0.51 to 1.07).

Prevalence over time of MASLD predominant, MetALD and ALD predominant fatty liver

A temporal trend analysis was done for the years 1999 to 2018 examining the change in prevalence of MASLD in the SLD population (Table S1). MASLD prevalence in the SLD population decreased significantly from the year 1999–2000 (71.83%, 95% CI: 69.73% to 78.84%) to the year 2017–2018 (67.10%, 95% CI: 65.19% to 68.96%) with an AAPC of –4.802% (P=0.001). When stratified by gender (*Figure 3A*), we found that MASLD prevalence also decreased significantly (AAPC –5.294%, P<0.001), from 1999–2000 (74.28%, 95% CI: 71.33% to 77.03%) to 2017–2018 (65.68%, 95% CI: 62.84% to 68.41%). No significant change was found in prevalence for males (AAPC –1.600%, P=0.15). Stratification by ethnicity (*Figure 3B*) revealed a significant decrease in prevalence for Mexican Americans (AAPC –4.400%, P=0.002), from 1999–2000 (67.74%, 95% CI: 63.86% to 71.40%) to 2017–2018 (56.47%, 95% CI: 51.57% to 61.24%). A significant decrease in prevalence

Table 1 Clinical characteristics of patients based on type of SLD

Characteristics	MASLD predominant (n=14,152)	MetALD (n=3,850)	ALD predominant (n=2,508)	P value
Age (years)	55.00 [40.00 to 67.00]	46.00 [34.00 to 58.00]	40.00 [30.00 to 51.00]	<0.001*
BMI (kg/m^2)	32.60 [29.69 to 36.70]	32.84 [29.70 to 37.05]	32.09 [28.90 to 36.20]	<0.001*
Waist circumference (cm)	109.40 [102.80 to 118.00]	108.70 [102.10 to 117.50]	108.00 [101.00 to 117.50]	<0.001*
Platelet count (1,000 cells/μL)	249.00 [209.00 to 295.00]	256.00 [214.00 to 305.00]	254.00 [215.00 to 296.00]	<0.001*
HbA1c (%)	5.70 [5.30 to 6.20]	5.50 [5.30 to 5.90]	5.50 [5.20 to 5.80]	<0.001*
Fasting glucose (mmol/L)	5.83 [5.33 to 6.72]	5.72 [5.27 to 6.33]	5.66 [5.29 to 6.27]	<0.001*
Total bilirubin (μmol/L)	10.26 [8.55 to 13.68]	10.26 [6.84 to 13.68]	10.26 [8.55 to 13.68]	<0.001*
LDL-cholesterol (mg/dL)	115.00 [92.00 to 140.00]	120.00 [95.00 to 145.00]	120.00 [99.00 to 144.00]	<0.001*
HDL-cholesterol (mg/dL)	45.00 [38.00 to 54.00]	47.00 [40.00 to 56.00]	43.00 [37.00 to 53.00]	<0.001*
Total cholesterol (mg/dL)	197.00 [170.00 to 226.00]	202.00 [174.50 to 231.00]	204.00 [177.00 to 232.00]	<0.001*
Triglyceride (mg/dL)	146.00 [103.00 to 209.00]	141.00 [99.00 to 202.00]	154.00 [106.00 to 225.50]	<0.001*
Aspartate aminotransferase (U/L)	23.00 [19.00 to 28.00]	23.00 [19.00 to 29.00]	25.00 [20.00 to 32.00]	<0.001*
Alanine aminotransferase (U/L)	23.00 [18.00 to 32.00]	24.00 [18.00 to 35.00]	28.00 [21.00 to 41.00]	<0.001*
Gamma glutamyl transferase (U/L)	25.00 [18.00 to 38.00]	27.00 [19.00 to 43.00]	34.00 [23.00 to 55.00]	<0.001*
FIB-4	1.01 [0.66 to 1.47]	0.83 [0.56 to 1.20]	0.73 [0.51 to 1.07]	<0.001*
Gender (%) (95% CI)				<0.001*
Male	51.76 (50.94 to 52.58)	47.01 (45.44 to 48.59)	71.25 (69.45 to 72.99)	
Female	48.24 (47.42 to 49.06)	52.99 (51.41 to 54.56)	28.75 (27.01 to 30.55)	
Hypertension (%) (95% CI)				<0.001*
No	45.30 (44.44 to 46.16)	57.96 (56.32 to 59.59)	65.78 (63.80 to 67.71)	
Yes	54.70 (53.84 to 55.56)	42.04 (40.41 to 43.68)	34.22 (32.29 to 36.20)	
Smoking (%) (95% CI)				<0.001*
Never	57.10 (56.27 to 57.93)	45.36 (43.78 to 46.95)	34.89 (33.02 to 36.82)	
Past	29.95 (29.19 to 30.73)	29.08 (27.65 to 30.55)	24.38 (22.71 to 26.13)	
Current	12.95 (12.39 to 13.52)	25.56 (24.19 to 26.97)	40.73 (38.78 to 42.70)	
Annual household income (%) (95% CI)				<0.001*
0–9,999	6.45 (5.93 to 7.02)	6.56 (5.62 to 7.64)	8.01 (6.71 to 9.54)	
10,000–24,999	24.77 (23.83 to 25.74)	20.06 (18.48 to 21.74)	24.60 (22.43 to 26.90)	
25,000–49,999	25.14 (24.19 to 26.12)	23.08 (21.41 to 24.84)	27.06 (24.81 to 29.42)	
45,000–74,999	19.49 (18.63 to 20.39)	21.48 (19.86 to 23.20)	20.24 (18.23 to 22.41)	
≥75,000	24.14 (23.20 to 25.11)	28.82 (27.01 to 30.70)	20.10 (18.10 to 22.26)	
Ethnicity (%) (95% CI)				<0.001*
Mexican American	19.21 (18.57 to 19.86)	21.12 (19.86 to 22.43)	34.61 (32.77 to 36.49)	
Other Hispanic	8.32 (7.88 to 8.79)	8.55 (7.70 to 9.47)	10.05 (8.93 to 11.29)	
Non-Hispanic White	44.15 (43.33 to 44.97)	42.99 (41.43 to 44.56)	36.60 (34.74 to 38.51)	
Non-Hispanic Black	21.44 (20.77 to 22.12)	21.95 (20.67 to 23.28)	14.23 (12.92 to 15.66)	
Other	6.88 (6.48 to 7.31)	5.40 (4.73 to 6.16)	4.51 (3.76 to 5.39)	

Table 1 *(continued)*

Table 1 *(continued)*

Characteristics	MASLD predominant (n=14,152)	MetALD (n=3,850)	ALD predominant (n=2,508)	P value
Weight categories (%) (95% CI)				<0.001*
Lean	1.29 (1.12 to 1.49)	1.87 (1.49 to 2.35)	3.27 (2.64 to 4.04)	
Overweight	25.38 (24.67 to 26.11)	24.49 (23.16 to 25.88)	31.10 (29.32 to 32.94)	
Obese	73.33 (72.59 to 74.05)	73.64 (72.22 to 75.00)	65.63 (63.75 to 67.46)	
Fibrosis (FIB-4) (%) (95% CI)				<0.001*
Low (<1.3)	67.09 (66.31 to 67.86)	80.07 (78.77 to 81.30)	83.61 (82.11 to 85.01)	
Intermediate (≥1.3 and <2.67)	29.44 (28.70 to 30.20)	17.46 (16.29 to 18.69)	13.94 (12.64 to 15.36)	
High (≥2.67)	3.47 (3.18 to 3.78)	2.48 (2.03 to 3.02)	2.44 (1.91 to 3.13)	

Data are presented as median [interquartile range] unless otherwise stated. *, P value ≤0.05 denotes statistical significance. SLD, steatotic liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction associated steatotic liver disease and increased alcohol intake; ALD, alcohol-associated liver disease; BMI, body mass index; 95% CI, 95% confidence interval; LDL, low density lipoprotein; HDL, high density lipoprotein.

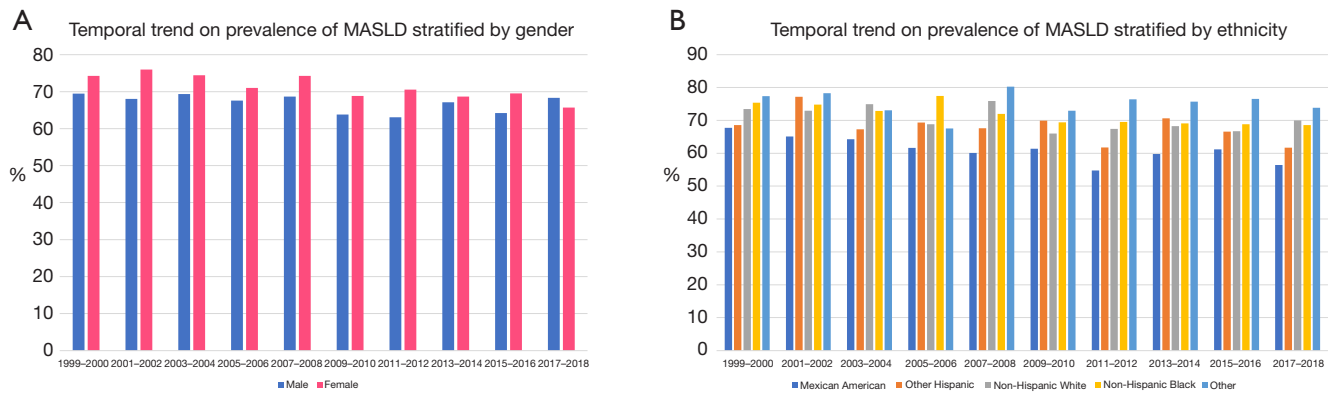

Figure 3 Temporal trends of prevalence of MASLD in study population. (A) Temporal trend on prevalence of MASLD stratified by gender; (B) temporal trend on prevalence of MASLD stratified by ethnicity. MASLD, metabolic dysfunction-associated steatotic liver disease.

was also found for Non-Hispanic Blacks (AAPC –0.642%, P=0.002), from 1999–2000 (75.37%, 95% CI: 70.51% to 79.65%) to 2017–2018 (68.57%, 95% CI: 64.54% to 72.33%). No significant changes in prevalence were observed for Other Hispanics (AAPC –1.897%, P=0.09), Non-Hispanic Whites (AAPC –2.198%, P=0.06), and other ethnicities (AAPC –0.103%, P=0.65).

Temporal analysis was conducted for MetALD prevalence in the SLD population over the years 1999 to 2018 (Table S2). The prevalence of MetALD in the SLD population increased significantly from 1999–2000 (15.93%, 95% CI: 14.33% to 17.67%) to 2017–2018 (21.50%, 95% CI: 19.89% to 23.20%), with an AAPC of +1.635% (P<0.001). When the analysis was stratified by gender (*Figure 4A*), there was a significant increase in MetALD prevalence in both males (AAPC +1.357%, P<0.001) and females (AAPC +1.840%, P<0.001) from 1999–2000 to 2017–2018. Stratification by ethnicity instead (*Figure 4B*) revealed that Mexican Americans (AAPC +2.413%, P=0.002), Non-Hispanic Blacks (AAPC +1.106%, P=0.006) and other ethnicities (AAPC +2.886%, P=0.04) saw a significant increase in MetALD prevalence from 1999–2000 to 2017–2018. There was no significant change in MetALD prevalence amongst the other Hispanic (AAPC +0.976%, P=0.39) and Non-Hispanic White (AAPC +1.169%, P=0.10) ethnicities from 1999–2000 to 2017–2018.

Temporal trend analysis was also performed for change in ALD prevalence in the SLD population from 1999–2000 to

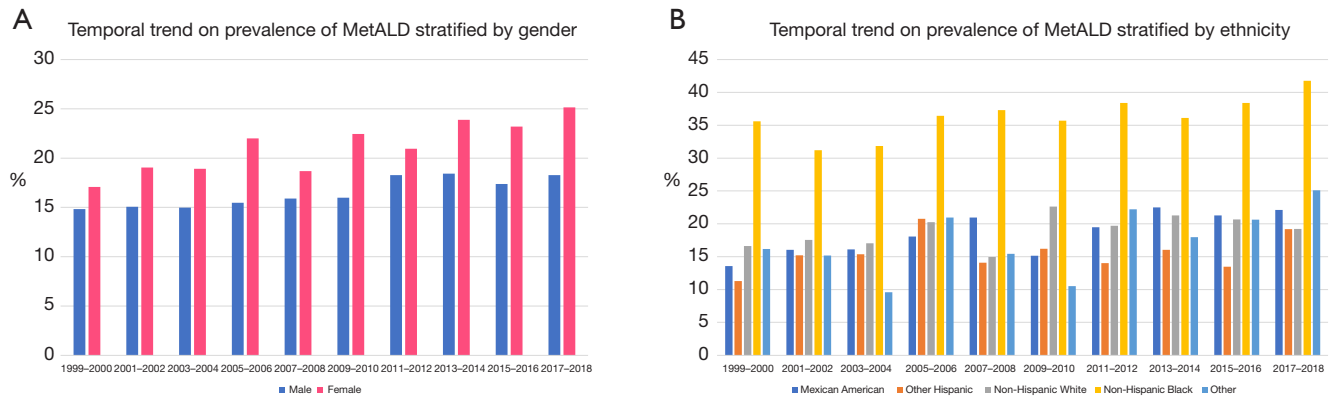

Figure 4 Temporal trends of prevalence of MetALD in study population. (A) Temporal trend on prevalence of MetALD stratified by gender; (B) temporal trend on prevalence of MetALD stratified by ethnicity. MetALD, metabolic dysfunction associated steatotic liver disease and increased alcohol intake.

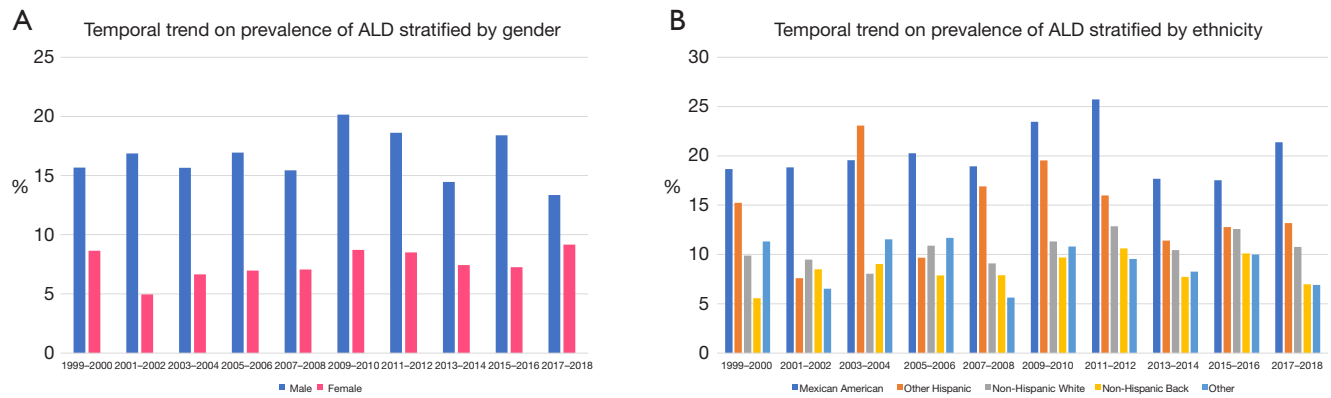

Figure 5 Temporal trends of prevalence of ALD in study population. (A) Temporal trend on prevalence of ALD stratified by gender; (B) temporal trend on prevalence of ALD stratified by ethnicity. ALD, alcohol-associated liver disease.

2017–2018 (Table S3). There was no significant change in ALD prevalence in the SLD population over the specified time period (AAPC +0.193%, P=0.73). Upon stratification by gender (*Figure 5A*), no significant change in prevalence was observed from 1999–2000 to 2017–2018 for males (AAPC –0.096%, P=0.90) or females (AAPC +1.043%, P=0.25). A similar analysis stratified by ethnicity was performed (*Figure 5B*). No significant change in prevalence was observed from 1999–2000 to 2017–2018 for Mexican Americans (AAPC +0.339%, P=0.62), Other Hispanics (AAPC –1.664%, P=0.27), Non-Hispanic Whites (AAPC +1.442%, P=0.07), Non-Hispanic Blacks (AAPC +0.822%, P=0.46) or other ethnicities (AAPC –1.882%, P=0.14).

Mortality associated with spectrum of alcohol intake

A summary of mortality risks is presented in *Table 2*. The median follow-up duration was 113 months (IQR: 59 to 173 months). In MASLD Predominant patients, 2,512 all-cause mortality events were recorded over the follow-up duration, with 570 CVD-related and 1,104 cancer-related mortality events. In MetALD, 366 all-cause, 570 CVD-related and 1,104 cancer-related mortality events were found. 228 all-cause, 52 CVD-related and 112 cancer-related mortality events were recorded in ALD Predominant patients. Cox proportional models were used to estimate the all-cause mortality risk in MASLD Predominant, MetALD

Table 2 Multivariate analysis of mortality in MetALD and ALD predominant with reference to MASLD predominant patients

Type of mortality	MetALD		ALD predominant	
	Effect size (95% CI)[a]	P value	Effect size (95% CI)[a]	P value
All-cause mortality	HR: 0.934 (0.832 to 1.048)	0.24	HR: 1.189 (1.026 to 1.378)	0.02*
CVD-related mortality	sHR: 0.966 (0.766 to 1.216)	0.77	sHR: 0.948 (0.693 to 1.298)	0.74
Cancer mortality	sHR: 0.927 (0.780 to 1.101)	0.39	sHR: 1.277 (1.032 to 1.579)	0.02*

*, P value ≤0.05 denotes statistical significance; [a], adjusted for smoking status, gender, age and ethnicity. MetALD, metabolic dysfunction associated steatotic liver disease and increased alcohol intake; ALD, alcohol-associated liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; 95% CI, 95% confidence interval; HR, hazard ratio; CVD, cardiovascular disease; sHR, subdistribution hazard ratio.

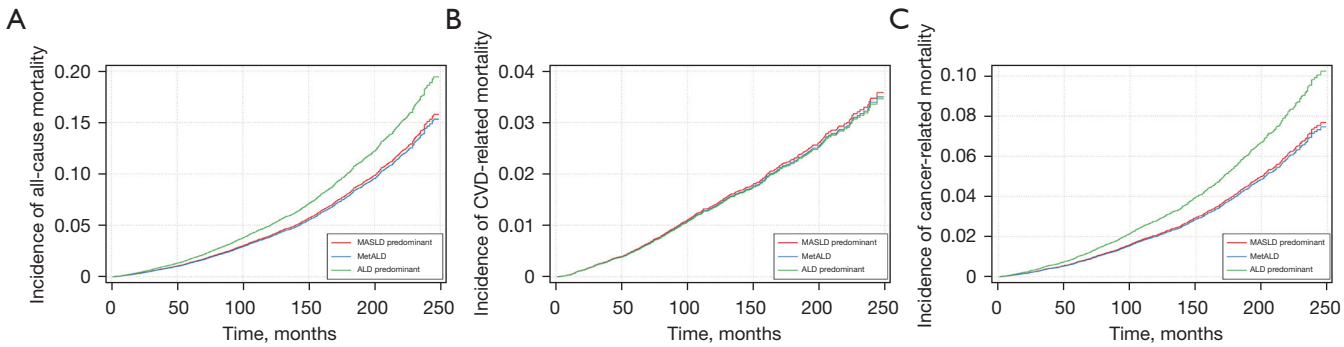

Figure 6 Survival curves for MASLD predominant, MetALD and ALD predominant. (A) Cox proportional survival curve for all-cause mortality; (B) competing risks survival curve for CVD-related mortality; (C) competing risks survival curve for cancer-related mortality. MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction associated steatotic liver disease and increased alcohol intake; ALD, alcohol-associated liver disease; CVD, cardiovascular disease.

and ALD Predominant. After adjustment for smoking status, gender, age, and ethnicity, a significantly higher mortality risk was observed (HR: 1.189, 95% CI: 1.026 to 1.378, P=0.02; *Figure 6A*) in ALD Predominant individuals compared to MASLD Predominant individuals. No significant difference (HR: 0.968, 95% CI: 0.863 to 1.086, P=0.58; *Figure 6A*) in all-cause mortality risk was found between MetALD and MASLD predominant individuals. A competing risk analysis was also done to find the risks of CVD and cancer-related mortality. After adjustment for smoking status, gender, age, and ethnicity, no significant difference was found in the risk of CVD-related mortality for MetALD (sHR: 0.977, 95% CI: 0.775 to 1.230, P=0.84; *Figure 6B*) and ALD predominant individuals (sHR: 0.966, 95% CI: 0.706 to 1.323, P=0.83; *Figure 6B*). Individuals with ALD were found to have a significantly higher risk of cancer-related mortality (sHR: 1.277, 95% CI: 1.032 to 1.579, P=0.02; *Figure 6C*) relative to MASLD predominant individuals. No significant difference was found in the risk of cancer-related mortality for MetALD individuals (sHR: 0.971, 95% CI: 0.817 to 1.153, P=0.73; *Figure 6C*) with reference to MASLD predominant people.

Discussion

The term SLD was proposed to encapsulate all aetiological variations of hepatic steatosis, but significant heterogeneity exists within the spectrum of alcohol intake. While the exact relation between volume of alcohol consumption and the variations of hepatic steatosis remains contentious (6,18,19), the subtypes were introduced to account for cases involving overlapping effects of significant alcohol consumption and metabolic dysfunction on hepatic steatosis, MetALD was devised as a separate category to characterise SLD individuals with a weekly alcoholic intake of 140–350 g in females and 210–420 g in males. Previous analysis has largely been focused on comparing mortality in MASLD and ALD, with limited studies comparing the above with mortality risks in MetALD as a newly defined category (8). The current study shows the growing burden of the new subtype MetALD in the US population particularly in the

female and Mexican American population.

In our analysis, we found a significant decrease in MASLD prevalence, a significant increase in MetALD prevalence from 1999 to 2018, but no significant change in ALD prevalence in the SLD population. The decreasing proportion of SLD attributable to MASLD may be associated with declining rates of diabetes in the US associated with improved screening processes (20,21), as well as improved screening rates for blood cholesterol (22). Increasing MetALD prevalence in the SLD population may be related to increased trends of occasional binge drinking which may sufficiently qualify for moderate alcohol intake (23). Rates of alcohol use disorder symptoms that indicate heavy alcohol use in the US population were also found to be steady (24,25), which may align with how no significant change in ALD prevalence was found.

Additionally, we found that patients who were ALD predominant were significantly more prone to all-cause mortality than their MASLD predominant counterparts. Similarly, competing risk analysis found that ALD predominant individuals were at a higher risk of cancer-related mortality than MASLD predominant individuals, but no significant differences in CVD-related mortality were found. However, patients described as MetALD were not at a statistically increased risk of overall, cardiovascular and cancer related mortality despite alcohol intake being a known association with higher mortality (26). The quantity of alcohol deemed safe for consumption remains in contention, with recent studies indicating that low alcohol consumption levels raise the risk of some diseases but lower the risk of others (27-29). In previous studies on MASLD, low alcohol consumption has been associated with reduced advanced fibrosis and steatohepatitis risk as compared to lifelong abstainers (28). Individuals with low alcohol consumption were found to have a reduced risk of several types of cancer as well as hypertension, stroke and type 2 diabetes mellitus (29,30). Despite previous studies reporting an increased incidence of CVD in MASLD (31), MetALD and ALD (10), this study found no significant difference in CVD-related mortality when comparing ALD predominant and MetALD against MASLD, possibly due to other causes such as liver-related or cancer-related having a larger influence on mortality in SLD (32). The current study thus shows that the recently introduced criteria in SLD for alcohol use do show distinguishment in segregating the risk of mortality associated with ALD.

Limitations

There are several limitations to the current study. In this study population, MASLD was ascertained using FLI or US-FLI instead of via imaging or biopsy which remains the diagnostic gold standard but diagnosis by imaging in the NHANES 1999–2018 dataset is not available (18). The present study is also unable to account for variations in the type of SLD over longitudinal follow up, such as development of cardiometabolic comorbidities that contribute to MASLD during follow up, which may have potential implications on the mortality outcomes measured. Additionally, self-reported data of alcohol use remains to be subjected by recall bias in participants. Objective data describing alcohol intake such as hair ethyl glucuronide levels were not available from the NHANES. Lastly, data regarding cancer site-specific mortality was not available, limiting our ability to compare association of different SLD types with hepatic versus extrahepatic cancer mortality. Similarly, we were unable to analyse liver-related mortality due to inherent limitations in the data. We were also unable to analyse emerging cardiometabolic and liver-related complications due to difficulties in retrieving complete and high-quality data for these conditions from ICD-10 codes. Lastly, we did not include a control subject group without SLD as the aim of the current study was to examine the differences in clinical outcomes along the spectrum of SLD.

Conclusions

Our study demonstrates that ALD predominant patients are more likely to suffer all-cause mortality and cancer-related mortality as compared to MASLD predominant patients but face no significant difference in CVD-related mortality risk. MetALD patients in turn suffer no significant differences in mortality differences relative to MASLD predominant patients. The present research indicates that the newly established criteria for alcohol use in SLD effectively differentiate and categorize the mortality risk linked to ALD.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical review and informed consent are not required in this article as no confidential patient information was involved.

References

1. Staufer K, Stauber RE. Steatotic Liver Disease: Metabolic Dysfunction, Alcohol, or Both? Biomedicines 2023;11:2108.
2. Cheemerla S, Balakrishnan M. Global Epidemiology of Chronic Liver Disease. Clin Liver Dis (Hoboken) 2021;17:365-70.
3. Aslam A, Kwo PY. Epidemiology and Disease Burden of Alcohol Associated Liver Disease. J Clin Exp Hepatol 2023;13:88-102.
4. American Association for the Study of Liver Diseases. New MASLD Nomenclature. 2023 Jun. Available online: https://www.aasld.org/new-nafld-nomenclature
5. Osna NA, Donohue TM Jr, Kharbanda KK. Alcoholic Liver Disease: Pathogenesis and Current Management. Alcohol Res 2017;38:147-61.
6. Lim WH, Tay P, Ng CH, et al. Meta-analysis: Prevalence and impact of alcohol abstinence in alcohol-associated cirrhosis. Aliment Pharmacol Ther 2024;59:730-41.
7. Toshikuni N, Tsutsumi M, Arisawa T. Clinical differences between alcoholic liver disease and nonalcoholic fatty liver disease. World J Gastroenterol 2014;20:8393-406.
8. Israelsen M, Torp N, Johansen S, et al. MetALD: new opportunities to understand the role of alcohol in steatotic liver disease. Lancet Gastroenterol Hepatol 2023;8:866-8.
9. Israelsen M, Juel HB, Detlefsen S, et al. Metabolic and Genetic Risk Factors Are the Strongest Predictors of Severity of Alcohol-Related Liver Fibrosis. Clin Gastroenterol Hepatol 2022;20:1784-1794.e9.
10. Moon JH, Jeong S, Jang H, et al. Metabolic dysfunction-associated steatotic liver disease increases the risk of incident cardiovascular disease: a nationwide cohort study. EClinicalMedicine 2023;65:102292.
11. NHANES - About the National Health and Nutrition Examination Survey [Internet]. 2023 [cited 2023 Sep 16]. Available online: https://www.cdc.gov/nchs/nhanes/about_nhanes.htm
12. NCHS Data Linkage - Mortality Data [Internet]. 2023 [cited 2023 Sep 16]. Available online: https://www.cdc.gov/nchs/data-linkage/mortality.htm
13. Ruhl CE, Everhart JE. Fatty liver indices in the multiethnic United States National Health and Nutrition Examination Survey. Aliment Pharmacol Ther 2015;41:65-76.
14. Bedogni G, Bellentani S, Miglioli L, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol 2006;6:33.
15. Rinella ME, Lazarus JV, Ratziu V, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. Ann Hepatol 2024;29:101133.

16. Health mortality from major cardiovascular diseases: United States [Internet]. 2019 [cited 2023 Sep 16]. Available online: https://www.cdc.gov/nchs/data/hestat/cardio2007/cardio2007.htm
17. List of causes and corresponding ICD-10 codes [Internet]. [cited 2023 Sep 16]. Available online: https://platform.who.int/mortality/about/list-of-causes-and-corresponding-icd-10-codes
18. Dumitrascu DL, Neuman MG. Non-alcoholic fatty liver disease: an update on diagnosis. Clujul Med 2018;91:147-50.
19. Xiao J, Ng CH, Chan KE, et al. Complete alcohol abstinence increases the risk of NAFLD but not severity. A population analysis with transient elastography. Scand J Gastroenterol 2023;58:76-82.
20. Selvin E, Ali MK. Declines in the Incidence of Diabetes in the U.S.-Real Progress or Artifact? Diabetes Care 2017;40:1139-43.
21. Fang M, Wang D, Coresh J, et al. Trends in Diabetes Treatment and Control in U.S. Adults, 1999-2018. N Engl J Med 2021;384:2219-28.
22. Gao Y, Shah LM, Ding J, et al. US Trends in Cholesterol Screening, Lipid Levels, and Lipid-Lowering Medication Use in US Adults, 1999 to 2018. J Am Heart Assoc 2023;12:e028205.
23. Kanny D, Naimi TS, Liu Y, et al. Trends in Total Binge Drinks per Adult Who Reported Binge Drinking - United States, 2011-2017. MMWR Morb Mortal Wkly Rep 2020;69:30-4.
24. Jager J, Keyes KM, Son D, et al. Cohort and age trends in age 35-45 prevalence of alcohol use disorder symptomology, by severity, sex, race, and education. Drug Alcohol Depend 2021;226:108820.
25. Wong ZY, Koh JH, Muthiah M, et al. Proton Pump Inhibitors Increases Longitudinal Risk of Mortality, Decompensation, and Infection in Cirrhosis: A Meta-Analysis. Dig Dis Sci 2024;69:289-97.
26. Wongtrakul W, Niltwat S, Charatcharoenwitthaya P. The Effects of Modest Alcohol Consumption on Non-alcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis. Front Med (Lausanne) 2021;8:744713.
27. Schrieks IC, Heil AL, Hendriks HF, et al. The effect of alcohol consumption on insulin sensitivity and glycemic status: a systematic review and meta-analysis of intervention studies. Diabetes Care 2015;38:723-32.
28. Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2018;392:1015-35.
29. Population-level risks of alcohol consumption by amount, geography, age, sex, and year: a systematic analysis for the Global Burden of Disease Study 2020. Lancet 2022;400:185-235.
30. Zhong L, Chen W, Wang T, et al. Alcohol and Health Outcomes: An Umbrella Review of Meta-Analyses Base on Prospective Cohort Studies. Front Public Health 2022;10:859947.
31. Chan KE, Ong EYH, Chung CH, et al. Longitudinal Outcomes Associated With Metabolic Dysfunction-Associated Steatotic Liver Disease: A Meta-analysis of 129 Studies. Clin Gastroenterol Hepatol 2024;22:488-498.e14.
32. Golabi P, Paik JM, Eberly K, et al. Causes of death in patients with Non-alcoholic Fatty Liver Disease (NAFLD), alcoholic liver disease and chronic viral Hepatitis B and C. Ann Hepatol 2022;27:100556.

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