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Characteristics and long-term mortality of individuals with MASLD, MetALD, and ALD, and the utility of SAFE score

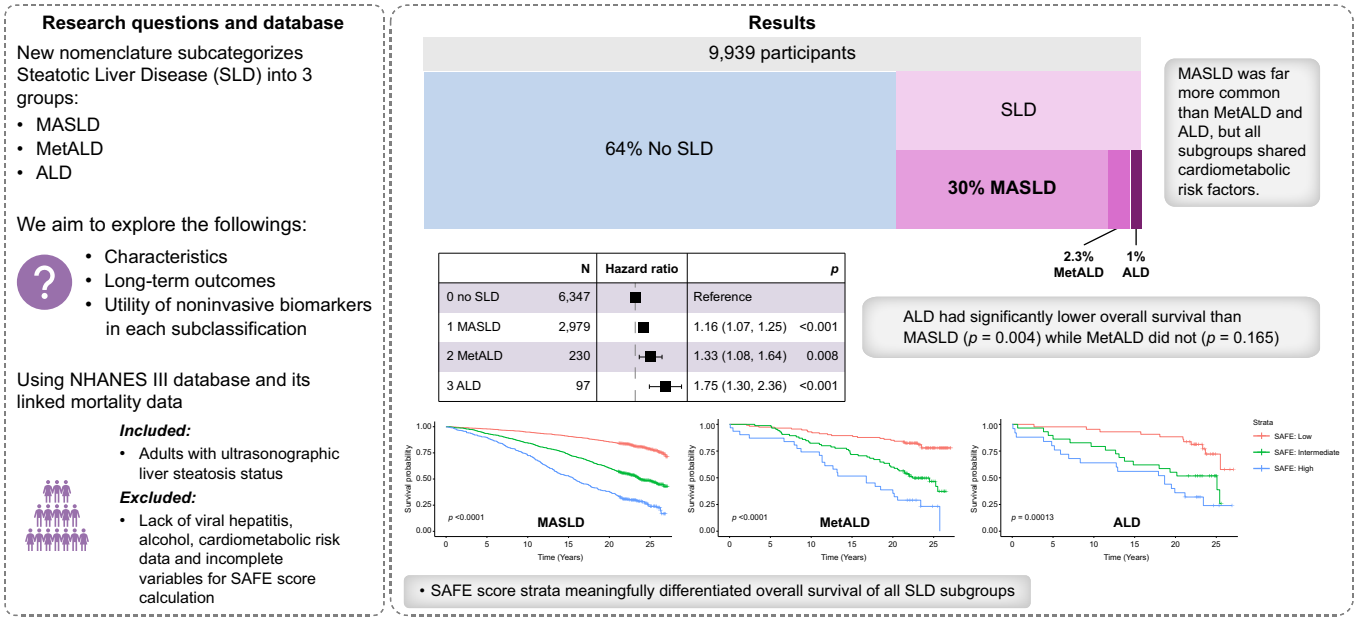
Authors

Pimsiri Sripongpun, Apichat Kaewdech, Prowpanga Udompap, W. Ray Kim

Correspondence

spimsiri@medicine.psu.ac.th (P. Sripongpun), wrkim@stanford.edu (W.R. Kim).

Graphical abstract



Highlights:

- MASLD was far more common than MetALD and ALD.
- ALD subgroup had the worst survival, pointing to the synergistic effect of alcohol and metabolic dysfunction.
- SAFE score clearly stratified long-term outcomes in all SLD subclassifications and might be a useful non-invasive tool.

Impact and implications:

"Steatotic liver disease (SLD)" is a recently introduced term covering three subgroups: MASLD (metabolic dysfunction-associated SLD), MetALD (MASLD with increased alcohol intake), and ALD (alcohol-related liver disease). We explored the characteristics and outcomes of these subgroups among the US population. We found that MASLD was far more common than MetALD and ALD, but all subgroups shared cardiometabolic risk factors. The ALD subgroup has the worst survival, pointing to the synergistic effect of alcohol and metabolic dysfunction. In addition, the SAFE (Steatosis-associated Fibrosis Estimator) score might be a useful non-invasive test to stratify long-term risk in all three SLD subgroups.

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Research article

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Characteristics and long-term mortality of individuals with MASLD, MetALD, and ALD, and the utility of SAFE score

Pimsiri Sripongpun[1,2,*], Apichat Kaewdech[1], Prowpanga Udompap[3], W. Ray Kim[2,*,†]

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Background & Aims: The new nomenclature of steatotic liver disease (SLD) was recently launched with sub-classifications of metabolic dysfunction-associated SLD (MASLD), MASLD with increased alcohol intake (MetALD), and alcohol-related liver disease (ALD). Herein, we aimed to evaluate the characteristics and long-term outcomes associated with these subgroups and the utility of non-invasive biomarkers.

Methods: Using NHANES III (the third National Health and Nutrition Examination Survey) and linked mortality data, all adult participants with available ultrasonographic liver steatosis status were included. Those with viral hepatitis, incomplete data on alcohol consumption, cardiometabolic risk, and missing data that hindered Steatosis-associated Fibrosis Estimator (SAFE) score calculation were excluded. The characteristics of those without SLD (no steatosis on ultrasound), MASLD, MetALD, and ALD were compared. Overall survival (OS) was determined and SAFE score strata were applied to SLD subgroups.

Results: A total of 9,939 participants were eligible; 64% had no SLD, while 30%, 2.3%, and 1% had MASLD, MetALD, and ALD, respectively. A higher proportion of men, as well as active smokers, was observed in the MetALD and ALD groups compared to the MASLD group. Diabetes was more prevalent in the MASLD group than in the MetALD and ALD groups. The ALD subgroup had significantly lower OS than the MASLD group (p = 0.004), but the MetALD did not (p = 0.165). SAFE score strata meaningfully differentiated OS of all SLD subgroups.

Conclusions: MASLD accounted for the largest proportion of SLD. MetALD shared the characteristics of both MASLD and ALD. The ALD subgroup had a significantly lower OS than the MASLD subgroup but there was no difference between MetALD and MASLD. The SAFE score can be used to stratify long-term outcomes in all SLD subgroups.

Introduction

Non-alcoholic fatty liver disease (NAFLD) was the previously recognized term for the disease characterized by hepatic steatosis (fat content of more than 5% in liver tissue) without a history of significant alcohol consumption. From the concept first proposed in the 1980s,[1,2] the disease has become a pandemic involving more than 30% of the global population and can lead to significant liver-related morbidity and mortality.[3] NAFLD is closely related with obesity, diabetes, metabolic syndrome, and the major causes of death in patients with NAFLD are cardiovascular disease and cancer rather than liver-related complications *per se*.[4] Moreover, there were some concerns about the term 'non-alcoholic' as it is potentially stigmatizing, and alcohol consumption greater than a minimal level (>20-30 g/day in women and men) in patients with metabolic risk factors may alter the disease course of fatty liver as well. Therefore, to encourage a better understanding of disease etiologies and pathophysiology, as well as to avoid stigmatization, new nomenclature from a multi-society consensus was recently proposed and announced at the International Liver Congress in June 2023.

The new nomenclature has an umbrella term of 'steatotic liver disease (SLD)' for any patients in whom hepatic steatosis is present.[5–7] There are new sub-classifications under the umbrella term, *i.e.* metabolic dysfunction-associated SLD (MASLD) in the presence of one or more of the following conditions: overweight/obesity, type 2 diabetes mellitus, and metabolic dysregulation; MASLD and increased alcohol intake (MetALD) which applies to individuals who have MASLD and consume between 20-50 g (for females) and 30-60 g (for males) of alcohol daily; and alcohol-related liver disease (ALD) for those who consumed more alcohol than the threshold for MetALD criteria.

The characteristics and long-term outcomes of these new subclasses, as well as the potential benefits of employing non-invasive biomarkers within these subgroups, remain uncertain.

* Corresponding authors. Addresses: Gastroenterology and Hepatology Unit, Division of Internal Medicine, Faculty of Medicine, Prince of Songkla University, 15 Karnchanavanit Road, Hat Yai, Thailand 90110 (P. Sripongpun), or Division of Gastroenterology and Hepatology, Stanford University School of Medicine, 430 Broadway Street, 3rd Floor C-327, Redwood City, CA 94063, USA (W.R. Kim).
E-mail addresses: spimsiri@medicine.psu.ac.th (P. Sripongpun), wrkim@stanford.edu (W.R. Kim).
† Senior author
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Recently, the Steatosis-associated Fibrosis Estimator (SAFE) score was introduced as a simple tool to screen for significant fibrosis (F2) in individuals with NAFLD in the primary care setting. It demonstrated a high negative predictive value, outperformed Fibrosis-4 (FIB-4) and NAFLD fibrosis score in the detection of F≥2 fibrosis, and is predictive of long-term mortality.[8] Therefore, we aimed to analyze the clinical characteristics, mortality rates, and utility of the SAFE score and FIB-4 in individuals with MASLD, MetALD, and ALD.

Materials and methods

Study design and study population

This is a secondary data analysis of the participants in the third National Health and Nutrition Examination Survey (NHANES III). NHANES III is a federally administered study that was undertaken between the years 1988 and 1994. Its primary objective was to assess and analyze the health and nutritional status of the population residing within the US. The survey comprises stratified samples that have been carefully constructed to ensure their representativeness of non-institutionalized citizens. The NHANES III dataset contains information on the ultrasonographic evaluation for hepatic steatosis, as well as linked mortality data of the participants. The mortality data was censored on December 31, 2015, allowing for the evaluation of long-term outcomes.

From the NHANES III dataset, all individuals who were 18 years of age or older and had available data on ultrasonographic determination of hepatic steatosis (graded as normal, mild, moderate, and severe steatosis) were identified. The exclusion criteria were as follows: 1) individuals with positive HBsAg and/or HCV antibody, 2) no available mortality and alcohol consumption data, 3) no available data on variables used to calculate the SAFE/FIB-4 scores, *i.e*., age, aspartate aminotransferase (AST), alanine aminotransferase (ALT), globulin level (serum total protein minus albumin), body mass index (BMI), platelet count, and diabetes status, and 4) no available data on cardiometabolic risks, *i.e*. BMI, waist circumference, diagnosis of whether they had hypertension, dyslipidemia, and diabetes.

Baseline demographic, clinical, laboratory, and mortality data were collected. The NHANES III dataset, which is publicly available (https://wwwn.cdc.gov/nchs/nhanes/nhanes3/Default.aspx), was obtained from the Center for Disease Control and Prevention.

This work was deemed exempt from human subject research by the Stanford Institutional Review Board and Human Research Ethic Committee, Faculty of Medicine, Prince of Songkla University, as the NHANES III dataset has already undergone deidentification, ensuring the anonymity of all participants' personal information (Exemption certification number: REC.66-337-14-1). The study was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki.

Definition of SLD subclassification and risk groups

Individuals with hepatic steatosis present on ultrasonography either mild, moderate, or severe grade were considered as having SLD. Among those with SLD, participants with at least one of the following cardiometabolic criteria: BMI ≥25 kg/m^2, waist circumference ≥80/90 cm in women and men, respectively, diagnosis of hypertension, diabetes or fasting serum glucose >5.6 mmol/L or HbA1c >5.7%, or hyperlipidemia/plasma triglyceride >1.7 mmol/L/plasma HDL-cholesterol <1.0 mmol/L *plus* history of alcohol intake <20/30 gm/day in women/men were categorized as the MASLD group. Participants with SLD who had ≥1 aforementioned cardiometabolic criteria and reported alcohol consumption of 20-50 g/day in women or 30-60 g/day in men were categorized into the MetALD group. Those with SLD who reported alcohol consumption of more than 50 g/day in women, or 60 g/day in men were categorized into the ALD group regardless of their cardiometabolic risk profile.

The SAFE score was then calculated in eligible participants using the following formula: SAFE = (2.97 × age) + (5.99 × BMI [BMI >40 set to 40]) + (62.85 × diabetes [0 if absent, 1 if present]) + (154.85 × Ln (AST)) – (58.23 × Ln (ALT)) + (195.48 × Ln (globulin, g/dl)) – (141.61 × Ln (platelets, $10^9/\mu l$)) – 75. The participants with SAFE score <0, 0∼100, and ≥100 were categorized into low-, intermediate-, and high-risk groups for long-term mortality, respectively.

The FIB-4 score was also calculated using the formula: (Age [year] x AST [U/L])/((platelets [10^9/L]) x (ALT [U/L])$^{(1/2)}$). For the FIB-4 score, we stratified those with SLD into three risk categories as follows: FIB-4 <1.3, 1.3∼2.67, and >2.67, respectively.

Assessment of long-term outcomes

The assessment of overall mortality involved calculating the elapsed time between the date of investigation in NHANES III entry and death from any cause. The data set only included information about the cause of death from cardiovascular disease, cancer, and some other causes (https://www.cdc.gov/nchs/data/datalinkage/public-use-2015-linked-mortality-file-description.pdf), however, the cause of death from liver disease was not specified. We examined mortality resulting from cardiovascular disease and cancer within each SLD subgroup.

Statistical analysis

Baseline characteristics between four participants group were determined; characteristics between other groups and the MASLD group were compared using t-test or Wilcoxon rank sum test for continuous variables, and the chi-square or fisher-exact test for categorical variables as appropriate. Long-term outcome, determined by overall survival (OS) of participants in each group, was demonstrated using the Kaplan-Meier method, and OS was compared using the log-rank test. Cox proportional hazard regressions were used to adjust the mortality risk for age, gender, race-ethnicity, and smoking status. Competing risk analyses were used to determine the cumulative incidence of specific causes of death in each SLD subclassification. We only used actual data from the NHANES III individuals, not the weighted data for population estimation in this analysis.

Results

Baseline characteristics

Among participants of NHANES III, ultrasonographic determination of hepatic steatosis was performed only in participants aged between 20 and 74 years. Thus, of 13,856 participants with available hepatic steatosis status data, 3,122 individuals

were excluded for missing alcohol consumption or follow-up data (n = 2,714) and for having positive hepatitis viral serology (n = 408), leaving 10,734 evaluable individuals. In addition, 102 individuals were missing information on cardiometabolic risk factors and 693 were missing laboratory data necessary for calculating SAFE and FIB-4 scores, and were thus excluded from parts of the analysis. Thus, the remaining 9,939 participants constituted the core analysis data set (Fig. S1).

In Table 1, hepatic steatosis was found in 3,592 patients (36.1%), of whom 2,980 (30.0% of the entire cohort), 230 (2.3%), and 97 (1.0%) were categorized into MASLD, MetALD, and ALD groups, respectively. The remaining 285 participants with steatosis but had no cardiometabolic factors or significant alcohol consumption were grouped as 'uncategorized'. The remaining 6,347 (63.9%) participants had no evidence of SLD.

Compared to individuals with MASLD, those with MetALD and ALD were younger, while those without SLD were the youngest. Men were over-represented in the MetALD and ALD groups. Alcohol consumption was progressively higher whereas BMI was progressively lower in the MetALD and ALD groups. Similarly, the prevalence of diabetes and dyslipidemia as well as non-smoking was lower in MetALD and ALD. By definition, individuals with MASLD and MetALD had at least one cardiometabolic comorbidity with most individuals having three risk factors. Of individuals who met the ALD diagnosis criteria, 92% had at least one cardiometabolic factor.

Table 2 reports laboratory data. Serum aminotransferase activities were modestly but significantly higher in those with MetALD compared to MASLD. As expected, serum AST activities were noticeably higher for ALD compared to other diagnoses. Parameters of hepatic synthetic function including serum albumin and bilirubin concentrations were normal across the groups. Both SAFE and FIB-4 scores estimated that most individuals in all of the categories were most likely to have low probability of significant and advanced fibrosis, respectively. Individuals with ALD tended to have higher SAFE and FIB-4 scores.

The baseline characteristics of those with uncategorized SLD were significantly different from individuals with MASLD. Individuals with uncategorized SLD appeared to be younger, more often female, predominately non-smokers, with a lower BMI, no cardiometabolic risk, and significantly better liver biochemistry values. Moreover, when we looked at the hepatic steatosis grading by ultrasound, 67.4% of uncategorized SLD were graded as 'mild hepatic steatosis', in contrast to only around 30% in those with MASLD, MetALD, and ALD. Patients in the 'uncategorized SLD' subgroup were not included in the further survival analyses.

Survival of individuals with SLD and prediction by non-invasive biomarkers

NHANES III participants were followed for up to 27 years. Fig. 1 displays Kaplan-Meier survival of individuals without SLD and those with MASLD, MetALD, and ALD. Survival was ordered in the expected direction, with individuals without SLD having the best survival, followed by those with MASLD, MetALD, and ALD. For example, the 20-year survival probability was 69.7%, 69.1%, and 64.9% for MASLD, MetALD and ALD, respectively. Fig. 2 shows the results of the multivariable Cox model. After adjustment for age, sex, race-ethnicity, and smoking status, MASLD, MetALD and ALD were associated with 16%, 33% and 75% higher mortality, respectively, compared to no SLD. When focused on only those with SLD and using individuals with MASLD as a reference group (Fig. S2), we found that those

Table 1. Characteristics of NHANES III participants according to the new definition of steatotic liver disease.

	No SLD	MASLD	MetALD	ALD	Uncategorized
Total number	6347	2,980	230	97	285
Age, years, median (IQR)	39 (29,55)	48 (36,62)	44 (32,57)*	44 (35,55)*	28 (24,37)*
Male sex, n (%)	3,158 (49.8)	1,603 (53.8)	166 (72.2)*	84 (86.6)*	93 (32.6)*
Race-Ethnicity, n (%)					
NH White	2,651 (41.8)	1,108 (37.2)	88 (38.3)	29 (29.9)	131 (46)*
NH Black	1,896 (29.9)	678 (22.8)	42 (18.3)	28 (28.9)	70 (24.6)
Mexican American	1,578 (24.9)	1,093 (36.7)	92 (40)	39 (40.2)	78 (27.4)
Other	222 (3.5)	101 (3.4)	8 (3.5)	1 (1)	6 (2.1)
Alcohol, g/day, median (IQR)	1.4 (0,8)	0 (0,4)	41.9 (32.4,47.9)*	83.8 (71.8,112)*	1.8 (0,8)*
BMI, kg/m^2, median (IQR)	25.4 (22.7,28.5)	29.4 (26.2,33.5)	28.4 (25.8,32.4)	26 (22.3,30.1)*	21.1 (19.8,22.6)*
Diabetes, n (%)	1,416 (22.3)	1,289 (43.3)	67 (29.1)*	24 (24.7)*	0*
Hypertension, n (%)	2,757 (43.6)	1,893 (63.7)	162 (71.1)*	68 (70.8)	0*
Dyslipidemia, n (%)	1,094 (17.2)	646 (21.7)	47 (20.4)	13 (13.4)	0*
Number of cardiometabolic risk, n (%)					
0	991 (16.3)	0	0	7 (7.8)*	285 (100)*
1	1,559 (25.7)	360 (12.7)	27 (13)	21 (23.3)	0
2	1,498 (24.7)	557 (19.7)	52 (25.1)	21 (23.3)	0
3	1,143 (18.8)	823 (29.1)	58 (28)	19 (21.1)	0
4	703 (11.6)	718 (25.4)	49 (23.7)	18 (20)	0
5	171 (2.8)	367 (13)	21 (10.1)	4 (4.4)	0
Smoking status, n (%)					
Non-smoker	2,791 (44)	1,274 (42.8)	59 (25.7)*	18 (18.6)*	152 (53.3)*
Ex-smoker	1,530 (24.1)	1,002 (33.6)	71 (30.9)	28 (28.9)	35 (12.3)
Current smoker	2,026 (31.9)	703 (23.6)	100 (43.5)	51 (52.6)	98 (34.4)

The comparisons were made between those with SLD, using MASLD as the reference group, using t-test or Wilcoxon rank sum test for continuous variables, and the chi-square or fisher-exact test for categorical variables as appropriate.

*p <0.05 compared to MASLD group. ALD, alcohol-related liver disease; BMI, body mass index; MASLD, metabolic dysfunction-associated SLD; MetALD, MASLD and increased alcohol intake; NH, non-Hispanic; SLD, steatotic liver disease.

Table 2. Laboratory characteristics of the NHANES III participants in this study.

	No SLD	MASLD	MetALD	ALD	Uncategorized
Total number	6,347	2,980	230	97	285
AST, U/L, median (IQR)	19 (16–22)	20 (17–26.2)	23 (19–35.8)*	29 (20–48)*	18 (15–22)*
ALT, U/L, median (IQR)	13 (10–18)	18 (13–26)	21 (14–33)*	21 (14–43)*	12 (9–17)*
ALP, U/L, median (IQR)	78 (65–95)	86 (72–104.2)	84 (72–100)	86 (74–101)	69 (56–85)*
Globulin, g%, median (IQR)	3.2 (2.9–3.5)	3.3 (3–3.6)	3.3 (2.9–3.5)	3.3 (3–3.7)	3.1 (2.8–3.3)*
Albumin, g%, median (IQR)	4.2 (3.9–4.4)	4.1 (3.9–4.4)	4.2 (4–4.4)*	4.3 (4–4.4)*	4.2 (4–4.4)*
Platelet, x10^9, median (IQR)	268.5 (228.5–312.5)	269.5 (229–318.5)	271.8 (230–1,313.4)	255.5 (219–302.5)	264.5 (225.5–304)*
SAFE, median (IQR)	-52.5 (-110.5 to 20.9)	14.1 (-52.2 to 86.8)	6.1 (-56.2 to 77)	25.5 (-40.4 to 106)	-122.7 (-161.7 to -78.9)*
SAFE risk group, n (%)					
Low	4,372 (68.9)	1,333 (44.7)	105 (45.7)	40 (41.2)	265 (93)*
Intermediate	1,416 (22.3)	1,025 (34.4)	83 (36.1)	30 (30.9)	17 (6)
High	559 (8.8)	622 (20.9)	42 (18.3)	27 (27.8)	3 (1.1)
FIB-4, median (IQR)	0.7 (0.5–1.1)	0.9 (0.6–1.3)	0.8 (0.6–1.3)	1.1 (0.7–1.6)*	0.6 (0.5–0.8)*
FIB-4 group, n (%)					
<1.3	5,239 (82.5)	2,300 (77.2)	170 (73.9)	56 (57.7)*	261 (91.6)*
1.3∼2.67	1,022 (16.1)	614 (20.6)	52 (22.6)	31 (32)	20 (7)
≥2.67	86 (1.4)	66 (2.2)	8 (3.6)	10 (10.3)	4 (1.4)

The comparisons were made between those with SLD, using MASLD as the reference group, using t-test or Wilcoxon rank sum test for continuous variables, and the chi-square or fisher-exact test for categorical variables as appropriate.
*p <0.05 compared other SLD to MASLD group. ALD, alcohol-related liver disease; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MASLD, metabolic dysfunction-associated SLD; MetALD, MASLD and increased alcohol intake; SAFE, Steatosis-associated Fibrosis Estimator; SLD, steatotic liver disease.

with MetALD showed a non-significantly higher long-term overall mortality at an adjusted hazard ratio (aHR) of 1.16 (95% CI 0.94-1.44). ALD was significantly associated with a 57% higher mortality than MASLD.

Fig. S3A graphically illustrates the association between the amount of alcohol use and risk of mortality among individuals with MetALD and ALD. The relationship is quite linear, without noticeable lower or upper bounds for alcohol consumption (as the lowest threshold for defining MetALD was 20 g/day). Fig. S3B demonstrates that the number of cardiometabolic factors correlates with future risk of mortality – a significantly higher mortality was observed in those with ≥3 risk factors.

Fig. 3A-C shows the association between the SAFE score strata and survival in individuals with MASLD, MetALD, and ALD. The score, in its three tiers, namely SAFE <0 (low risk), 0∼100 (intermediate risk) and ≥100 (high risk), was able to stratify all three groups according to their probability of mortality. Fig. 4A shows this association in a multivariable model. Compared to low-risk SAFE scores, intermediate- and high-risk SAFE scores were associated with a 31% and 90% increase in mortality, respectively. In contrast, when the analysis was repeated for FIB-4, only the highest stratum (FIB-4 ≥2.67) was significantly associated with an increased risk of mortality, with a 53% risk increase. In both analyses, other significant variables included age, male sex, 'other' race and smoking status. ALD was associated with an approximately 47-50% increase in mortality and MetALD with a 14-15% increase, compared to MASLD.

In those with MASLD, nearly the same proportions of death were attributed to cancer (22.8%) and cardiovascular disease (22.1%). In individuals with MetALD and ALD, death from malignancy was more commonly observed than that of cardiovascular disease (28.6% *vs*. 22% in MetALD, and 28.9% *vs.* 17.8%, respectively). The cumulative incidence of death from

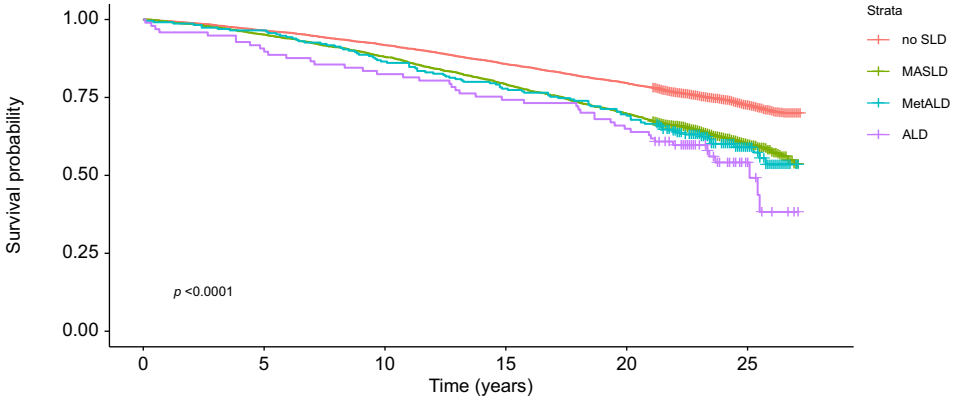


Fig. 1. Kaplan-Meier survival curves of all four groups of participants according to the new nomenclature. Level of significance: p <0.0001 (log-rank test). ALD, alcohol-related liver disease; MASLD, metabolic dysfunction-associated SLD; MetALD, MASLD and increased alcohol intake; SLD, steatotic liver disease.

Variable		N	Hazard ratio	p
Group	0 no SLD	6,347	Reference	
	1 MASLD	2,979	1.16 (1.07, 1.25)	<0.001
	2 MetALD	230	1.33 (1.08, 1.64)	0.008
	3 ALD	97	1.75 (1.30, 2.36)	<0.001
Age		9,653	1.09 (1.08, 1.09)	<0.001
Male		9,653	1.31 (1.21, 1.42)	<0.001
Race/Ethnicity	NH White	3,876	Reference	
	NH Black	2,643	1.22 (1.12, 1.34)	<0.001
	Mexican American	2,802	1.05 (0.96, 1.15)	0.318
	Other	332	0.70 (0.54, 0.89)	0.004
Smoking	Non-smoker	4,142	Reference	
	Ex-smoker	2,631	1.26 (1.15, 1.38)	<0.001
	Current smoker	2,880	1.97 (1.79, 2.17)	<0.001

Fig. 2. The adjusted hazard ratios for long-term mortality of participants in each group, using Cox proportional hazard regressions. Levels of significance as shown in the table. ALD, alcohol-related liver disease; MASLD, metabolic dysfunction-associated SLD; MetALD, MASLD and increased alcohol intake; NH, non-Hispanic; SLD, steatotic liver disease.

cardiovascular cause, malignancy, and other causes are shown in Fig. 5. Although not statistically significant, there was a trend towards increased risk of cardiovascular death in the MetALD group compared to the MASLD group. Death from malignancy was highest in those with ALD, followed by MetALD, and MASLD.

Discussion

In the present study, we describe the characteristics of individuals with SLD among US adults according to the new nomenclature and definitions. Based on the NHANES III data, we report the prevalence of MASLD, MetALD, and ALD as 30%, 2.3%, and 1.0%, respectively. Among those with ALD, at least one cardiometabolic risk factor was present in 92%, suggesting an important role of insulin resistance in liver disease in heavy alcohol users in the US. MASLD in our study was associated with a 16% increase in mortality compared to those without SLD, with higher mortality in MetALD and ALD (33% and 75% increases, respectively). In addition to these diagnostic categories, factors that independently influenced future risk of mortality included age, male sex, current and past smoking, and indicators of liver fibrosis, including the SAFE and FIB-4 scores.

Our data as a whole validate one of the goals of the nomenclature process, namely to preserve the conceptual definition of NAFLD, while employing an affirmative, rather than exclusionary, and non-stigmatizing term. To date, an extensive overlap has been reported, with ~99% of individuals with NAFLD in NHANES and other data sets meeting the criteria for MASLD.[9] In our study, the HR associated with MASLD (1.16) was similar to that in a prior NHANES III study by Alvarez *et al.*, which noted a 20% increase in all-cause mortality for individuals with NAFLD (HR 1.20; 95% CI 1.08, 1.34).[10]

Intuitively, survival for MetALD is expected to fall between MASLD and ALD. Indeed, in our data, MetALD was associated with slightly and non-significantly higher risk of overall mortality compared to MASLD, whereas ALD was associated with more than 50% higher mortality than MASLD. When cause-specific mortality was assessed, somewhat similar trends could be discerned. Whether individuals with MetALD follow the pattern of MASLD or ALD may be dependent on the amount of alcohol exposure. Given the data shown in Fig. S3, proportions of individuals consuming different levels of alcohol would determine the prognosis when the entire group is assessed together. Prior studies highlighted that coexistence of alcohol and metabolic syndrome can accelerate hepatic fibrosis,[11,12] increase non-malignant liver-related mortality,[13] as well as hepatocellular carcinoma development.[14] It is increasingly recognized that no level of alcohol intake is safe,[11,15,16] whereas abstaining from alcohol could mitigate its harmful effects.[17]

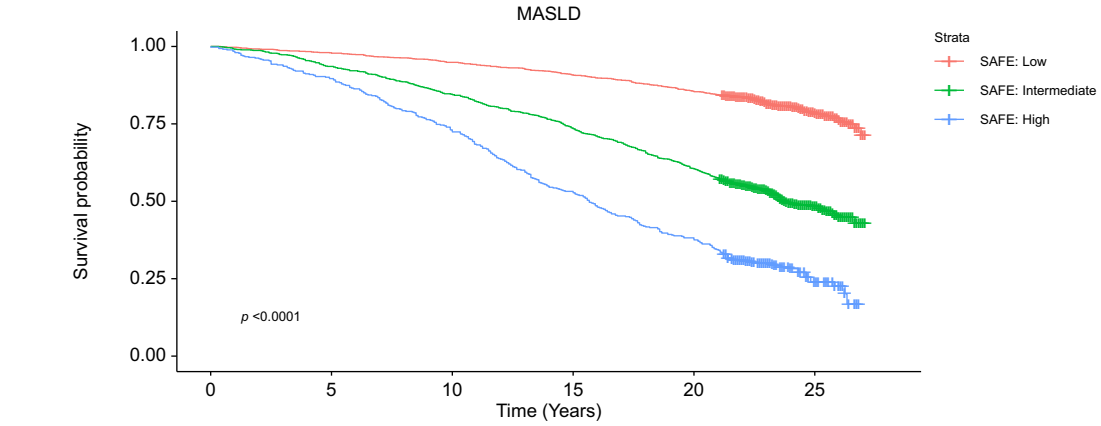
A small proportion (7.9%) of participants with evidence of hepatic steatosis were not able to be categorized into any of the SLD subgroups given that they did not have cardiometabolic risk factors. Collectively, the characteristics of patients in the uncategorized SLD subgroup were akin to those without SLD rather than any SLD subclassification. We believe that this is in part explained by the incorrect diagnosis of steatosis on ultrasound.

The current AASLD practice guidance on the clinical assessment and management of NAFLD recommends using FIB-4 score as a primary assessment for patients with clinical suspicion for NAFLD. With the new nomenclature, when FIB-4 is used to correlate with future survival in individuals with MASLD, MetALD, and ALD, a significantly increased risk of long-term mortality was observed only in the highest FIB-4 stratum (>2.67). The SAFE score was better able to stratify individuals with MASLD, MetALD, and ALD across the risk levels. This is consistent with its design – the SAFE score was developed to detect earlier stages of fibrosis in patients with NAFLD,[8] whereas FIB-4 was designed to diagnose advanced fibrosis[18] and has limited sensitivity in differentiating early stage fibrosis *vs*. no fibrosis.[19]

There are several limitations to our study. As the NHANES III survey was conducted in 1988-1994, as discussed above, ultrasonography is not highly sensitive or specific for the diagnosis of steatosis. Undoubtedly, there were misclassifications both ways. However, given our sample size, we believe the trend we observed benefits from the law of large numbers. For example, our demographic and clinical data appear internally consistent with the profile of patients with SLD. We also acknowledge that the number of individuals classified as ALD was small (n = 97), accounting for only 1% of the entire cohort (2.9% of the entire SLD population), providing barely sufficient power (85%) in the survival analysis. We suspect that this is a result of underreporting of alcohol consumption in the survey. Such underreporting would shift patients with ALD to MetALD and those with MetALD to MASLD, potentially negating differences between groups.

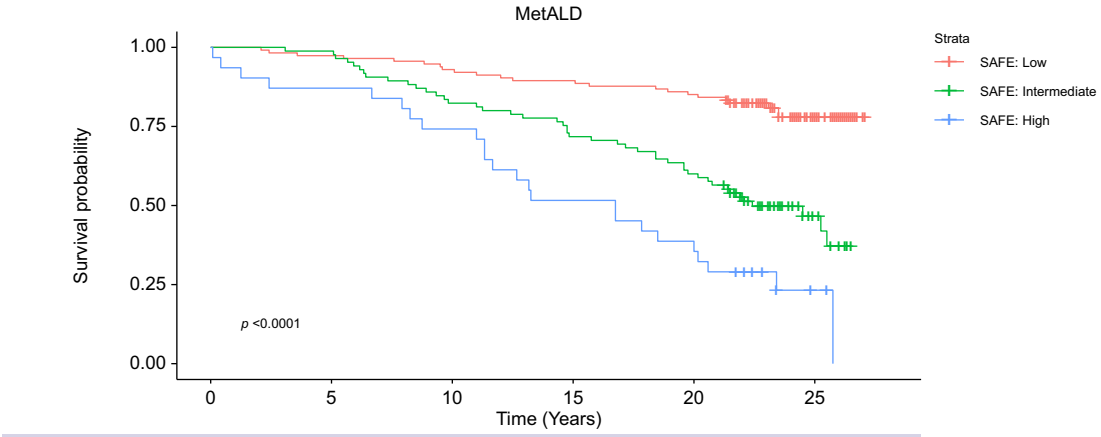
Other limitations include that this study is based only on the data collected at a single time point to predict long-term outcomes. Incorporating data over time may refine correlation of the predictors with long-term mortality. The survey was conducted three decades ago and some of the descriptive data may no longer be representative of patients with SLD today, including the prevalence of obesity and the metabolic syndrome and the race/ethnicity makeup of the population. We

A



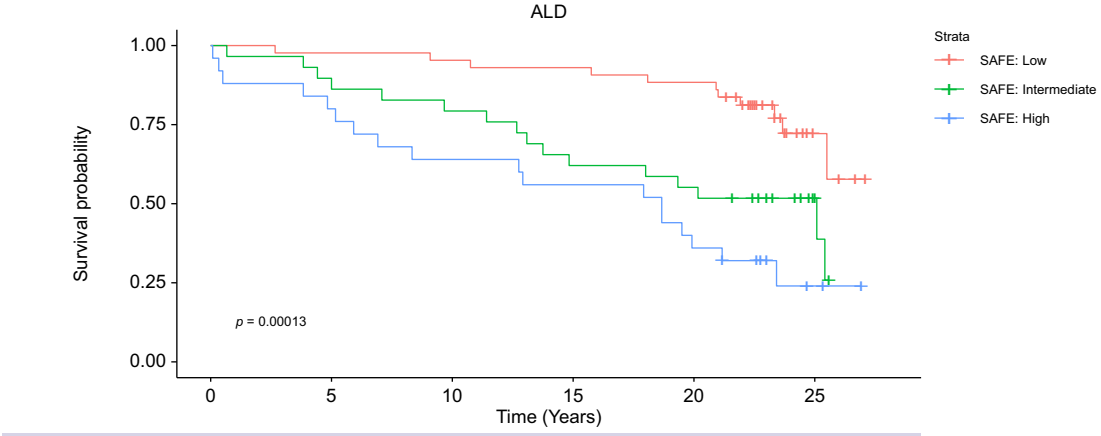
N° at risk						
SAFE: Low	1,519	1,488	1,441	1,380	1,300	351
SAFE: Intermediate	1,008	943	853	743	611	137
SAFE: High	453	406	331	241	173	30

B



N° at risk						
SAFE: Low	114	111	106	102	97	28
SAFE: Intermediate	85	84	70	61	51	11
SAFE: High	31	27	23	16	12	2

C



N° at risk						
SAFE: Low	43	42	41	40	38	5
SAFE: Intermediate	29	26	23	18	16	5
SAFE: High	25	20	16	14	9	2

Fig. 3. Kaplan-Meier survival curves of MASLD, MetALD, and ALD subgroups categorized by SAFE score strata. (A) MASLD; level of significance: p <0.0001 (log-rank test); (B) MetALD; level of significance: p <0.0001 (log-rank test); (C) ALD; level of significance: p = 0.00013 (log-rank test). ALD, alcohol-related liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, MASLD and increased alcohol intake; NH, non-Hispanic; SAFE, Steatosis-associated Fibrosis Estimator.

A

Variable		N	Hazard ratio	p
Group	1 MASLD	2,979	Reference	
	2 MetALD	230	1.12 (0.90, 1.39)	0.296
	3 ALD	97	1.42 (1.05, 1.93)	0.023
SAFE_level	<0	1,675	Reference	
	0~100	1,122	1.31 (1.13, 1.53)	<0.001
	≥100	509	1.90 (1.60, 2.26)	<0.001
Age		3,306	1.08 (1.07, 1.08)	<0.001
Male		3,306	1.15 (1.02, 1.30)	0.019
Race-Ethnicity	NH White	1,225	Reference	
	NH Black	747	1.02 (0.88, 1.18)	0.798
	Mexican American	1,224	0.92 (0.80, 1.05)	0.207
	Other	110	0.60 (0.41, 0.87)	0.008
Smoking	Non-smoker	1,351	Reference	
	Ex-smoker	1,101	1.24 (1.08, 1.43)	0.002
	Current smoker	854	2.08 (1.79, 2.42)	<0.001

B

Variable		N	Hazard ratio	p
Group	1 MASLD	2,979	Reference	
	2 MetALD	230	1.14 (0.92, 1.42)	0.234
	3 ALD	97	1.47 (1.09, 2.00)	0.013
FIB4_level	<1.3	2,525	Reference	
	1.3~2.67	697	1.09 (0.96, 1.24)	0.195
	≥2.67	84	1.53 (1.18, 1.99)	0.001
Age		3,306	1.08 (1.08, 1.09)	<0.001
Male		3,306	1.15 (1.02, 1.29)	0.027
Race-Ethnicity	NH White	1,225	Reference	
	NH Black	747	1.13 (0.97, 1.30)	0.112
	Mexican American	1,224	0.96 (0.84, 1.10)	0.545
	Other	110	0.65 (0.44, 0.95)	0.025
Smoking	Non-smoker	1,351	Reference	
	Ex-smoker	1,101	1.26 (1.10, 1.44)	0.001
	Current smoker	854	2.02 (1.74, 2.34)	<0.001

Fig. 4. Survival stratified by SAFE and FIB-4 scores. (A) SAFE score stratification but not (B) FIB-4 stratification is significantly associated with survival after adjustment with age, sex, ethnicity, and smoking status in individuals with steatotic liver disease (using Cox proportional hazard regressions; levels of significance as shown in the table). ALD, alcohol-related liver disease; FIB-4, Fibrosis-4; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, MASLD and increased alcohol intake; SAFE, Steatosis-associated Fibrosis Estimator.

believe, however, the biological associations reported here would likely hold.

In summary, following the new nomenclature and classification, we provide updated data on the characteristics and long-term outcomes of US adults with MASLD, MetALD, and ALD. SLD was prevalent with the majority belonging in the MASLD category. MetALD shared the characteristics of MASLD and ALD. Multiple cardiometabolic risks were commonly seen in these individuals, including those with ALD. Fibrosis indicators, including the SAFE and FIB-4 scores, were predictive of subsequent mortality of US adults with SLD. These data obtained in the sample of US adults generalizable to the population enhance our knowledge of the epidemiology and impact of the entities defined in the recent nomenclature. The continuous impact of alcohol on future mortality and the high prevalence of cardiometabolic factors in individuals with ALD highlight the need for further research focused on the individuals subject to liver injury from concomitant alcohol use and insulin resistance.

Characteristic	N	N Event	Years 10	Years 20	p value[1]
Death from cardiovascular cause					
SLD_group	3,307	275			>0.9
1 MASLD			3.2% (2.6%, 3.9%)	6.9% (6.1%, 7.9%)	
2 MetALD			4.8% (2.5%, 8.1%)	7.4% (4.5%, 11%)	
3 ALD			1.0% (0.09%, 5.1%)	5.2% (1.9%, 11%)	
Death from malignancy					
SLD_group	3,307	294			0.10
1 MASLD			3.2% (2.6%, 3.9%)	7.1% (6.2%, 8.0%)	
2 MetALD			3.9% (1.9%, 7.0%)	9.2% (5.9%, 13%)	
3 ALD			10% (5.3%, 17%)	11% (6.0%, 19%)	
Death from other causes					
SLD_group	3,307	684			0.6
1 MASLD			5.5% (4.7%, 6.4%)	16% (15%, 17%)	
2 MetALD			4.4% (2.2%, 7.6%)	14% (9.8%, 19%)	
3 ALD			6.2% (2.5%, 12%)	19% (12%, 27%)	

[1] Gray's Test

Fig. 5. Cumulative incidences of cardiovascular, cancer, and other cause of death among individuals with SLD, using competing risk analyses. Levels of significance as shown in the table (Grey's test). ALD, alcohol-related liver disease; MASLD, metabolic dysfunction-associated SLD; MetALD, MASLD and increased alcohol intake; SLD, steatotic liver disease.

Affiliations

[1]*Gastroenterology and Hepatology Unit, Division of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Hat Yai, Thailand;* [2]*Division of Gastroenterology and Hepatology, Department of Medicine, Stanford University, Redwood City, California, USA;* [3]*Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, USA*

Abbreviations

ALD, alcohol-related liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, Fibrosis-4; MASLD, metabolic dysfunction-associated SLD; MetALD, MASLD and increased alcohol intake; NAFLD, non-alcoholic fatty liver disease; NHANES III, the third National Health and Nutrition Examination Survey; OS, overall survival; SAFE score, Steatosis-associated Fibrosis Estimator score; SLD, steatotic liver disease.

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Conflict of interest

All authors have no potential competing interest related to this research article. All investigators had access to the study data, reviewed and approved the final manuscript.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Sripongpun P and Kim WR designed the study. Sripongpun P and Kaewdech A wrote the study protocol. Sripongpun P collected the data and performed the data analysis. Sripongpun P, Kaewdech A, and Udompap P interpret the data and wrote the manuscript. Kim WR supervised the study and performed critical revision of the manuscript. Guarantor of the article: Sripongpun P, MD.

Data availability statement

The NHANES III datasets used for the analysis in this study are publicly available. Access to the resource can be obtained at the following URL: https://wwwn.cdc.gov/nchs/nhanes/nhanes3/Default.aspx.

Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2024.101127.

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