Original research

Prevalence of steatotic liver disease, advanced fibrosis and cirrhosis among community-dwelling overweight and obese individuals in the USA

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ABSTRACT

Background There are limited prospective data among overweight and obese individuals on the prevalence of advanced fibrosis, and cirrhosis using advanced MRI-based methods in the USA. The aim of this study was to fill that gap in knowledge by prospectively determining the MRI-based prevalence of steatotic liver disease (SLD) and its subcategories, advanced fibrosis and cirrhosis among overweight and obese individuals residing in the USA.

Methods This is a cross-sectional analysis of prospectively enrolled overweight or obese adults aged 40–75 years from primary care and community-based settings in Southern California. Participants were classified as having SLD if MRI proton density fat fraction ≥5%, and subclassified as metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction and alcohol-associated liver disease (MetALD) and alcohol-related liver disease (ALD) consistently with the new nomenclature guidance per AASLD–EASL–ALEH. Advanced fibrosis and cirrhosis were defined as magnetic resonance elastography (MRE) ≥3.63 kPa and MRE ≥4.67 kPa, respectively.

Results The cohort included 539 participants with mean (±SD) age of 51.5 (±13.1) years and body mass index of 32.6 (±6.2) kg/m^2, respectively. The prevalence of SLD, advanced fibrosis and cirrhosis was 75%, 10.8% and 4.5%, respectively. The prevalence of MASLD, MetALD and ALD was 67.3%, 4.8% and 2.6%, respectively. There was no difference in prevalence of advanced fibrosis and cirrhosis among subcategories.

Conclusions Using advanced MRI methods among community-dwelling overweight and obese adults, the prevalence of cirrhosis was 4.5%. Most common SLD subcategory was MASLD with 67% of individuals, whereas MetALD and ALD were less common. Systematic screening for advanced fibrosis among overweight/obese adults may be considered.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ With the introduction of the new nomenclature of steatotic liver disease (SLD), there have been several studies describing the prevalence of SLD and its subcategories. However, none provided prospectively collected data using advanced MRI methods and measurements of quantitative alcohol biomarkers, including urine ethyl glucuronide and blood-based phosphatidylethanol, on the prevalence of advanced fibrosis and cirrhosis among overweight and obese Americans across the spectrum of SLD.

WHAT THIS STUDY ADDS

⇒ This cross-sectional analysis of a prospective cohort study conducted in the USA using MRI proton density fat fraction and magnetic resonance elastography among overweight and obese individuals, demonstrated that the prevalence of advanced fibrosis and cirrhosis was 10.8% and 4.5%, respectively. The prevalence of SLD was 75%, with 67.3% having metabolic dysfunction-associated steatotic liver disease, 4.8% having metabolic dysfunction and alcohol-associated liver disease and 2.6% having alcohol-related liver disease.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings support a systematic screening for advanced fibrosis in overweight and obese adults.

INTRODUCTION

Historically, steatotic liver disease (SLD) was subcategorised into non-alcoholic fatty liver disease (NAFLD), which by definition excluded more than modest alcohol use, and alcohol-related liver disease (ALD). NAFLD is estimated to affect one-quarter of the global population and more than 80 million in the USA,[1] with an estimated 3.3 million with advanced fibrosis.[2] Alcohol is the leading cause of cirrhosis globally and accounts for up to 60% of cirrhosis in Europe and North America.[3] In 2023, a new nomenclature was developed that recognised the spectrum of SLD, including metabolic dysfunction-associated liver disease (MASLD), metabolic and alcohol-associated liver disease (MetALD) and ALD based on the presence of metabolic risk factors and/or significant

alcohol use.[4] The nomenclature change created a new diagnostic category, MetALD, that acknowledges the potential for both alcohol and metabolic risk factors to contribute to the development and severity of disease.[5–7]

There are limited prospective data characterising the prevalence and severity of the new categories of SLD. Publications using the NHANES demonstrated SLD prevalence between 34.6% and 42.15%, MASLD of 31.1%–37.7%, MetALD of 2%–3.9% and ALD 0.17%–1.1%, and advanced fibrosis of 7.6%–20.86% in MASLD, 5.9%–9.5% in MetALD and 1.3%–19.5% in ALD.[8–10] The existing analyses used vibration controlled transient elastography (VCTE) and controlled attenuation parameter (CAP) to categorise disease prevalence which has limited sensitivity and specificity. Data on disease prevalence for SLD categories specifically among patients with overweight and obesity is also limited. Accurate assessments of prevalence of SLD disease subcategories using rigorous diagnostic methods including MRI with proton density fat fraction (PDFF) for liver fat quantification and magnetic resonance elastography (MRE) for liver stiffness assessment are lacking. Using a prospective and uniquely well-characterised cohort design, we aimed to examine the prevalence of SLD, advanced fibrosis and cirrhosis, and the prevalence of MASLD, MetALD and ALD among overweight and obese individuals residing in Southern California with advanced MRI methods such as MRI proton density fat fraction (MRI-PDFF) for liver fat quantification and MRE for liver fibrosis quantification.

MATERIALS AND METHODS

Study design

This cross-sectional study assessed the prevalence of steatosis, advanced fibrosis and cirrhosis due to SLD in a cohort of prospectively enrolled overweight or obese individuals residing in the greater San Diego area from the San Diego Liver Study. The San Diego Liver Study is a large, prospective, population-based, multiethnic cohort study started on 5 November 2020, and is still ongoing (figure 1). Participants were recruited from primary care and community-based strategies, including the distribution of educational brochures, ads in local newspapers, local fairs and social media. The study participants underwent a standardised research visit, including history with validated alcohol questionnaires, physical examination, laboratory investigation, MRI-PDFF with MRE as well as VCTE with CAP assessment between 2020 and 2023 at the UCSD MASLD Research Center.

Inclusion and exclusion criteria

Inclusion criteria included participants between 40 and 75 years, with a body mass index (BMI)≥25 kg/m^2. Participants were excluded from the study if they met any of the following: (1) evidence of other causes of chronic liver diseases (viral hepatitis, autoimmune and cholestatic liver diseases, metabolic liver disease and drug-induced liver injury), (2) history of gastrointestinal bypass surgery or medications known to produce steatosis (eg, glucocorticoids, high-dose oestrogen, tamoxifen, methotrexate, amiodarone or tetracycline) within last 6 months, (3) creatinine >2 mg/dL, (4) nursing or pregnant female, (5) life expectancy less than 5 years, (6) known HIV infection, (7) contraindications to CT or MRI.

Clinical assessment and laboratory tests

All patients underwent a standardised research visit with (1) medical and medication history, (2) physical examination including vital signs, height, weight and anthropometric measurements, (3) fasting blood draw including complete blood count, complete metabolic panel, iron studies, lipid profile, hepatitis panel, (4) assessment of alcohol use by standardised validated questionnaires, including Alcohol Use Disorder Identification Test (AUDIT) to screen for current heavy drinking and/or active alcohol abuse or dependance,[11] and lifetime drinking history questionnaire to obtain quantitative indices of alcohol consumption patterns,[12] (5) assessment of alcohol use disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) diagnostic criteria for alcohol abuse and dependence,[13] (6) measurement of quantitative alcohol

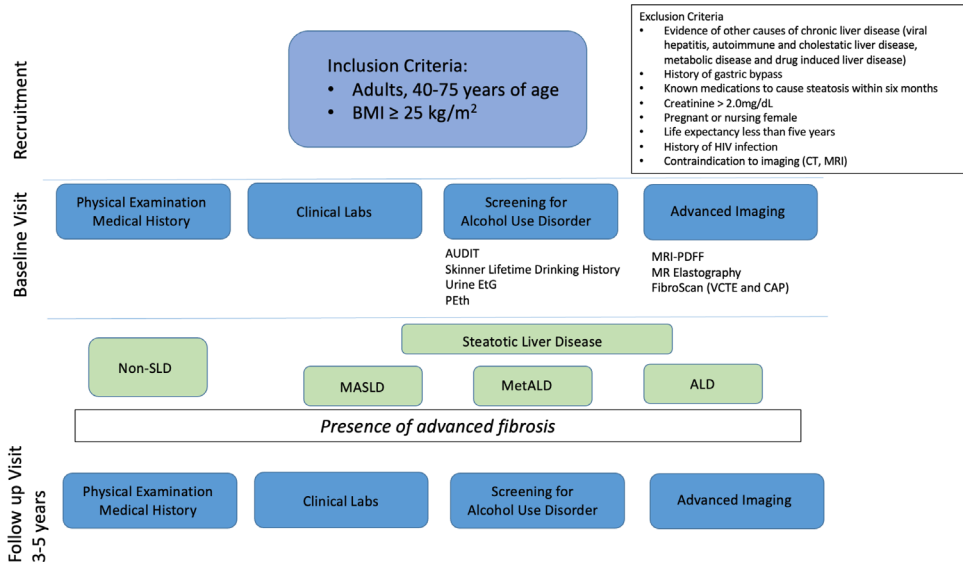

Figure 1 Study diagram of the San Diego Liver Study. ALD, alcohol-related liver disease; AUDIT, Alcohol Use Disorder Identification Test; BMI, body mass index; CAP, controlled attenuation parameter; EtG, ethyl glucuronide; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol associated steatotic liver disease; MRI-PDFF, MRI proton density fat fraction; PEth, phosphatidylethanol; SLD, steatotic liver disease; VCTE, vibration controlled transient elastography.

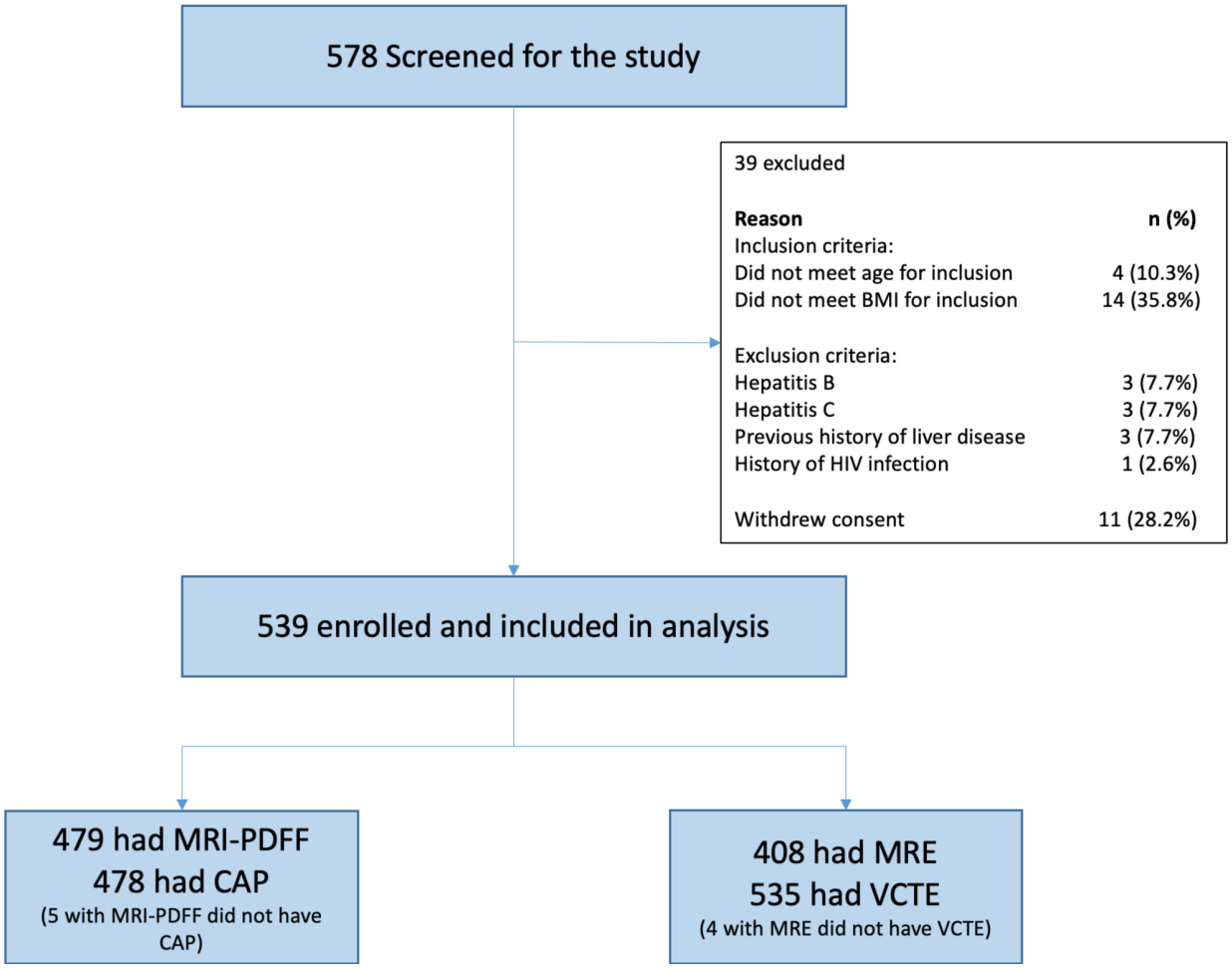

Figure 2 Derivation of study cohort. CAP, controlled attenuation parameter; MRE, magnetic resonance elastography; MRI-PDFF, MRI-proton density fat fraction; VCTE, vibration controlled transient elastography.

biomarkers, including urine ethyl glucuronide (uEtG) and blood-based phosphatidylethanol (PEth). Participants were instructed to fast for a minimum of 8 hours before collection of laboratory tests. Calculations of average daily alcohol consumption were made from data obtained from the LDH questionnaire, considering one standard unit of alcohol equal to 14 g of ethanol.[14]

MRI

MRI-PDFF is an accurate, objective, quantitative, precise, reproducible and non-invasive biomarker of liver fat content[15 16] and is the best non-invasive test to detect SLD and quantify liver fat content.[17–19] MRE is an accurate, objective, quantitative, precise, reproducible and non-invasive biomarker of liver stiffness, and it is the best non-invasive test to detect liver fibrosis. It has been shown to accurately quantify fibrosis in both ALD and NAFLD,[20–24] and is better than FibroScan assessed liver stiffness measurement among patients with obesity.[25 26] These newer technologies provide an assessment of the entire liver, remove operator dependence and are applicable in obese patients.[27]

Participants underwent a non-contrast magnetic resonance examination with liver fat quantification and liver stiffness assessment using MRI-PDFF and MRE. Imaging was performed at the Altman Clinical Translational Research Institute under the supervision of the Liver Imaging Group at UCSD using a 3T research scanner (GE 750; GE Healthcare, Waukesha, WI). Liver stiffness data was obtained using 2D MRE at 60 Hz. PDFF and MRE data were analysed by experienced, study-trained analysts under the supervision of an abdominal radiologist and blinded to clinical and laboratory data.

CAP and VCTE

CAP for the detection of liver fat and VCTE for the quantification of liver stiffness were obtained using FibroScan (Echosens). All examinations were performed by an experienced technician after a minimum fast of 4 hours as recommended. During patient breath holding, a minimum of 10 repeated valid measurements were assessed automatically by the FibroScan system. All participants were first scanned using the M probe (3.5 MHz). If indicated on initial assessment, participants were re-scanned using the XL probe (2.5 MHz).

Outcome measures

Primary outcome

SLD and its subcategories were defined in accordance with the new nomenclature[4] as follows: (1) SLD, defined as either (a) PDFF≥5% or CAP≥288 dB/m if MRI-PDFF was not available or (b) advanced fibrosis based on MRE≥3.63 kPa or VCTE≥8.6 kPa if MRE not available[28]; (2) MASLD, defined as the presence of SLD in conjunction with at least one cardiometabolic risk factor and alcohol consumption <20 g/day for women and <30 g/day for men, and AUDIT score <8, and absence of

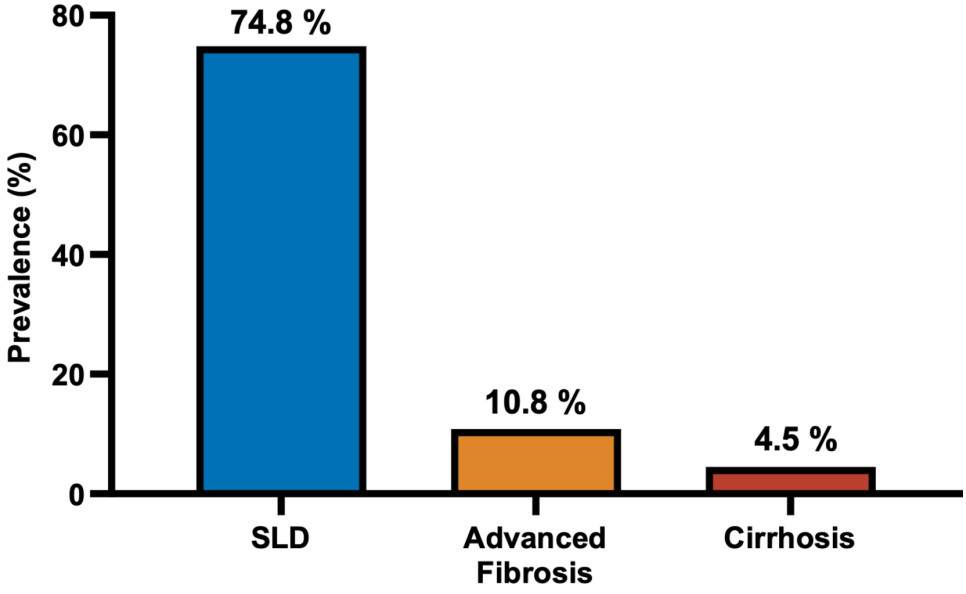

Figure 3 Prevalence of SLD, advanced fibrosis and cirrhosis. SLD, steatotic liver disease.

alcohol use disorder according to DSM-V (<2 symptoms out of 11); (3) MetALD, defined as presence of SLD with at least one cardiometabolic risk factor and an average alcohol consumption of 20–50 g/day for women and 30–60 g/day for men, or medium level of alcohol problems by AUDIT score 8–15, or mild alcohol use disorder according to DSM-V (2–3 symptoms out of 11); (4) ALD, defined as presence of SLD with an average alcohol consumption >50 g/day for women and >60 g/day for men, or high level of alcohol problems by AUDIT score ≥16, or moderate-severe alcohol use disorder according to DSM-V (≥4 symptoms out of 11). Advanced fibrosis was defined as MRE≥3.63 kPa[29] or VCTE≥8.6 kPa,[28] and cirrhosis was defined as MRE≥4.67 kPa[22] or VCTE≥13.1 kPa.[28]

Secondary outcomes

We assessed cofactors associated with advanced fibrosis, including demographic, clinical and laboratory markers.

Statistical analysis

For patient characteristics, a t-test was performed on continuous variables presented as mean (SD), and Wilcoxon rank-sum was performed on those presented as median (IQR). χ^2 or Fisher's exact test was performed as appropriate for all categorical variables. The Cochran-Armitage test was used to test for trends in advanced fibrosis and cirrhosis proportions across the subcategories of liver disease. Sensitivity analyses were performed: (1) defining advanced fibrosis and cirrhosis as VCTE≥12.1 kPa and ≥14.9 kPa (90% specificity thresholds),[28] respectively, if MRE was not available and (2) defining advanced fibrosis and cirrhosis as Agile 3+≥0.679 and Agile 4≥0.565,[30] respectively, if MRE not available. All statistical analyses were performed using SAS V.9.4 (SAS Institute), and a p value less than 0.05 was considered statistically significant.

RESULTS

Characteristics of the study population

578 participants were screened, and a total of 539 overweight or obese participants were enrolled (figure 2). 136 (25%) were categorised as having no SLD, and 403 (75%) as having SLD; the prevalence of fibrosis and cirrhosis was 10.8% and 4.5%, respectively (figure 3).

Clinical characteristics of the study cohort are shown in table 1. In the overall cohort, participants had a mean age (±SD) of 51.5 (±13.1) years and were predominately women (55.2%). The mean BMI was 32.6 (±6.2) kg/m^2, and the mean daily alcohol intake was 5.6 (±16.9) g/day. The median haemoglobin A1c was 5.7 (IQR 0.9) %, median alanine aminotransferase (ALT) 33 (IQR 25) U/L and median fibrosis-4 index (FIB-4) 0.9 (IQR 0.6).

The median liver fat by MRI-PDFF was 10.9 (IQR 13.8) %, and the median liver stiffness by MRE was 2.2 (IQR 0.6) kPa. The median CAP was 305 (IQR 78) dB/m, and the median liver stiffness by VCTE was 5.3 (IQR 3.0) kPa. The characteristics of those with and without MRE data are displayed in online supplemental table 1.

Prevalence of SLD subcategories

Among overweight and obese individuals, 363 (67.3%) of the overall cohort were categorised as MASLD, 26 (4.8%) as MetALD and 14 (2.6%) as ALD (figure 4). Compared with other subcategories of SLD, MASLD participants had a higher BMI (33.3±6.7 kg/m^2) and a higher percentage of metabolic syndrome (71.5%). They also had more metabolic risk factors (median 4, IQR 3) and lower amount of alcohol intake (2.4 g/day). Consistently, they had lower PEth value (<10 ng/mL) and lower percentage of positive uEtG (11%). MASLD patients had lower aspartate aminotransferase (AST) (28 U/L). Median MRI-PDFF and MRE stiffness were 14.5% and 2.2 kPa, respectively. Median CAP and VCTE liver stiffness were 320 dB/m and 5.7 kPa, respectively. 14.9% of the MASLD group had advanced fibrosis, and 5.8% had cirrhosis.

The prevalence of MetALD in the overall cohort was 4.8%. Participants with MetALD had lower BMI (32.0±4.3 kg/m^2), the lowest number of metabolic risk factors (median 2.5) and a mean daily alcohol intake of 20.9 g/day. The median PEth value was 55 ng/mL and 42% of subjects had positive uEtG. In terms of biochemical profile, the MetALD participants had the lowest haemoglobin A1c (median 5.5%), the highest high-density lipoprotein (HDL) (49 mg/dL) and triglycerides (148.5 mg/dL), and

Table 1 Characteristics of the overall cohort by SLD subcategories

	Total (N=539)	No SLD (N=136)	MASLD (N=363)	MetALD (N=26)	ALD (N=14)	P value
Demographics						
Age in years, mean (SD)	51.5 (13.1)	52.5 (14.3)	51.3 (12.7)	49.7 (13.1)	53.1 (11.7)	0.6452
Women, n (%)	297 (55.2%)	74 (54.8%)	208 (57.3%)	12 (46.2%)	3 (21.4%)	**0.0466**
BMI, mean (SD)	32.6 (6.2)	30.8 (4.6)	33.3 (6.7)	32.0 (4.3)	32.9 (4.7)	**0.0011**
Ethnicity, n (%)						0.6843
White	187 (35.1%)	48 (35.3%)	122 (34.2%)	10 (38.4%)	7 (50.0%)	
Hispanic	226 (42.4%)	59 (43.4%)	150 (42.0%)	12 (46.2%)	5 (35.7%)	
Asian	78 (14.6%)	15 (11.0%)	59 (16.5%)	2 (7.7%)	2 (14.3%)	
Other	42 (7.9%)	14 (10.3%)	26 (7.3%)	2 (7.7%)	0 (0%)	
Hypertension, n (%)	200 (37.1%)	45 (33.1%)	136 (37.5%)	12 (46.2%)	7 (50.0%)	0.4121
Hyperlipidaemia, n (%)	153 (28.4%)	42 (30.9%)	102 (28.1%)	5 (19.2%)	4 (28.6%)	0.6814
Diabetes mellitus, n (%)	154 (28.6%)	38 (27.9%)	108 (29.7%)	5 (19.2%)	3 (21.4%)	0.6290
Metabolic syndrome*, n (%)	260 (52.5%)	42 (32.8%)	198 (59.5%)	11 (50.0%)	9 (75.0%)	**<0.0001**
Obesity, n (%)	334 (62.2%)	68 (50.0%)	238 (65.9%)	18 (69.2%)	10 (71.4%)	**0.0008**
Number of metabolic risk factors, median (IQR)	3 (3)	3 (4)	4 (3)	2.5 (3.0)	3 (3)	**0.0038**
GLP-1 RA and GIP/GLP-1 RA, n(%)	38 (7.1%)	11 (8.1%)	27 (7.4%)	0	0	0.4752
Alcohol use assessment						
Alcohol (g/day), mean (SD)	5.6 (16.9)	4.9 (17.3)	2.4 (4.6)	20.9 (15.0)	70.0 (53.5)	**<0.0001**
PEth (ng/mL), median (IQR)	9 (3)	9 (5)	9 (0)	55 (132)	59.5 (163)	**<0.0001**
Positive urine EtG, n(%)	50 (13.9%)	12 (13.3%)	27 (11.0%)	8 (42.1%)	3 (42.9%)	**0.0009**
Biochemical profile, median (IQR)						
HOMA-IR	4.2 (4.1)	2.6 (0.12)	5.0 (4.9)	5.4 (3.2)	5.8 (5.1)	**<0.0001**
Fasting insulin	16.7 (14)	10.8 (8.3)	19.3 (14.5)	20.7 (11.1)	16.1 (16.7)	**<0.0001**
HbA1c (%)	5.7 (0.9)	5.6 (0.7)	5.9 (1.1)	5.5 (0.7)	5.9 (1.2)	**<0.0001**
Total cholesterol (mg/dL)	183 (53)	175 (45)	184 (53)	185.5 (95)	188 (42)	**0.0047**
LDL (mg/dL)	107 (48)	102 (43)	108 (48)	98.5 (82)	112 (21)	**0.0174**
HDL (mg/dL)	45 (17)	48.5 (17)	44 (16)	49.0 (19)	39.5 (6)	**0.0002**
Triglycerides (mg/dL)	127 (78)	100 (58)	135 (77)	148.5 (126)	137 (96)	**<0.0001**
Platelet count (10^9/L)	254 (81)	259 (76)	253 (81)	242 (107)	223 (100)	0.5336
INR	1.1 (0.1)	1.1 (0.1)	1.1 (0.1)	1.1 (0.1)	1.1 (0.2)	0.2948
ALT (U/L)	33 (25)	22 (16.5)	37 (25)	37 (28)	32 (23)	**<0.0001**
AST (U/L)	26 (13)	21 (8.5)	28 (14)	29 (18)	31 (55)	**<0.0001**
Alkaline phosphatase (U/L)	78.5 (31)	75 (27.5)	80 (33)	74.5 (36)	72 (49)	0.2834
Total bilirubin (mg/dL)	0.5 (0.3)	0.5 (0.2)	0.5 (0.3)	0.6 (0.6)	0.5 (0.3)	0.1926
Albumin	4.6 (0.5)	4.5 (0.5)	4.5 (0.3)	4.7 (0.5)	4.2 (0.6)	0.5082
Ferritin	138.5 (195)	115.5 (120)	157.0 (210)	150.5 (474)	164 (429)	**0.0024**
FIB-4	0.9 (0.6)	1 (0.6)	0.9 (0.6)	0.8 (0.8)	1.4 (0.9)	0.2073
Imaging, median (IQR)						
MRI-PDFF (%)	10.9 (13.8)	3 (1.8)	14.5 (11.8)	15.5 (15.6)	15.7 (18.6)	**<0.0001**
MRE (kPa)	2.2 (0.6)	2.1 (0.4)	2.2 (0.6)	2.2 (0.6)	2.1 (0.6)	0.1191
VCTE CAP (dB/m)	305 (78)	257 (60.0)	320 (63)	303 (78)	334 (66)	**<0.0001**
VCTE (kPa)	5.3 (3.0)	4.4 (2.0)	5.7 (3.7)	6.3 (3.0)	5.1 (2.1)	**<0.0001**

Bold values denote statistical significance at p-value less than 0.05.
*Defined according to ATPIII criteria.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAP, controlled attenuation parameter; EtG, ethyl glucuronide; FIB-4, fibrosis-4 index; HbA1c, haemoglobin A1c; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; INR, international normalised ratio; LDL, low-density lipoprotein; MRE, magnetic resonance elastography; MRI-PDFF, MRI proton density fat fraction; PEth, phosphatidylethanol; SLD, steatotic liver disease; VCTE, vibration controlled transient elastography.

the lowest ferritin (150.5). Median MRI-PDFF and MRE stiffness were 15.5% and 2.2 kPa. Median CAP and VCTE liver stiffness were 303 dB/m and 6.3 kPa. 7.7% of the MetALD group had advanced fibrosis, and 3.9% had cirrhosis.

The prevalence of ALD in the overall cohort was 2.6%. These participants had a mean BMI of 32.9 kg/m^2, and 57.1% of the group had metabolic syndrome. The median number of metabolic risk factors was three and the mean alcohol intake was 70.0 g/day. The median PEth value was 59.5 ng/mL and 43% of subjects had positive uEtG. In terms of biochemical profile, this group had the lowest fasting insulin (16.1), HDL (39.5 mg/dL) and ALT (32 U/L), and the highest ferritin (164) and FIB-4 (1.4). Median MRI-PDFF and MRE stiffness were 15.7% and 2.1 kPa. Median CAP and VCTE liver stiffness were 334 dB/m and 5.1 kPa. 14.3% of the ALD group had advanced fibrosis/cirrhosis. There was no significant difference in advanced fibrosis and cirrhosis among the subcategories (table 2). Results of sensitivity analyses (1) defining advanced fibrosis and cirrhosis as VCTE≥12.1 kPa

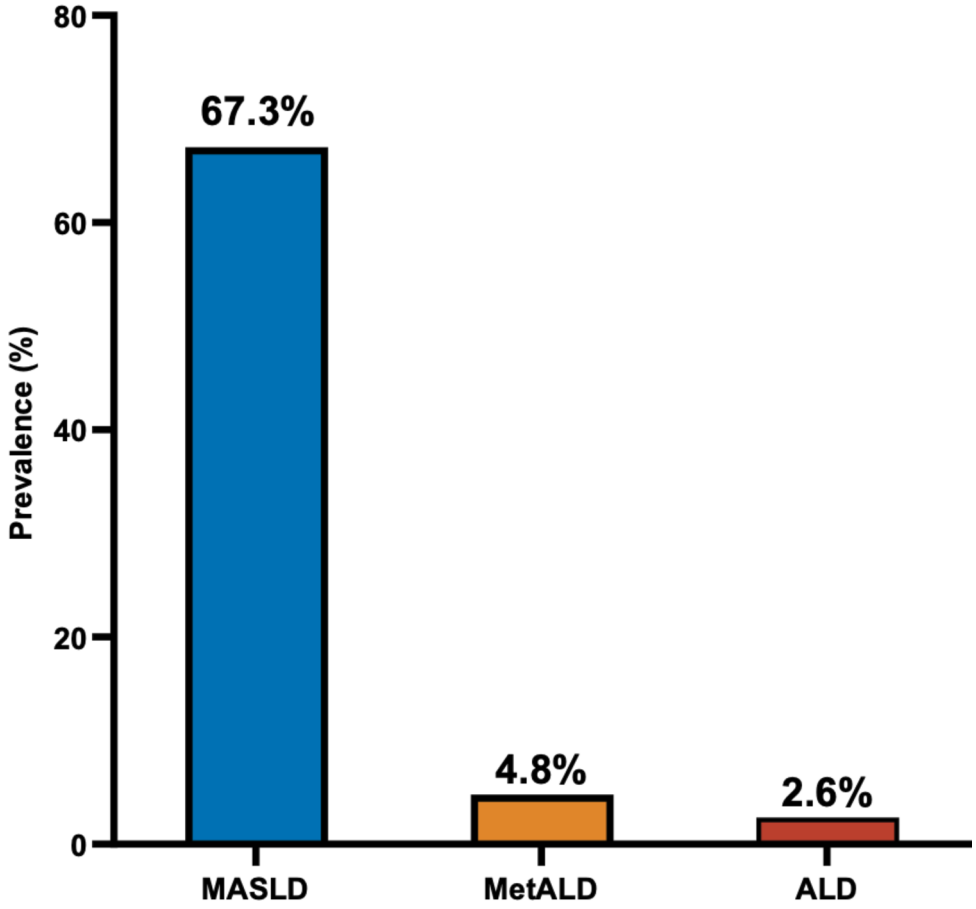

Figure 4 Prevalence of MASLD, MetALD and ALD. ALD, alcohol-related liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol associated steatotic liver disease.

and ≥14.9 kPa (90% specificity thresholds), respectively, if MRE not available, and (2) defining advanced fibrosis and cirrhosis as Agile 3+≥0.679 and Agile 4≥0.565, respectively, if MRE not available, are displayed in online supplemental tables 2 and 3.

Characteristics associated with advanced fibrosis

The prevalence of advanced fibrosis in the overall cohort was 10.8% (table 3). Compared with those without advanced fibrosis, those with advanced fibrosis had higher BMI (37.5 vs 32.0 kg/m^2), prevalence of diabetes mellitus (58.6% vs 25.0%), prevalence of obesity (82.5% vs 59.8%), number of metabolic risk factors (4 vs 3), homeostasis model assessment of insulin resistance (9.8 vs 3.9), fasting insulin (29.2 vs 15.6), haemoglobin A1c (7.1% vs 5.7%), AST (40 vs 25 U/L), ALT (43.5 vs 31 U/L), alkaline phosphatase (94.5 vs 77 U/L), total bilirubin (0.6 vs 0.5 mg/dL) and FIB-4 (1.7 vs 0.9), as well as lower platelets (222 vs 259×10^3 cells) and albumin (4.4 vs 4.6 mg/dL), respectively. The median liver stiffness by MRE among those with advanced fibrosis was 4.4 kPa and 2.2 kPa in those without advanced fibrosis. On VCTE, the median liver stiffness was 12.8 kPa in the advanced fibrosis group and 5.1 kPa in those without advanced fibrosis. Notably, individuals with and without advanced fibrosis had a similar MRI-PDFF (12.4% vs 10.9%), but those with advanced fibrosis had a higher VCTE CAP (352 vs 302 dB/m). Results of sensitivity analyses (1) defining advanced fibrosis as VCTE≥12.1 kPa (90% specificity threshold) if MRE not available and (2) defining advanced fibrosis as Agile 3+≥0.679 if MRE not available, are displayed in online supplemental tables 4 and 5.

Table 2 Distribution of advanced fibrosis and cirrhosis among MASLD, MetALD and ALD

	MASLD (N=363)	MetALD (N=26)	ALD (N=14)	P value*	P value† (trend)
Advanced fibrosis, n (%)	54 (14.9%)	2 (7.7%)	2 (14.3%)	0.7050	0.5594
Cirrhosis, n (%)	21 (5.8%)	1 (3.9%)	2 (14.3%)	0.3011	0.3833

Advanced fibrosis defined as MRE≥3.63 kPa or VCTE≥8.6 kPa.
Cirrhosis defined as MRE≥4.67 kPa or VCTE≥13.1 kPa.
*Fisher's exact test.
†Cochran-Armitage test for trend.
ALD, alcohol-related liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol associated steatotic liver disease; MRE, magnetic resonance elastography; VCTE, vibration controlled transient elastography.

DISCUSSION

Main findings

This cross-sectional analysis of a prospective study conducted in the USA using MRI-PDFF and MRE among overweight and obese participants demonstrated that the prevalence of advanced fibrosis and cirrhosis was 10.8% and 4.5%, respectively. SLD was prevalent in 75% of the cohort, with 67.3% having MASLD, 4.8% having MetALD and 2.6% having ALD. The prevalence of advanced fibrosis was not significantly different across the SLD subcategories. Advanced fibrosis was associated with higher

Table 3 Clinical, demographics and imaging characteristics by advanced fibrosis status

	Total (N=539)	No advanced fibrosis (N=481)	Advanced fibrosis (N=58)	P value
Demographics				
Age in years, mean (SD)	51.5 (13.1)	51.2 (13.2)	54.7 (12.2)	0.0527
Women, n (%)	297 (55.2%)	259 (54.0%)	38 (65.5%)	0.0945
BMI, mean (SD)	32.6 (6.2)	32.0 (5.6)	37.5 (8.1)	**<0.0001**
Ethnicity, n (%)				0.5352
White	187 (35.1%)	169 (35.4%)	18 (32.7%)	
Hispanic	226 (42.4%)	198 (41.4%)	28 (50.9%)	
Asian	78 (14.6%)	72 (15.1%)	6 (10.9%)	
Other	42 (7.9%)	39 (8.2%)	3 (5.5%)	
Hypertension, n (%)	200 (37.1%)	179 (37.2%)	21 (36.2%)	0.8808
Hyperlipidaemia, n (%)	153 (28.4%)	138 (28.7%)	15 (25.9%)	0.6518
Diabetes mellitus, n (%)	154 (28.6%)	120 (25.0%)	34 (58.6%)	**<0.0001**
Metabolic syndrome, n (%)	260 (52.5%)	215 (48.9%)	45 (81.8%)	**<0.0001**
Obesity, n (%)	334 (62.2%)	287 (59.8%)	47 (82.5%)	**0.0008**
Number of metabolic risk factors, median (IQR)	3 (3)	3 (3)	4 (2)	**0.0029**
GLP-1 RA and GIP/GLP-1 RA, n(%)	38 (7.1%)	30 (6.2%)	8 (13.8%)	0.0513
Alcohol use assessment				
Alcohol (g/day), mean (SD)	5.6 (16.9)	5.6 (16.2)	5.7 (22.3)	0.9662
PEth (ng/mL), median (IQR)	9.0 (3.0)	9.0 (5.0)	9.0 (0)	**0.0031**
Positive urine EtG, n(%)	50 (13.9%)	50 (15.7%)	0	**0.0017**
Biochemical profile, median (IQR)				
HOMA-IR	4.2 (4.1)	3.9 (3.6)	9.8 (11)	**<0.0001**
Fasting insulin	16.7 (14)	15.6 (12.7)	29.2 (23.2)	**<0.0001**
HbA1c (%)	5.7 (0.9)	5.7 (0.7)	7.1 (2)	**<0.0001**
Total cholesterol (mg/dL)	183 (53)	183 (55)	178.5 (50)	0.1560
LDL (mg/dL)	107 (48)	107 (49)	105 (46)	0.1422
HDL (mg/dL)	45 (17)	46 (16)	39 (21)	**0.0140**
Triglycerides (mg/dL)	127 (78)	127 (76)	127.5 (84.5)	0.3290
Platelet count (10^9/L)	254 (81)	259 (78)	222 (76)	**<0.0001**
INR	1.1 (0.1)	1.1 (0.1)	1.1 (0.1)	**0.0086**
ALT (U/L)	33 (25)	31 (26)	43.5 (41)	**<0.0001**
AST (U/L)	26 (13)	25 (12)	40 (29)	**<0.0001**
Alkaline phosphatase (U/L)	78.5 (31)	77 (30)	94.5 (36)	**<0.0001**
Total bilirubin (mg/dL)	0.5 (0.3)	0.5 (0.3)	0.6 (0.3)	**0.0315**
Albumin	4.6 (0.5)	4.6 (0.4)	4.4 (0.4)	**<0.0001**
Ferritin	138.5 (195)	138 (194)	148.5 (228)	0.8485
FIB-4	0.9 (0.6)	0.9 (0.6)	1.7 (1.3)	**<0.0001**
Imaging, median (IQR)				
MRI-PDFF (%)	10.9 (13.8)	10.9 (13.9)	12.4 (11.3)	0.3075
MRE (kPa)	2.2 (0.6)	2.2 (0.5)	4.4 (1.5)	**<0.0001**
VCTE CAP (dB/m)	305 (78)	302 (76)	352 (70)	**<0.0001**
VCTE (kPa)	5.3 (3.0)	5.1 (2.4)	12.8 (9.4)	**<0.0001**

Advanced fibrosis defined as MRE≥3.63 kPa or VCTE≥8.6 kPa.
Bold values denote statistical significance at p-value less than 0.05.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; EtG, ethyl glucuronide; FIB-4, fibrosis-4 index; HbA1c, haemoglobin A1c; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; INR, international normalised ratio; LDL, low-density lipoprotein; MRE, magnetic resonance elastography; MRI-PDFF, MRI proton density fat fraction; PEth, phosphatidylethanol.

BMI, prevalence of diabetes mellitus, as well as metabolic risk factors. This study used AUDIT and Skinner (lifetime drinking history) questionnaires that were then further validated by both blood-based PEth and urine ethinyl glucuronide (EtG) that adds to the novelty of phenotyping and increases the credibility of these findings across the spectrum of SLD.

In context with published literature

Although with the introduction of the new classification of SLD, there have been several studies describing the prevalence of MASLD, MetALD and ALD, none provided prospectively collected data using advanced MRI-PDFF and MRE, the most accurate non-invasive measures of hepatic steatosis and fibrosis, respectively, on the prevalence of advanced fibrosis and cirrhosis among overweight and obese Americans. Indeed, available studies have employed diagnostic methods with less robust accuracy than MRI-PDFF and MRE for steatosis grading and fibrosis staging. Additionally, existing literature has been limited to specific subpopulations that limit the generalisability of findings and/or use of retrospective data.[8–10 31–35] Within this context,

three studies used the NHANES database between 2017 and 2020 when VCTE and CAP were available. Kalligeros *et al* used a CAP and VCTE cut-off of 263 dB/m and 8.6 kPa, respectively, for steatosis and advanced fibrosis. Among 15 560 participants, they reported an SLD prevalence of 37.8%, MASLD of 32.45%, MetALD of 2.56%, and ALD of 1.1%, and noted advanced fibrosis of 20.86% in MASLD and 8.98% MetALD.[8] Lee *et al* used cut-offs of 288 dB/m and 11.7 kPa and found among 7367 participants, 34.6% had SLD, 31.1% had MASLD, 2% had MetALD, 0.7% had ALD, and a prevalence of advanced fibrosis of 7.6%, 5.9% and 1.3%, respectively.[9] Ciardullo *et al* used cut-offs of 274 dB/m and 8.0 kPa. They found a prevalence of 42.1% with SLD in a cohort of 3173 participants within the SLD population, 89.45 with MASLD, 7.7% with MetALD and 0.4% with ALD. They noted a prevalence of advanced fibrosis of 15.2%, 9.5% and 19.5% in MASLD, MetALD and ALD, respectively.[10] Moon *et al* used the Korean nationwide health screening database and defined SLD as fatty liver index ≥60 and found that of 351 068 participants, 47.2% had MASLD, 6.4% MetALD and 2.1% had ALD.[34] Overall, the prevalence of SLD was 34.8%–42.1%, MASLD 31.1%–37.7%, MetALD 2%–7.7%, ALD 0.4%–1.1%, and advanced fibrosis in MASLD 7.6%–20.86%, MetALD 5.9%–9.5% and ALD 1.3%–19.5%. Finally, a retrospective study by Lee *et al* collected 2535 participants who underwent MRI-PDFF with MRE across five primary care clinics in Korea. Using an MRI-PDFF cut-off of 5.0% to categorise steatosis, SLD prevalence was found to be 39.1%, 29.3% with MASLD, 5.64% with MetALD and 2.6% with ALD. The authors also found that those with MetALD and ALD had a higher mean MRE.[35] Overall prevalence of SLD was 39.1%–52%, MASLD 29.3%–39%, MetALD 5.64%–10%, ALD 2.6%–3%.

Our data showed an SLD prevalence of 75%, MASLD at 67.3%, MetALD at 4.8% and ALD at 2.6%, and advanced fibrosis in MASLD at 14.9%, MetALD at 7.7% and ALD at 14.3%. The higher prevalence of SLD is likely a result of our cohort including overweight and obese participants, while the prevalence of subcategories is similar to other studies. Israelsen *et al* demonstrated an increase in hepatic decompensation risk with MetALD and ALD.[36] In our cohort, we found that there was no significant difference in advanced fibrosis and cirrhosis among the subcategories.

Strengths and limitations

The study's main strength is a prospective, diverse cohort who completed a comprehensive clinical assessment with detailed characterisation using high-quality, advanced imaging techniques and testing of biomarkers of alcohol quantification such as PEth and EtG. In addition, all testing was done on the same day to provide a true cross-sectional evaluation of participants in laboratory and imaging evaluations. The main limitation comes from being a single centre. However, our study comprised a multiethnic population: 35% white, 42% Hispanic and 15% Asian. Patients were also recruited from primary care and community settings that are representative of patients at risk for MASLD, MetALD and ALD in the community. Additional studies in biologically and geographically diverse cohorts from various populations would add to the knowledge of the prevalence of MASLD, MetALD and ALD. Another limitation is that the subclassification of SLD into MASLD, MetALD and ALD was based on patient's self-reported alcohol intake by questionnaires which are the current gold standard of alcohol detection but often inaccurate.[37–39] However, we did collect data on direct alcohol biomarkers, such as PEth and uEtG. Further studies are needed to examine the association between questionnaire-based SLD subcategories and biomarker-based SLD subcategories.

IMPLICATIONS FOR FUTURE RESEARCH

In this cross-sectional analysis using a well-designed prospective cohort study and advanced imaging techniques including MRI-PDFF and MRE done on the same day as laboratory and physical examination, 75% of 539 participants were found to have SLD, 67.3% with MASLD, 4.8% with MetALD and 2.6% with ALD. Advanced fibrosis and cirrhosis prevalence were 14.9% and 5.8% in those with MASLD, 7.7% and 3.9% in those with MetALD, and 14.3% in those with ALD. Future directions include establishing similar protocoled examinations with advanced imaging techniques to describe prevalence of SLD subcategories in different populations to understand the burden of MASLD, MetALD and ALD. Additionally, larger cohorts would be needed to understand whether there are differences in advanced fibrosis and cirrhosis among the SLD subcategories, and to further explore the synergistic effects of alcohol and metabolic risk factors, as well as consider different cut-off values for alcohol use to properly capture the effect of alcohol use in liver disease progression. In clinical practice, this should raise awareness of higher prevalence of advanced fibrosis in those with significant alcohol use and require more diligent screening.

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