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REVIEW

Steatotic Liver Diseases (SLDs): A Review

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Liver steatosis is now the politically correct term for excessive fat in the liver (fatty liver). Its incidence and prevalence, in lockstep with diabetes and obesity, continue to climb to over 2 billion persons worldwide. It is the most common cause of chronic liver disease and the leading cause of liver-related morbidity and mortality. This treatise, resulting from a selection of PubMed literature of relevant steatosis studies since the nomenclature change in 2023, will include the change in the names for the steatotic liver entities, documenting the contribution of metabolic dysfunctions (obesity, diabetes, hypertension, and dyslipidemias) to the pathology of insulin resistance and alcohol in the evolution of these liver diseases. The various modalities for measuring the degree of fat, fibrosis, and cirrhotic scarring of the liver will be discussed, followed by a review of the mortality implications of the subcategories of liver steatosis, including intrahepatic cirrhosis and malignancy, extrahepatic malignancies, and cardiovascular disease. Finally, a review of treatments to address these entities will be briefly reviewed.

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Even in scientific studies, words matter. Steatosis is a synonym for "fatty liver disease." As pointed out in an opinion piece by Meagher,[1] non-alcoholic fatty liver disease (NAFLD and its inflammatory next stage, non-alcoholic steatohepatitis–NASH) have been studied for decades. However, the word "fatty" has been felt to be stigmatizing and via a modified Delphi process in 2023,[2] the steatotic liver diseases have been renamed to metabolic dysfunction-associated *steatotic* liver disease (MASLD) and metabolic dysfunction-associated *steatohepatitis* (MASH), in recognition of the pathogenic role metabolic dysfunction plays in fat accumulation in the liver. Recognizing the dual pathogenesis of dysfunctional metabolism *and* alcohol on inflammatory excess liver fat, a new novel disease is now recognized—metabolic *and* alcoholic liver disease, or MetALD. Diagnosing MetALD requires at least one of the metabolic disturbances (see below) along with weekly alcohol use between 20 and 50 grams for females and between 30 and 60 grams for males. Persons with predominantly excessive alcohol abuse (defined as >50 gm/day for females and >60gm/day for males) as the cause for their liver disease are labeled alcoholic liver disease (ALD**).** The word "alcoholic" was also felt to be stigmatizing, but no reasonable synonym could be found for its replacement. It should be noted that 98% of patients with ALD have at least one metabolic risk factor,[3] highlighting the interaction between alcohol use and metabolic risk factors for severe liver disease development.[4] Steatotic liver disease (SLD)

is now the overarching term to encompass the various etiologies of steatosis.

Non-alcoholic fatty liver disease (NAFLD), then name-changed to metabolic-associated fatty liver disease (MAFLD) in 2020 (proposed to underscore the heterogeneous entity of NAFLD and its association with metabolic risk factors that may co-exist with other liver diseases[5]), has been recognized as the most common cause of chronic liver disease worldwide.[6] The global prevalence estimates of these diseases in the general adult population increased from around 25% in the early 2000s to 32% over the past decade, affecting up to 2 billion individuals worldwide, mirroring the obesity and diabetes epidemic.[7]

There is a correlation between MASLD and obesity (although not all persons with MASLD are obese, which will be discussed later in this article). Per the most recent National Health and Nutrition Examination Survey (NHANES) study, over 1 billion adults globally are obese (BMI ≥30), with higher rates in North and South America and North Africa. In the United States, 40.3% of adults are obese (BMI ≥30), and another 30.7% of adults are overweight (BMI 25-29.9), resulting in 71% of adults being either overweight or obese. Of US adults, 9.2% are severely obese (BMI ≥40), with the rate of severe obesity having doubled from 2000 to 2018.

DEFINITIONS

Excessive fat in the liver (liver steatosis) is defined as >5% of hepatocytes with macrovesicular steatosis containing visible intracellular triglycerides or steatosis affecting at least 5% of the liver volume/weight.

The cardiometabolic risk factors (CMRFs) are as follows:[8]

1. Body mass index (BMI) ≥25 (≥23 in Asians) kg/m^2 or increased waist circumference (≥94 cm in males and ≥80 cm in females).
2. Hemoglobin A1c (HbA1c) ≥5.7%, use of antidiabetic medication, or type 2 diabetes present on ≥1 inpatient or ≥2 outpatient codes ≥30 days apart
3. Blood pressure ≥130/85 mmHg on use of antihypertensive medication
4. Triglycerides ≥150 mg/dL or use of lipid-lowering medication
5. High-density lipoprotein ≤40 mg/dL in males and ≤50 mg/dL in women, or use of lipid-lowering medication.

A reasonable and pertinent question might be, "Are these new classifications of the old NAFLD/NASH disease categories just new names (MASLD, MASH, MetALD) for the same older diseases?" The MASLD-predominant group is defined based on the presence of at least 1 in 5 of these cardiometabolic risk factors. In a study of 6429 patients diagnosed with NAFLD, 99% met the criteria for MASLD.[9] This study concluded that while MASLD may carry a slightly increased mortality risk, it exhibits comparable clinical profiles and thresholds for non-invasive tests across both conditions, suggesting the potential for interchangeable use of these terminologies. However, in a cross-sectional study involving 500 participants who had undergone both liver ultrasound and vibration-controlled transient elastography, it was found that the MASLD criteria captured more lean patients compared to the MAFLD definition, and also that MAFLD better identified patients likely to have a higher risk of liver fibrosis and of disease progression.[10] And certainly, the disease category MetALD is a new addition to the family of steatotic lung diseases. This suggests that historical studies of NAFLD/MAFLD/MASLD may not be in total sync with regards to prognosis.

DIAGNOSING STEATOTIC LIVER DISEASE

Defining a population with MASLD has generally required ultrasonography of the liver, although the condition may be incidentally

found on computed tomography (CT) of the abdomen, and may rarely present with symptoms such as fatigue, malaise, and vague right upper abdominal discomfort, with hepatomegaly only occasionally recognized. Current studies of a general population suggest that most persons with MASLD have normal or near-normal liver function tests (LFTs). When elevated, the AST and ALT are typically 2 to 5 times the upper limit of normal, with an AST to ALT ratio of less than one. Interestingly, the degree of aminotransferase elevation does not correlate with the degree of liver inflammation or fibrosis.[11,12] The alkaline phosphatase may be elevated by 2 to 3 times the upper limit of normal. Serum albumin and bilirubin levels are typically normal except in the setting of cirrhosis. Elevated serum ferritin concentration or transferrin saturation may be elevated in persons with MASLD. A serum ferritin greater than 1.5 times the upper limit of normal has been associated with increased risk of steatohepatitis and advanced fibrosis.[13]

A Finnish population study[14] used ALT levels with cutoffs of >20 U/L in females and >30 U/L in males, which were intentionally high sensitivity cutoffs that allowed them to identify most persons with steatosis but at the expense of increased false positives. These ALT measurements were shown to discriminate steatosis with an area under the receiver operating characteristic (AUROC) of 0.93. They also used FLI (see below), which detected hepatic steatosis with a positive predictive value up to 99%, but again with increased false positives.

In persons with MASLD, ultrasound often shows a hyperechoic texture or a "bright liver" because of diffuse fatty infiltration. In a meta-analysis of 49 studies including 4720 individuals, the sensitivity and specificity of ultrasound detecting moderate to severe fatty liver were 85% and 94% respectively, using liver biopsy as the reference standard.[15]

Some researchers use the Fatty Liver Index (FLI) to identify persons with SLD. It is a non-invasive, readily available index that measures readily available clinical measurements of triglycerides (in mg/dL), BMI (kg/m^2), gamma-glutamyl transferase (GTT in U/L), and waist circumference (in cm).[16] FLI is readily available as a calculator on the internet.

The Enhanced Liver Fibrosis (ELF) test is a non-invasive blood test used to assess the severity of liver fibrosis. It measures three biomarkers: 1) hyaluronic acid (HA), a component of the extracellular matrix, elevated in liver fibrosis, 2) procollagen III amino-terminal peptide (PIIINP), a precursor to collagen, also elevated in liver fibrosis, and 3) tissue inhibitor of metalloproteinase 1 (TIMP-1), an enzyme that inhibits the breakdown of collagen, also elevated in liver fibrosis. In a systematic review of 36 studies, the ELF test showed good diagnostic performance in NAFLD (AUC 0.85 to 0.97) and ALD (AUC 0.93 to 0.94), with liver biopsy as the reference standard.[17]

Danish authors validated a scoring system called Steatosis-Associated Fibrosis Estimator (SAFE) score, along with ultrasound, in their analysis of the NHANES 2017-2020 cycle with data on liver stiffness by transient elastography and the SAFE score on persons without heart failure. This scoring system included globulins, age, BMI, diabetes, AST and ALT levels, and platelets. The SAFE score yielded an AUC of 0.75 in the detection of clinically significant fibrosis. Higher SAFE scores were increasingly associated with a higher prevalence of liver stiffness ≥8.0 kPa. Interestingly, the ability to rule out clinically relevant fibrosis was especially good in patients with excessive alcohol consumption (NPV 0.98). However, test performance strongly depended on age categories: it had good overall diagnostic accuracy in detecting fibrosis when the ages were 40-60 years, and in this age range, it outperformed FIB-4.[18]

Progressive inflammation (steatohepatitis), fibrosis, and liver cirrhosis are the potential serious outcomes of steatotic liver diseases. Liver biopsy is the most accurate method for determining the severity of architectural

distortion, cellular injury, and inflammation, but may be complicated by bleeding and is not appropriate for large-scale investigative studies. Short of liver biopsy, vibration-controlled transient elastography (VCTE), which goes by the brand name Fibroscan, assesses liver stiffness measurement (LSM). Another less common ultrasound-based method is acoustic radiation force impulse (AFRI). VCTE is highly reproducible and interobserver variability is low. The controlled attenuation parameter (CAP) feature is also added to the hand probe. The results are expressed in decibels per meter (dB/m), ranging from 100 to 400 dB/m, but in studies done on MASLD, kPa units are used. LSM <8 kPa by VCTE corresponds to a low-risk fibrosis score and excludes clinically significant fibrosis. LSM 8 to 12 kPa by VCTE is indeterminate, and often magnetic resonance elastography (MRE) is recommended. If the LSM by MRE is also indeterminant for significant fibrosis (ie, 2.55 kPa to 3.63 kPa), then liver biopsy may be required. A measurement <2.55 kPa by MRE corresponds to a low-risk fibrosis score, whereas a measurement >3.63 kPa suggests advanced fibrosis or cirrhosis. VCTE is normally the first step in evaluating for liver fibrosis, but MRE is more accurate than VCTE for staging fibrosis in persons with MASLD. As an alternative to imaging, Fibrosis (FIB)-4 Index may stratify a person's risk for fibrosis, with VCTE then recommended for persons with FIB-4 ≥1.3. The FIB-4 Index predicts advanced fibrosis by combining laboratory values (platelet count, ALT, and AST) and age in a calculator: FIB-4 index.[19,20]

Lin et al[21] compared elastography to noninvasive and invasive tests for prognosis over time in MASLD in 10,209 persons with 51 months of median follow-up. They compared elastography-based parameters Agile 3+ (that included AST/ALT ratio, platelet count, gender, diabetes status, and age), Agile 4 (that included these factors along with LSM using VCTE), and FAST (Fibroscan-AST), along with other noninvasive parameters FIB4 and AST/ALT ratios. The Agile scores consistently outperformed the other noninvasive tests in predicting life-related events (hepatocellular carcinoma, hepatic decompensation [ascites, variceal hemorrhage, encephalopathy, or hepatorenal symptoms], liver transplant and liver-related deaths) at 3 and 5 years in subgroups stratified by age, sex, presence of diabetes, BMI, and reliability of liver stiffness measurement (LSM). The Agile scores were also stable over time. The authors concluded that the Agile 3+ score was preferable for prognostic purposes, whereas the main value of the Agile 4 score was for the diagnosis of MASLD-related cirrhosis. They did acknowledge that the superiority of the Agile scores over LSM alone were marginal.

Finally, just as type-2 diabetes mellitus occurs in some individuals who are not overweight (BMI <25), liver steatosis can also occur in non-obese persons, and is referred to as 'lean' or 'non-obese' MASLD, with an occurrence of 5% to as high as 20% in some populations (particularly in middle-aged persons in Asian countries).[22,23]

ASSESSING THE PREVALENCE OF MASLD, METALD, ALD

The global prevalence estimates for NAFLD in the general adult population has increased from around 25% in the early 2000s to 32% over the last decade, affecting up to 2 billion individuals worldwide.[24,25] Paik et al[26] estimated the age-standardized prevalence of the 3 subtypes (MASLD, MetALD, and ALD) among US adults, using 2017 to 2023 data from the National Health and Nutrition Examination Survey (NHANES). Overall, the prevalence of MASLD was 32.4%, MetALD was 2.2%, and ALD was 1.3%. Men had higher prevalence of all 3 compared to women. The highest prevalence of MASLD was in Mexican Americans (44%) and the lowest in Black Americans (27.4%). MetALD was most prevalent among non-Hispanic

Whites at 2.6%. Between 2017-2020 and 2021-2023, there was a significant rise in ALD prevalence, from 0.93% to 1.7%, an 81% increase. The prevalence of advanced fibrosis with any of the subtypes also rose between the surveys, from 2.5% to 3.3%.

Another study[27] extracted data from the NHANES registries between 1999 and 2018 and used the Fatty Liver Index (FLI) to identify 20,510 individuals with SLD which were classified into MASLD predominant (69%), MetALD (18.8%) and ALD predominant (12.3%) groups. This study showed that the MetALD prevalence in the SLD population increased from 1999-2018, but no significant change in ALD prevalence was found. Compared to MASLD predominant individuals, ALD predominant individuals had higher risks of all-cause (HR 1.89, 95% CI 1.03-1.38) and cancer-related mortality (HR 1.28, 95% CI 1.03-1.58).

ASSESSING THE MORTALITY OF MASLD, METALD, ALD

Among MASLD patients, cardiovascular disease and extrahepatic cancer were the leading causes of death in those without cirrhosis, while liver disease predominated in those with cirrhosis.[28] In contrast, individuals with alcohol-associated liver disease (ALD), irrespective of cirrhosis, primarily die due to liver disease.[29,30]

In a Swedish population-based cohort study, 13,100 MASLD individuals were matched with 119,000 controls. The primary outcome was cause-specific mortality using ICD codes for 11 causes of death, and the secondary outcome was all-cause mortality. Adjusted hazard ratios (HRs) for each cause were estimated using Cox regression. All-cause mortality was higher in MASLD (20.4 vs 11.0 per 1000 person-years (PY): HR 1.85, 95% CI 1.74-1.96), with increased mortality from all causes except mental health disorders, with the strongest associations for non-hepatocellular carcinoma (non-HCC), liver-related (HR26.9), and hepatocellular carcinoma (HCC) deaths (HR 35.0). The most common causes of death were non-HCC cancer (5.7/1000 PY—HR 1.47) and cardiovascular disease (5.3/1000 PY—HR 1.54). The association with all-cause mortality was strongest in the first year (HR 3.17), declining thereafter (HR1.68). All-cause mortality was nearly twice as high in MASLD persons compared to the general population, with liver and HCC-related deaths showing the highest relative risk, while non-HCC cancer and cardiovascular disease accounted for the highest absolute mortality.[31]

In a large (366,433) VA study,[32] cardiovascular disease and extrahepatic cancer were the primary causes of death in persons without cirrhosis across all SLD subtypes. MetALD and ALD were associated with progressively increasing risks of liver-related mortality compared to MASLD. Although this VA study was predominantly male, 28,215 women were also included in this study, validating results regardless of gender. The authors of this study used a validated natural language processing algorithm applied to imaging reports (ultrasound, CT, MRI), and they measured recent alcohol consumption using the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) questionnaire. Scores of 0-3 indicated low-risk drinking, scores of 4-7 indicated moderate-risk drinking, and scores of 8-12 indicated high-risk drinking (see Table 1).

Although it is now generally accepted that there is no absolutely safe level of alcohol ingestion, the Department of Veterans Affairs (VA) and Department of Defense (DoD) currently consider a screen positive for unhealthy alcohol use if AUDIT-C scores 4 points or higher. They also relied on a determination of historical alcohol consumption by an alcohol use disorder (AUD) diagnosis (≥1 inpatient or ≥2 outpatient codes ≥30 days apart).

The 10-year cumulative incidence of death from extrahepatic cancer was 7.5% (95% CI 7.3-7.7) for MASLD, 7.4% (95% CI 7.0-7.7) for

Table 1. AUDIT-C (Alcohol Use Disorders Identification Test)

Question	Answer	Score
1. How often did you have a drink containing alcohol in the past year?	Never	0 points
	Monthly or less	1 point
	2-4 times per month	2 points
	2-3 times per week	3 points
	4 or more times per week	4 points
2. On days in the past year when you drank alcohol, how many drinks did you typically drink?	0,1, or 2	0 points
	3 or 4	1 point
	5 or 6	2 points
	7-9	3 points
	10 or more	4 points
3. How often did you have 6 or more (for men) or 4 or more (for women and everyone 65 and older) drinks on an occasion in the past year?	Never	0 points
	Less than monthly	1 point
	Monthly	2 points
	Weekly	3 points
	Daily or almost daily	4 points

MetALD, and 7.4% (95% CI 6.8-8.1) for ALD (again, roughly equal for all 3 categories).[32]

Among causes of extrahepatic cancer-related death, lung cancer and gastrointestinal cancer accounted for 10-year cumulative incidences of 2.1% and 1.5% for MASLD, 2.4% and 1.5% for MetALD, and 2.6% and 1.7% for ALD. When stratified by age, persons aged 18 to 64 years with non-cirrhotic MASLD had >8-fold higher 10-year cumulative incidences of death from CVD (4.3% [95% CI 4.104.5]) and extrahepatic cancer (4.1% [95% CI 3.9-4.3]) than liver disease (0.5% [95% CI 0.4-0.5]). Persons aged 65+ years had >20-fold higher cumulative incidences of death from CVD (13.5% [95% CI 13.0-13.9]) than liver disease (0.6% [95% CI 0.5-0.7]) over the same timeframe. In adjusted cause-specific Cox regression models, compared with MASLD, the HR of liver-related death was 3.38 (95% CI 3.02-3.78; p<0.001) for MetALD and 6.99 (95% CI 6.08-8.04; p<0.001) for ALD.[32]

At the end of the 12-year study period, in patients with cirrhosis, 42% with MASLD, 40% with MetALD, and 42% with ALD had died. Among persons with MASLD, CVD was the most common cause of death, followed by liver disease. In contrast, among patients with MetALD and ALD, liver disease was the leading cause of death, followed by CVD.[32]

The 10-year cumulative incidence of death from liver disease was 9.2% (95% CI 8.0-10.5) for MASLD, 17.7% (95% CI 15.6-20.1) for MetALD, and 22.1% (95% CI 18.4-26.3) for ALD. The 10-year cumulative incidence of death from CVD was 17.3% (95% CI 15.6-19.3), 13% (95% CI 11.2-16.1), and 11.5% (95% CI 9.0-14.5) for MASLD, MetALD and ALD, respectively.[32]

When stratified by sex, female patients with cirrhotic MASLD had a >60% higher cumulative incidence of death from liver disease (15.1% [95% CI 3.7-26.2] vs 9.0% [95% CI 7.8-10.4]) than their male counterparts. In adjusted cause-specific Cox regression models compared with MASLD, the HR of liver-related death was 1.99 (95% CI 1.71-2.32; p,0.001) for MetALD and 2.40 (95% CI 1.95-2.95) for ALD.[32]

Again, from Denmark and regarding the utility of the SAFE score, a 10-year cumulative incidence of death from cardiovascular disease (CVD) was 8.1% (95% CI 7.8-8.3) for MASLD, 7.5% (95% CI 7.2-7.9) for MetALD,

and 8.1% (95% CI 7.5-8.8) for ALD (roughly equal for all three categories). Death from CVD would be expected because MASLD shares the same risk metabolic risk factors as does CVD, and the higher the metabolic risk factor burden, the higher the risk for CVD, especially in those with ≥3 metabolic risk factors.[33]

An obvious problem with all steatotic studies is the correct estimation of an individual's alcohol intake; misrepresentation here may misclassify MetALD and ALD especially, skewing estimates of liver mortality. Measurement of phosphatidylethanol (PEth) levels may help to solve this dilemma. PEth is a quantitative, objective alcohol biomarker with high sensitivity and specificity for alcohol use. It is generated in the cell membrane of circulating red blood cells and can only be formed in the presence of alcohol. A cross-sectional analysis of 391 community-dwelling adults with overweight/obesity (mean BMI 33) and SLD as defined by magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF) ≥5% assessed with their admitted alcohol use and PEth levels. As PEth levels increased, insulin resistance and hemoglobin A1c decreased, while blood pressure and high-density lipoprotein cholesterol (HDL-C) increased. 15.9% (95% CI 12.2-19.5) of individuals with SLD underreported their alcohol consumption. Male gender, absence of type 2 diabetes, and non-Hispanic Whites were the strongest independent factors associated with alcohol underreporting in this population. The use of PEth in addition to self-reported alcohol use resulted in a 4-fold and 3-fold increase in MetALD and ALD diagnosis, respectively. Male gender, aspartate aminotransferase, mean corpuscular volume, HDL-C, and MRI-PDFF were the strongest independent factors associated with higher PEth. The authors concluded that PEth may objectively quantify alcohol use and help identify SLD subcategories alongside clinical history, mitigating diagnostic misclassification.[34]

THERAPY FOR THE STEATOTIC LIVER DISEASES

Abstinence from alcohol consumption must lead this list. In the setting of MetALD and ALD, any alcohol consumption is exceedingly harmful. Obviously, with the change in nomenclature of the steatotic liver diseases to include metabolic-dysfunction diseases (ie, hypertension, obesity, diabetes, dyslipidemias), modifying these risk factors will be important from a mortality standpoint. Although not all persons with MASLD are obese, the majority are, and weight loss must be a primary focus. Certainly, the usual recommendations for diet and exercise are usually stressed, but these foci are rarely sufficient to achieve the minimal goal of 5% loss of body weight. As with so many other pathologies, off-label drug use with glucagon-like peptide-1 receptor agonist (GLP-1 RA) semaglutide and tirzepatide (dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA are showing to be beneficial. These medicines not only achieve the needed 10+% total body weight loss but help reverse the effects of insulin resistance that plays a significant role in the genesis of SLDs.

A SPECIAL NOTE TO LIFE AND DISABILITY INSURANCE UNDERWRITERS

It should be obvious that a major problem for the insurance industry lies in the great population of persons with SLD who are undiagnosed. All of us "know a guy who lives down the street who is overweight or obese and drinks a few beers now and again." Unfortunately, the primary care physicians and specialists who are perhaps treating their cardiometabolic-associated diseases, in our siloed medical system, often do not think to investigate the possibility of their patients also having SLD. For high-dollar applications, adding Fib-4 might prove to be a reasonable expense, assuming the cardiometabolic-associated diseases are low-burden and are well-treated.

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