ULTRA SONO GRAPHY

The new definition of metabolic dysfunction–associated steatotic liver disease: the role of ultrasound and elastography

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In 2023, nonalcoholic fatty liver disease was renamed metabolic dysfunction–associated steatotic liver disease by the American and European liver associations. This new nomenclature recognizes metabolic dysfunction as the central driver of the disease, and the diagnostic criteria now require the presence of hepatic steatosis plus at least one of five cardiometabolic risk factors. B-mode ultrasonography remains the most common and practical method for detecting hepatic steatosis, although newer ultrasound techniques based on attenuation, backscatter, and speed of sound have gained traction as tools to diagnose and quantify hepatic steatosis. Additionally, ultrasound elastography is increasingly used in routine clinical practice to assess liver fibrosis, diagnose cirrhosis, and identify clinically significant portal hypertension.

Keywords: Attenuation coefficient; Hepatic steatosis; Liver stiffness measurement; Non-alcoholic fatty liver disease; Vibration-controlled transient elastography

Key points: The new nomenclature and definition of metabolic dysfunction-associated steatotic liver disease (MASLD) recognizes the contribution of cardiometabolic risk factors in the pathogenesis of the disease. Ultrasound technique to detect and quantify hepatic steatosis is central to the diagnosis of MASLD. Noninvasive test of liver fibrosis has been well validated in MASLD and carries important prognostic information.

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Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is currently the most common chronic liver disease globally, affecting around 30% of the adult population [1,2]. The prevalence of MASLD has increased over the past few decades (Fig. 1) [3,4], paralleling the rising rates of obesity and type 2 diabetes. In the last decade, the prevalence of MASLD has risen most rapidly

in the Middle East, North Africa, and East Asia [4,5]. While most patients with MASLD exhibit simple steatosis, 20%–30% develop metabolic steatohepatitis—the progressive form that may advance to liver fibrosis, cirrhosis, and liver-related mortality. In the United States, MASLD has become the second most common etiology for liver transplantation [6]. Meanwhile, MASLD is emerging as an etiology of hepatocellular carcinoma [7]. Among patients with type 2 diabetes, the prevalence of MASLD is around 70% [8], highlighting its close association with insulin resistance, type 2 diabetes, and other metabolic syndromes such as obesity, hypertension, and dyslipidaemia [9]. These associations lead to various extrahepatic complications, including cardiovascular disease, chronic kidney disease, and non-hepatic cancers, which are more frequently observed than liver-related complications in most patients with MASLD [10]. To emphasize the link between hepatic steatosis and metabolic dysfunction, revisions in nomenclature have been proposed recently. This review discusses the evolution of MASLD-related terminology and the clinical implications of its updated definition, specifically examining the role of conventional transabdominal ultrasonography (US) alongside newer ultrasound modalities in diagnosis, monitoring of disease regression and progression, and prediction of treatment outcomes and prognosis.

History of Nomenclature Change

In 1836, Addison first described fatty liver in the context of alcohol consumption [11]. It was not until the 1970s that pathologists and clinicians recognized that fatty liver could occur in patients with metabolic diseases. In 1980, Ludwig et al. [12] coined the term nonalcoholic steatohepatitis (NASH), a term that quickly gained acceptance. Subsequently, nonalcoholic fatty liver disease (NAFLD) was adopted as an umbrella term, with NASH reserved for cases in which hepatic steatosis is accompanied by necroinflammation.

Although NAFLD and NASH were widely used over the following four decades, their limitations soon became evident. Above all, the names only state what the disease is not. For the world's most prevalent chronic liver disease, it is inappropriate to use terminology that fails to describe the underlying cause. Moreover,

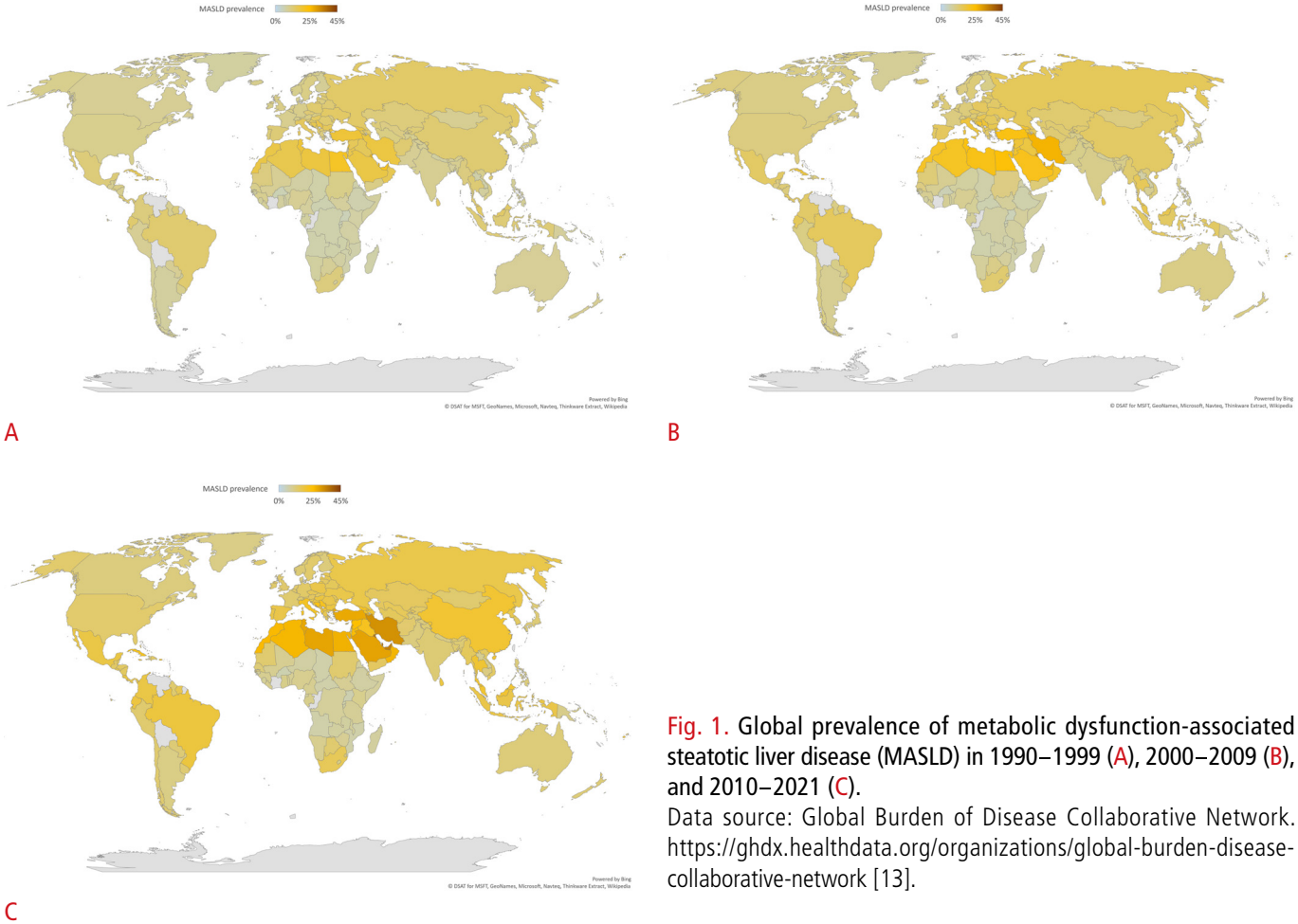

Fig. 1. Global prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) in 1990–1999 (A), 2000–2009 (B), and 2010–2021 (C).
Data source: Global Burden of Disease Collaborative Network. https://ghdx.healthdata.org/organizations/global-burden-disease-collaborative-network [13].

both "alcoholic" and "fatty" are perceived as stigmatizing [14]. Furthermore, the "non-" prefix may trivialize the condition, potentially undermining public awareness, influencing policymakers' perceptions, and affecting funding opportunities. Consequently, an international panel of experts proposed a new nomenclature and definition for metabolic (dysfunction)-associated fatty liver disease (MAFLD) to replace NAFLD [15].

Subsequently, because the MAFLD proposal was viewed as insufficiently reviewed and lacking representation beyond hepatology, the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver, in collaboration with the Asociación Latinoamericana para el Estudio del Hígado, initiated a Delphi process. This process engaged hepatologists, gastroenterologists, pediatricians, endocrinologists, pathologists, public health and obesity experts, as well as representatives from industry, regulatory agencies, and patient advocacy organizations [16]. In the end, the term "steatotic liver disease" was chosen as the overarching label for the spectrum of conditions characterized by increased hepatic steatosis. MASLD replaced NAFLD, and metabolic dysfunction-associated steatohepatitis (MASH) replaced NASH. A new term, MASLD and increased alcohol intake (MetALD), was introduced to describe patients whose hepatic steatosis results from both metabolic conditions and alcohol consumption.

Definitions of Fatty/Steatotic Liver Disease

Studies have consistently demonstrated a high degree of overlap among patients classified as having NAFLD, MAFLD, or MASLD [17]. Nonetheless, subtle but significant differences exist among these definitions. NAFLD is defined solely by the presence of hepatic steatosis in the absence of alternative liver diseases or secondary causes, such as systemic steroid use. In contrast, both MAFLD and MASLD permit the coexistence of other liver diseases, thereby acknowledging the contribution of hepatic steatosis and metabolic conditions to the natural history of coexisting disorders like chronic viral hepatitis. To meet the criteria for MAFLD and MASLD, patients must also present cardiometabolic risk factors, although the two definitions differ slightly in this regard (Table 1). Given these risk factors, it is not surprising that patients meeting the MAFLD or MASLD criteria face a higher risk of major adverse cardiovascular events and mortality than those with NAFLD without such risk factors [18].

Another key differentiator among the definitions is alcohol consumption. To fulfill the definition of NAFLD and MASLD, a patient must not have excessive alcohol consumption, which is defined as ≥30 g/day in men and ≥20 g/day in women [19]. Under the steatotic liver disease umbrella, patients are classified as having MetALD if their alcohol consumption is 30–59 g/day in men and 20–49 g/day in women, and alcohol-associated liver disease if their alcohol consumption is ≥60 g/day in men and ≥50 g/day in women.

Table 1. Comparison of the definitions of NAFLD, MAFLD, and MASLD

	NAFLD	MAFLD	MASLD
Hepatic steatosis	Required	Required	Required
Alcohol consumption	<30 g/day in men and <20 g/day in women	Can coexist with excessive alcohol consumption	<30 g/day in men and <20 g/day in women
Viral hepatitis and other liver diseases	Should be excluded	Can coexist	Can coexist
Secondary causes of hepatic steatosis	Should be excluded	Can coexist	Would be classified as drug-induced liver injury or monogenic diseases
Presence of cardiometabolic risk factors	Not required	Need to have type 2 diabetes, overweight/obesity, or 2 other cardiometabolic risk factors listed below:[a] - Waist circumference ≥102/88 cm in Caucasian men and women (≥90/80 cm in Asians) - Blood pressure ≥130/85 mmHg - Plasma triglycerides ≥150 mg/dL - Plasma HDL-cholesterol <40 mg/dL in men and <50 mg/dL in women - Prediabetes - HOMA-IR ≥2.5 - High-sensitivity C-reactive protein >2 mg/L	Need to have at least 1 cardiometabolic risk factor listed below:[a] - Body mass index ≥25 kg/m^2 (≥23 kg/m^2 in Asians) or waist circumference >94/80 cm in men and women or ethnicity adjusted equivalent - Prediabetes or diabetes - Blood pressure ≥130/85 mmHg - Plasma triglycerides ≥150 mg/dL - Plasma HDL-cholesterol <40 mg/dL in men and <50 mg/dL in women

NAFLD, nonalcoholic fatty liver disease; MAFLD, metabolic (dysfunction)-associated fatty liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance.

[a]Fulfilling the criteria or receiving treatments for the corresponding cardiometabolic conditions.

Conversely, the diagnosis of MAFLD is compatible with concomitant excessive alcohol consumption, even in the range of alcohol-associated liver disease and alcohol use disorder.

Clinical Implications of the New Definition of Steatotic Liver Disease

Although the inclusion of metabolic risk factors in the MASLD/MAFLD diagnosis initially raised concerns about whether the population identified by the previous NAFLD definition was equivalent to that diagnosed under the new criteria, these issues have been addressed. One study—including 277 individuals with intrahepatic triglyceride content ≥5% and 414 individuals with biopsy-proven NAFLD—demonstrated a greater than 95% overlap between patients diagnosed with NAFLD and those meeting the new MASLD definition. Similarly, a study involving over 12,000 patients reported excellent concordance between NAFLD and MAFLD diagnoses [20]. Consequently, findings from NAFLD research should remain applicable under the new MASLD/MAFLD definitions.

The new definition of MASLD, which emphasizes the role of metabolic burden, identifies a higher-risk population due to the presence of metabolic factors. Multiple longitudinal studies have confirmed an increased risk of morbidity and mortality under the new MASLD/MAFLD criteria. For instance, a retrospective cohort study of 7,761 patients in the United States followed for a median of 23 years found that patients with MAFLD had a 17% higher risk of all-cause mortality (hazard ratio [HR], 1.17; 95% confidence interval [CI], 1.04 to 1.32). Furthermore, a subset of patients who met the criteria for MAFLD but not NAFLD exhibited a 1.7-fold increase in all-cause mortality (HR, 1.66; 95% CI, 1.19 to 2.32) [21]. This finding was reinforced by studies in other ethnic groups. In prospective cohort studies involving Asian patients, MASLD independently increased all-cause mortality, particularly among those with diabetes and/or at least two cardiometabolic risk factors [22,23].

The most common causes of mortality in patients with NAFLD are cardiovascular disease, non-hepatic malignancies, and liver-related events, with cardiovascular disease being the primary cause among patients without cirrhosis [24]. Long-term cohort studies indicate a heightened risk of cardiovascular disease and related mortality in patients with MASLD/MAFLD [25]. For example, a study using a Korean nationwide health screening database that included approximately 9.8 million patients with MAFLD found a higher risk of cardiovascular disease (adjusted HR, 1.43; 95% CI, 1.41 to 1.45) compared to those meeting only the NAFLD criteria (adjusted HR, 1.09; 95% CI, 1.03 to 1.15) over a median follow-up of 10 years [18]. Similarly, metabolic dysregulation in MASLD has been linked to an increased risk of non-hepatic malignancies [26]. An umbrella meta-analysis of 374 studies suggested elevated risks for breast, urinary tract, lung, and gastrointestinal cancers [27]. Although the causal relationship between MASLD and non-hepatic malignancies requires further clarification, liver disease remains the leading cause of mortality among patients with cirrhosis. In a territory-wide study of over 30,000 MASLD patients in Hong Kong, liver disease accounted for 36.8% of all deaths among those with cirrhosis [10]. Nonetheless, the impact of metabolic dysregulation on liver-related events and mortality warrants additional investigation [28].

The Role of Ultrasonography

Hepatic steatosis is a key diagnostic criterion for steatotic liver disease and is most often first detected using B-mode US. B-mode US is the most commonly employed first-line imaging modality for various intra-abdominal conditions due to its widespread availability and versatility. As a result, hepatic steatosis may be identified incidentally during examinations for other conditions or as part of routine health checks, as well as deliberately when steatotic liver disease is suspected. Typical ultrasonographic features of hepatic steatosis include hyperechogenic liver parenchyma and increased attenuation of ultrasound waves in deeper regions as steatosis worsens. This "bright liver" appearance often facilitates prompt diagnosis [29]. The radiological assessment of the severity of hepatic steatosis is usually graded using a 4-point scale: normal (grade 0), mild (grade 1), moderate (grade 2), and severe (grade 3) (Fig. 2) [30]. In practice, grading hepatic steatosis with B-mode US is challenging and operator-dependent, with limited reliability and sensitivity for mild steatosis. Additional limitations include technical difficulties in obese patients, intraobserver and interobserver variability, and insufficient sensitivity to detect moderate to advanced fibrosis or even early cirrhosis [31]. Moreover, severe hepatic steatosis can obscure features indicative of cirrhosis. Nevertheless, B-mode US is recommended as one of the initial screening tools for steatotic liver disease in individuals with overweight/obesity, type 2 diabetes, or metabolic syndrome because of its wide availability, low cost, and lack of radiation or contrast agent exposure [32].

Quantitative Assessment of Hepatic Steatosis Using Ultrasound-Based Techniques

Various manufacturers have developed quantitative ultrasound (QUS) techniques based on radiofrequency data to measure liver fat, aiming to overcome the limitations of conventional B-mode US. These techniques include the attenuation coefficient (AC), backscatter coefficient (BSC), composite quantitative approaches,

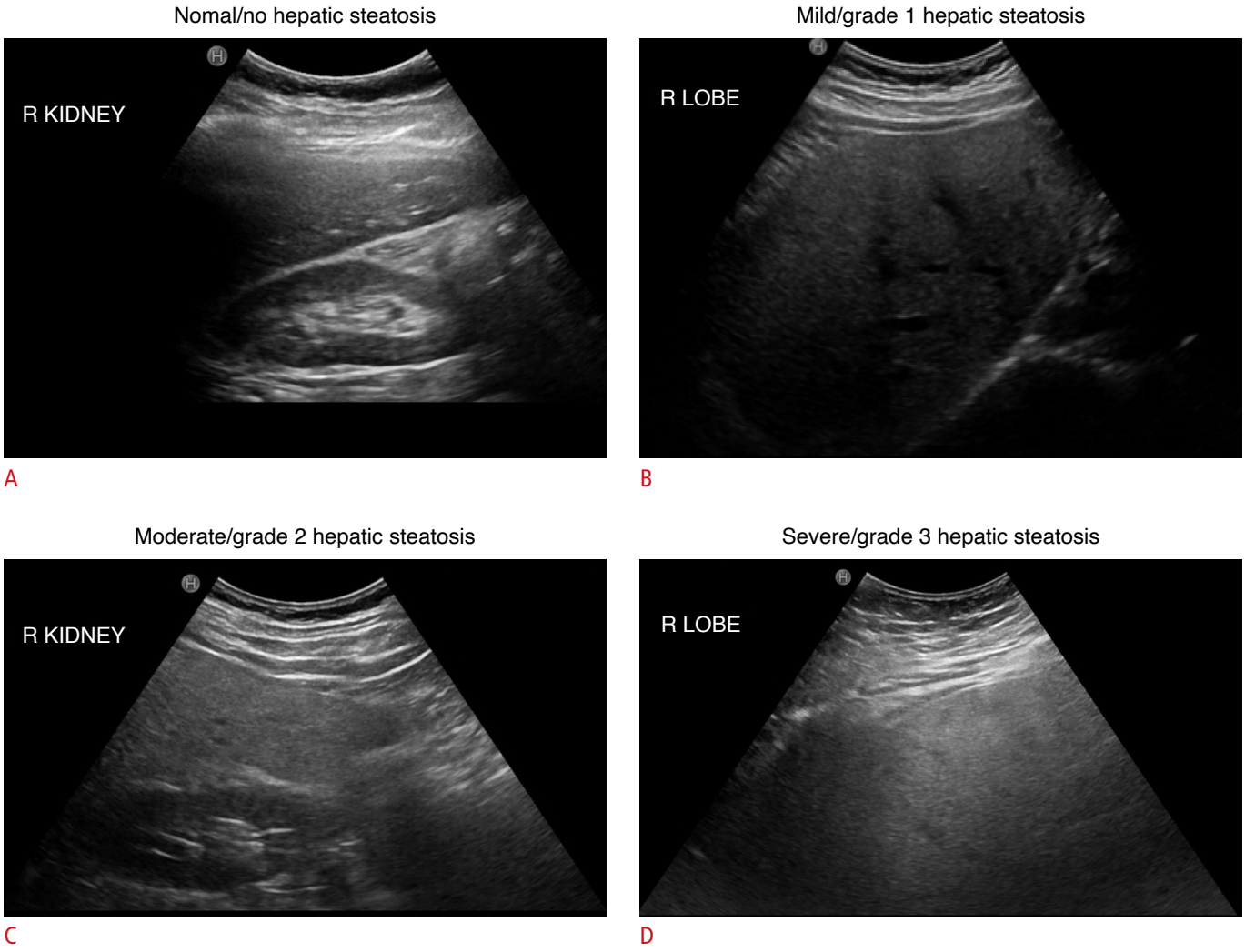

Fig. 2. Radiological features of patients with various degree of hepatic steatosis: (A) normal: no hepatic steatosis, (B) mild: grade 1 hepatic steatosis, (C) moderate: grade 2 hepatic steatosis, and (D) severe: grade 3 hepatic steatosis.

and speed of sound (SoS) measurements (Fig. 3) [29,33,34]. Among these, AC is the most advanced and is offered under various proprietary names by major ultrasound vendors. In contrast, BSC is not commercially available as a standalone technique, and SoS is still in the early stages of development.

Acoustic waves are attenuated to varying degrees as they pass through steatotic liver tissue compared to normal liver parenchyma—a variation that is captured through AC measurements [35]. As these waves propagate through tissue, their amplitude decreases due to energy absorption and scattering.

The controlled attenuation parameter (CAP) (Echosens) is the most widely clinically studied AC measurement. CAP uses a vibration-controlled transient elastography device to measure ultrasound attenuation at the probe's center frequency, which correlates with the degree of hepatic fat accumulation [36]. CAP values, reported in decibels per meter (dB/m), range from 100 to 400 dB/m, indicating increasing severity of hepatic steatosis [36]. CAP has demonstrated area under the receiver-operating characteristic curve (AUROC) values of 0.81–0.84 for ≥S1, 0.85–0.88 for ≥S2, and 0.86–0.91 for ≥S3 [37,38]. When the XL probe was used in patients with MASLD, the AUROC was 0.82 for ≥S1 and 0.75 for ≥S2 [39].

Other AC-based technologies include the ultrasound attenuation parameter, attenuation imaging (ATI), attenuation measurement function, attenuation plane-wave ultrasound, tissue attenuation imaging, liver fat quantification, AC, ultrasound-guided attenuation parameter (UGAP), Q-attenuation imaging, attenuation, and ultrasound attenuation [29,40]. Several vendors have included the AC algorithm in their systems. B-mode US is used to position the region of interest (ROI) for measurement, thus facilitating the selection of an area free of artifacts. The AUROCs for AC were 0.74–

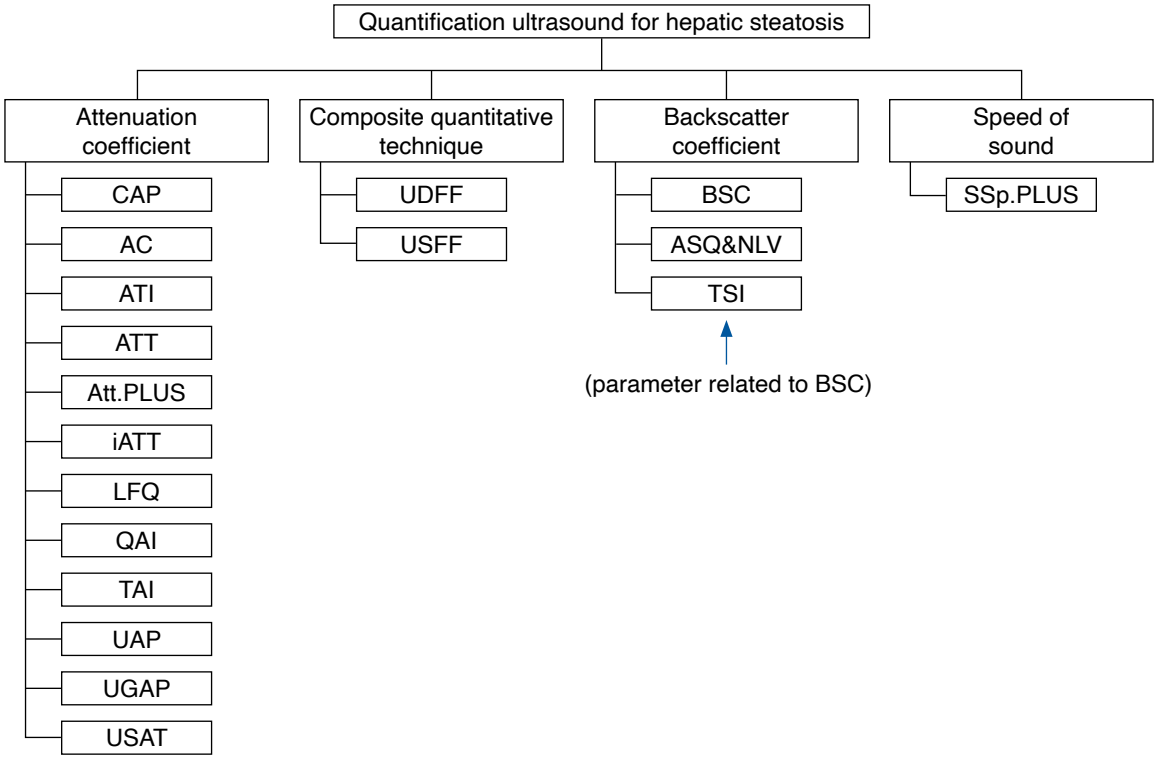

Fig. 3. Classification of ultrasound-based algorithms for the assessment and quantification of hepatic steatosis. AC, attenuation coefficient; ATI, attenuation imaging; ATT, attenuation measurement function; Att. PLUS, attenuation plane-wave ultrasound; ASQ, acoustic structure quantification; BSC, backscatter coefficient; CAP, controlled attenuation parameter; iATT, attenuation; LFQ, liver fat quantification; NLV, normalized local variance; QAI, Q-attenuation imaging; Ssp.PLUS, plane-wave ultrasound speed of sound; TAI, tissue attenuation imaging; TSI, tissue scattering imaging; UAP, ultrasound attenuation parameter; UDFF, ultrasound-derived fat fraction; UGAP, ultrasound-derived fat fraction; USAT, ultrasound attenuation; USFF, ultrasound fat fraction.

0.97 for ≥S1, 0.90–0.99 for ≥S2 and 0.77–0.97 for S3 [29]. AC has shown acceptable to good discrimination for hepatic steatosis, but research has mainly focused on CAP, ATI, and UGAP, which are widely used and have shown promising results. Other AC-based methods require further validation to confirm their accuracy, and variability in cutoff values due to differences in protocols, algorithms, and cohort characteristics underscores the need for standardization.

BSC measures the ultrasound energy scattered by reflectors that are equal to or smaller than the ultrasound wavelength and that return to the transducer. The accumulation of fat vacuoles in hepatocytes increases ultrasound scattering, resulting in greater echogenicity and a brighter liver appearance on ultrasound imaging [41]. The acoustic structure quantification normalized local variance, and tissue scatter-distribution imaging are commercial BSC-based techniques [40]. In a cross-sectional study of 204 adults using magnetic resonance imaging proton density fat fraction (MRI-PDFF) as the reference standard, BSC demonstrated a high AUROC (98%) in detecting hepatic steatosis, with a sensitivity of 87% and specificity of 91% [42].

A composite QUS technique combining AC and BSC, known as the ultrasound-derived fat fraction (UDFF), provides results in percentage form and enhances the precision of liver fat estimation. The AUROC of UDFF was 0.94 ≥S1, 0.88 for ≥S2, and 0.83 for S3, reflecting strong diagnostic potential [43].

The SoS represents the velocity at which longitudinal acoustic waves propagate, and it varies according to tissue composition. Increased liver fat reduces the SoS by altering tissue density and resistance to compression [44]. SoS estimation (SSE) and sound speed plane-wave ultrasound (SSp.PLUS) are newer US techniques used for assessing the severity of hepatic steatosis. Both SSE and Ssp.PLUS have exhibited good performance for detecting hepatic steatosis, with AUROCs of 0.88–0.95 and 0.82, respectively [45,46].

These QUS techniques assess tissue properties rather than directly quantifying fat content [47]. They evaluate factors such as attenuation, scattering, and SoS, all of which can be influenced by various confounders. Moreover, the implementation of a standardized protocol is crucial to ensure accurate and reliable measurements. Accordingly, the World Federation for Ultrasound in Medicine and Biology issued guidance in 2024, recommending a protocol for AC measurement [29].

Ultrasound Elastography

Ultrasound elastography systems are categorized based on their underlying physical principles into strain imaging and shear wave imaging. Strain elastography measures tissue deformation under stress, which can be induced by external manual compression or internal physiological motion, whereas shear wave imaging relies on dynamic compression stress. This stress is generated either externally by a transient mechanical impulse, as in one-dimensional transient elastography (1DTE), or internally via an acoustic radiation force impulse (ARFI), as used in point-shear wave elastography (pSWE) and bidimensional shear wave elastography (2D-SWE) (Table 2) [48–53].

Table 2. Comparison of ultrasound elastography platforms

	1DTE	pSWE	2D-SWE
Depth	2.5–6.5 cm M probe 3.5–7.5cm XL probe	4–5 cm	4–5 cm
Cost	Low	Moderate	Moderate
Availability	High	Moderate	Moderate
Shear wave generation	Mechanical external vibration	ARFI	ARFI
Shear wave duration	Transient	Transient	Transient
Imaging	A-mode	B-mode	B-mode
Frequency of shear wave	40–50 Hz	100–500 Hz	100–500 Hz
ROI	Little	Little	Moderate
Parameter (unit)	Young modulus (kPa)	Shear wave speed (/ms) Young modulus (kPa)	Shear wave speed (/ms) Young modulus (kPa)
Failure rate [50–53]	About 6%–25%	About 2%	About 5%
Reproducibility	Good (interobserver agreement lower in patients with mild hepatic fibrosis, steatosis or high body mass index)	Excellent	Excellent
Confounder	Technical and biological confounders (mentioned in text)		
	Operator experience Ascites		Operator experience
Advantage	- Validated technique - Point of care for clinician - Rapid learning for operators - Well defined criteria - Better performance for higher degree of fibrosis - Portable	- Can be integrated with routine liver ultrasound if the device is equipped with the appropriate software - B-mode guidance is available, which enables operator-selected ROI - Shear wave generated directly within the liver tissue itself, rather than needing to pass through external tissues, even the condition like obesity and ascites	- Can be integrated with routine liver ultrasound if the device is equipped with the appropriate software - B-mode guidance is available, which enables operator-selected ROI with large size and color display - Shear wave generated directly within the liver tissue itself, rather than needing to pass through external tissues, even the condition like obesity and ascites - Rapid data acquisition of extensive quantitative elastograms - Real time imaging - Broad applicability
Limitations	- Maintenance requirement: the probe needs regular recalibration within a specified timeframe (6-12 months) - Need for a specialized device to perform the elastography - No B-mode guidance (ROI cannot be chosen)	- Less optimal for use at the point of service - Higher tissue energy absorption affect reliability - Different systems or manufacturers introduce variability - Higher tissue energy absorption in pSWE may reduce measurement accuracy	- Less optimal for use at the point of service - Higher tissue energy absorption affect reliability - Different systems or manufacturers introduce variability - Require high end of electronics

1DTE, 1-dimensional transient elastography; pSWE, point-shear wave elastography; 2D-SWE, bidimensional shear wave elastography; ARFI, acoustic radiation force impulse; ROI, region of interest.

1DTE uses a specialized probe that integrates an ultrasound transducer with a small mechanical vibrator. This vibrator produces a light external pulse that generates shear waves propagating along a longitudinal axis. The ultrasound transducer then tracks the speed of these shear waves, with velocity serving as an indicator of tissue stiffness. 1DTE provides a time-motion-mode graph and an A-mode graph to facilitate accurate localization and visualization of structural movement over time, capturing positions along a single line to create a 1DTE propagation map for each measurement [49].

pSWE employs ARFI excitation to generate shear waves that propagate laterally from the point of excitation, resulting in perpendicular tissue displacement [54]. This displacement is tracked, allowing for the selection and recording of an ROI for reliable follow-up studies [48].

Building on the principles of pSWE, 2D-SWE also utilizes ARFI excitation [48]. This technique delivers multiple ARFI push pulses at different locations, generating shear waves that traverse the tissue and cover a large field of view. Consequently, a large ROI can be selected to obtain an accurate measurement of shear wave speed [48]. Real-time imaging is displayed both numerically and as a color-coded elastogram superimposed on the B-mode image [55].

1DTE exhibited greater diagnostic accuracy for advanced fibrosis (F3) and cirrhosis (F4) than for significant fibrosis (F2). Several meta-analyses [56–59] and review studies [37,60] have reported similar results, with AUROC values of 0.77–0.87 for F2, 0.80–0.94 for F3, and 0.89–0.96 for F4. The reported sensitivity values were 62–90% for F ≥2, 84–100% for F ≥3, and 90–100% for F4, while specificities ranged from 74–100% for F ≥2, 83–97% for F ≥3, and 75.9–94.8% for F4.

Additionally, several meta-analyses have evaluated the diagnostic efficacy of pSWE [50,61] (AUROC, 0.86 for F2, 0.89–0.94 for F3, 0.90–0.95 for F4) and 2D-SWE [61–63] (AUROC, 0.75–0.86 for F2, 0.72–0.89 for F3, 0.88–0.93 for F4). Although ARFI-based shear wave elastography techniques demonstrate good accuracy in diagnosing various stages of fibrosis in MASLD patients, the evidence remains limited, and these methods are not yet widely adopted in clinical practice. Further research is needed to fully assess their diagnostic potential and clinical applicability in this patient population.

Furthermore, both technical and biological confounders can affect the accuracy of ultrasound elastography methods, including vibration-controlled transient elastography (VCTE) and ARFI-SWE. Factors such as hepatic inflammation and steatosis, extrahepatic cholestasis, liver congestion, acute hepatitis, liver lesions, congestive heart failure, amyloidosis, as well as variations in excitation frequencies, measurement depth, and operator- or device-dependence, all contribute to variability in results [49,64,65].

Although various ultrasound technologies measure liver stiffness and elasticity, most studies have historically been based on VCTE. Since different technologies can yield slightly different liver stiffness values, caution is warranted when interpreting study results and applying these findings in clinical practice.

Role of Ultrasound Technologies for Prognostication

The hepatic venous pressure gradient (HVPG) is the gold standard for measurement of portal pressure [66], despite ongoing concerns regarding its accuracy in evaluating portal pressure in patients with MASLD [67,68]. As the field of hepatology shifts toward noninvasive assessments, HVPG measurement has become obsolete in routine clinical practice outside research settings. Liver stiffness measurement (LSM) by VCTE provides a noninvasive method to assess liver stiffness and the degree of portal hypertension. In clinical practice, LSM can predict events such as the presence of varices, hepatic decompensation, and liver-related mortality in various chronic liver diseases, including MASLD [37,69,70].

In the ANTICIPATE study, 518 patients with compensated advanced chronic liver disease (cACLD) underwent paired VCTE-LSM and HVPG measurements. A model combining VCTE-LSM and platelet count was developed to evaluate portal hypertension and was later incorporated into the Baveno VII consensus for predicting clinically significant portal hypertension (CSPH) [71,72]. In non-obese MASLD patients (i.e., body mass index [BMI] <30 kg/m^2), a VCTE-LSM of ≥25 kPa demonstrated a positive predictive value exceeding 90% for diagnosing CSPH, indicating the presence of varices and a higher risk of hepatic decompensation in patients with cACLD [72]. However, in patients with obese MASLD (BMI ≥30 kg/m^2), the combination of VCTE-LSM and platelet count performed suboptimally because LSM tends to overestimate actual portal pressure in obesity [73]. Incorporating BMI into the ANTICIPATE model (i.e., the ANTICIPATE-NASH model) resolved this issue, with subsequent studies confirming the model's accuracy in predicting CSPH in obese MASLD patients [73,74].

Apart from LSM, spleen stiffness measurement (SSM) can be obtained using VCTE. VCTE-derived SSM performs even better than VCTE-LSM in predicting liver-related events and mortality [75]. In MASLD, VCTE-SSM has demonstrated high accuracy in both ruling in and ruling out CSPH [76,77]. Furthermore, a recent study involving 407 patients with cACLD (40% with MASLD) developed an SSM-based model that combined VCTE-SSM, VCTE-LSM, BMI, and platelet count (i.e., the NICER model). This model achieved a significantly higher area under the curve for predicting CSPH than the ANTICIPATE±NASH model (0.91 [0.86–0.95] vs. 0.86 [0.81–

0.92], P=0.012 in the validation cohort) [78]. It is anticipated that LSM and SSM derived from VCTE, along with other noninvasive parameters, will gain increasing importance in the evaluation and management of MASLD.

Role of Ultrasound Technologies as Monitoring and Response Biomarkers

In routine clinical practice, patients are seen repeatedly over time, making it essential to understand the clinical significance of changes in noninvasive tests. According to the Food and Drug Administration-National Institutes of Health Biomarker Working Group, monitoring biomarkers are measured serially to assess disease status over time, whereas response (or pharmacodynamic) biomarkers are measured serially to evaluate potentially beneficial treatment responses [79]. Due to challenges in obtaining high-quality longitudinal data, most studies correlating serial noninvasive tests with liver histological changes have emerged from secondary analyses of completed clinical trials, while other studies have compared serial noninvasive tests against clinical outcomes. As expected, noninvasive tests of fibrosis correlate more strongly with major adverse liver outcomes (MALOs) than do biomarkers of steatosis and inflammation.

In the multicenter VCTE-Prognosis study, 10,920 MASLD patients who underwent serial VCTE examinations were followed for MALOs. Baseline Agile 3+ and Agile 4 scores—which incorporate VCTE-LSM, platelet count, aminotransferases, diabetes, age, and sex—proved superior to histological fibrosis staging in predicting MALOs, although the prognostic performance of VCTE-LSM alone was similar to that of histology [80]. Importantly, a relative change of ≥20% or ≥30% in either the Agile scores or VCTE-LSM corresponded to a significant change in the incidence of MALOs. For example, among patients with a baseline VCTE-LSM >15 kPa, the incidence of MALOs was 7.8, 19.4, and 38.7 per 1,000 person-years for those whose follow-up VCTE-LSM was <10, 10–15, and >15 kPa, respectively. Similarly, changes in LSM measured by magnetic resonance elastography (MRE) have correlated with MALOs, although MRE studies are limited by smaller patient numbers due to the cost and availability of MRI [81].

One caveat should be noted. Ultrasound elastography (and MRE) is known to have a high negative predictive value but only a modest to moderate positive predictive value for significant or advanced fibrosis [82]. Thus, an improvement in LSM over time may indicate genuine fibrosis regression, or it may reflect a patient without advanced fibrosis who had previously received a false-positive LSM. In either scenario, a favorable prognosis is anticipated.

Regarding response biomarkers, a relative improvement in MRI-PDFF of ≥30% correlates with a ≥2-point improvement in the histological NAFLD activity score, resolution of MASH, and fibrosis regression [83]. This relationship has been confirmed in multiple drug trials, including the recent phase 3 MAESTRO-NASH study that led to the conditional approval of resmetirom [84]. Moreover, relative improvements of ≥50% and ≥70% in MRI-PDFF have been proposed to identify "super responders" who exhibit an even greater histological response.

Ultrasound biomarkers of hepatic steatosis have also been evaluated as response biomarkers; however, their performance has so far been modest, likely due to higher measurement variability compared with MRI-PDFF. For example, the serial FibroScan-aspartate aminotransferase score—which comprises CAP, LSM, and serum aspartate aminotransferase—achieved only an AUROC of 0.69 in predicting MASH resolution without worsening fibrosis in the phase 2b semaglutide trial [85]. The introduction of continuous CAP via the VCTE SmartExam and the development of newer ultrasound technologies may reduce this variability and improve their utility as monitoring tools, but prospective data are still needed [86].

Conclusion

Recent updates in nomenclature reflect an improved understanding of the epidemiology and pathophysiology of MASLD, particularly emphasizing its close association with metabolic dysfunction, insulin resistance, and the impact of alcohol intake. Notably, several studies have demonstrated a significant overlap between patients classified under the NAFLD and MASLD/MAFLD definitions, suggesting that findings from NAFLD research remain relevant under the new nomenclature. The revised MASLD/MAFLD definitions play a critical role in identifying patients at higher risk of morbidity and mortality due to coexisting metabolic risk factors. Noninvasive ultrasound-based assessments are crucial for enhancing the detection, monitoring, evaluation of treatment response, and prognostication in MASLD. Despite drawbacks such as operator-dependent variability and limited reliability, B-mode ultrasound remains the primary imaging modality for detecting hepatic steatosis. In contrast, newer ultrasound technologies—such as transient elastography and shear wave elastography—provide more accurate evaluations of liver fibrosis, while attenuation or backscatter-based techniques are better suited for assessing hepatic steatosis. These latter techniques hold promise for improving diagnostic accuracy and may serve as effective monitoring tools. Although technical and biological confounders can affect the accuracy of ultrasound elastography, this modality has been validated for monitoring disease progression, assessing treatment response, and predicting clinical outcomes. Consequently, invasive procedures like liver biopsy and HVPG measurements are now reserved for specific clinical scenarios,

underscoring the pivotal role of noninvasive ultrasound-based techniques in the comprehensive management of MASLD.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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