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Guidelines

WFUMB Guidelines/Guidance on Liver Multiparametric Ultrasound. Part 2: Guidance on Liver Fat Quantification

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ABSTRACT

The World Federation for Ultrasound in Medicine and Biology (WFUMB) has promoted the development of this document on multiparametric ultrasound. Part 2 is a guidance on the use of the available tools for the quantification of liver fat content with ultrasound. These are attenuation coefficient, backscatter coefficient, and speed of sound. All of them use the raw data of the ultrasound beam to estimate liver fat content. This guidance has the aim of helping the reader in understanding how they work and interpret the results. Confounding factors are discussed and a standardized protocol for measurement acquisition is suggested to mitigate them.
The recommendations were based on published studies and experts' opinion but were not formally graded because the body of evidence remained low at the time of drafting this document.

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Introduction

New ultrasound (US)-based biomarkers that non-invasively quantify liver fat content are currently available [1–3]. Due to the steatotic liver disease (SLD) "epidemic," their use to assess the presence and severity of hepatic steatosis is attractive.

In 2021, the World Federation for Ultrasound in Medicine and Biology (WFUMB) released a position paper on liver fat quantification providing expert's opinion [1]. Since then, several further studies have been published. However, confounding factors that may affect the US estimation of liver fat are inadequately understood, and a protocol for the acquisition of these parameters that mitigate the differences in values between observers or between algorithms from different manufacturers is lacking.

Therefore, the WFUMB leadership has promoted the development of a document on multiparametric US, which includes both new evidence on the role of shear wave elastography in chronic liver disease (presented in part 1) and the available data on the quantitative US evaluation of liver fat content (Part 2).

For the guidance on the use of the US biomarkers for the quantification of liver fat content the recommendations were based on published studies and experts' opinion but were not graded because the body of evidence remained low at the time of drafting this document.

Quantification of liver fat content: the clinical needs

Hepatic steatosis is the defining feature of metabolic dysfunction-associated steatotic liver disease (MASLD), previously termed metabolic dysfunction-associated fatty liver disease (MAFLD) or nonalcoholic fatty liver disease (NAFLD) [4]. MASLD has become the most common chronic liver disease worldwide, affecting at least 30% of the global adult population [5]. It is also the second leading indication for liver transplantation in the United States and an important cause of hepatocellular carcinoma (HCC) [6]. Further, MASLD is associated with increased risk of type 2 diabetes and cardiovascular disease [7].

Hepatic steatosis can coexist with other chronic liver diseases such as viral hepatitis and is also a key feature of alcohol-related liver disease. Concomitant MASLD increases the risk related to other liver disease as for example evident in patients with both MASLD and hepatitis B who have a higher risk of developing cirrhosis and HCC [8]. Likewise, liver-related events are more common in patients with hepatic steatosis due to both metabolic syndrome and excessive alcohol consumption than either alone [9]. This condition is currently referred to as metabolic dysfunction and alcohol-related steatotic liver disease (MetALD) [4].

Most imaging techniques allow not only the diagnosis but also the estimation of the severity of liver steatosis. Although patients with MASLD have increased risk of liver-related events [10], the severity of hepatic steatosis does not appear to affect the liver-related prognosis.

Hepatic steatosis is more dynamic than fibrosis, responding to weight changes from nutrition intake, physical activity, pharmacotherapy, or bariatric surgery [11].

Hepatic steatosis often decreases or even disappears as a patient progresses to cirrhosis, thus explaining the fact that MASLD is the most common underlying etiology of cryptogenic cirrhosis [12].

Although the absolute severity of hepatic steatosis may not impact survival, the change in hepatic steatosis has attracted much interest. In secondary analyses of clinical trial data, a reduction of hepatic steatosis, as measured by a change in magnetic resonance imaging proton density fat fraction (MRI-PDFF), correlated with histological improvements in metabolic dysfunction-associated steatohepatitis (MASH) [13]. In particular, patients with a 30% or greater relative reduction in MRI-PDFF during MASH treatment are more likely to have a ≥2-point reduction in the NAFLD activity score and resolution of MASH. One study in a nontreatment cohort also suggests that the MRI-PDFF response might correlate with improvement in liver fibrosis, though this remains to be confirmed in treatment cohorts [14]. For these reasons, the MRI-PDFF response is often used as the primary or key secondary endpoint in early phase clinical trials in MASH, with a ≥30% relative reduction in MRI-PDFF representing treatment response, and ≥50% or ≥70% relative reduction representing super-responders. This approach allows early readouts in a noninvasive manner. In contrast, there are limited data on the accuracy and reliability of US techniques to determine treatment response, though such methods are sometimes used in investigator-initiated studies due to their relatively low cost.

There is a lack of longitudinal studies relating the severity of hepatic steatosis, assessed with controlled attenuation parameter (CAP) or ultrasound attenuation technologies, with development of cardiometabolic outcomes. Although the severity of hepatic steatosis determined by B-mode ultrasound is considered inconsistent, it has been associated with development of type 2 diabetes mellitus [15]. Some studies in large cohorts have reported that the severity of liver steatosis is associated with an increased risk of cardiovascular events [16–18].

Of note, a very recent study including 391 adult subjects with type 2 diabetes has reported that high liver fat content, assessed with MRI-PDFF, implied an increased cardiovascular risk independently of age, gender, ethnicity and body mass index (BMI) [19]. The results of this study highlight that the importance of steatosis grading in SLD is often overlooked [20].

Another relevant question in the field is whether hepatic steatosis affects liver stiffness measurement (LSM). Some studies suggest that severe hepatic steatosis is associated with increased LSM independent of the degree of liver fibrosis [21], but this is not shown in all studies [22]. One study also showed that correction for the CAP could reduce false-positive diagnosis of advanced liver fibrosis by LSM using vibration controlled transient elastography (VCTE) [23]. Moreover, hepatic steatosis is strongly linked to obesity, and a very high BMI has been repeatedly demonstrated to confound results of LSM [24,25]. It is yet unclear if confounding is primarily caused by hepatic steatosis, thickness of subcutaneous and prehepatic fat, or technical issues related to obesity. In any case, careful consideration of these confounding factors related to the severity of hepatic steatosis may improve the interpretation of LSM results.

MASLD in pregnancy is now a common occurrence, as many women begin pregnancy overweight or obese. Previous studies have found that hepatic steatosis increased the risk of gestational diabetes mellitus, pregnancy-associated hypertension, and preterm birth [26,27]. Perinatal MASLD has also been associated with maternal insulin resistance, gestational diabetes mellitus and increased risk of obesity, cardiometabolic risk, type 2 diabetes and MASLD in offspring [28]. Furthermore, autopsy and MRI studies have shown a relationship between MASLD in stillborn and live neonates, and chronic pre-conception maternal type 2 diabetes and gestational diabetes mellitus, reflecting a metabolically unfavorable intrauterine environment and potential metabolically adverse start to life [29,30]. If MASLD in intrauterine life and early childhood persists with other metabolic risk factors, then the journey towards future type 2 diabetes, cardiovascular disease and cirrhosis may begin early in life. Although, data are sparse and guidelines have previously not included MASLD in pregnancy, opportunistic assessment of the severity of MASLD in at-risk pregnant women, using US-based technologies may provide a window to future intergenerational health.

Reference standard

Assessment of SLD requires on one hand quantification of liver fat, and on the other hand assessment of additional components of liver disease, namely inflammation and fibrosis, associated with risk of progression and liver-related events [31–33].

Liver biopsy is still considered the reference standard to assess SLD given that it can provide data on each of its histological components. From histology, the degree of steatosis, hepatocyte ballooning and lobular inflammation are combined in the so-called NAFLD activity score [31], identifying steatohepatitis at values ≥4. Staging of fibrosis is done

on the same specimen [34]. However, liver biopsy is invasive with possible significant complications, and there is a large inter-observer variability in interpreting specimens, particularly regarding hepatocyte ballooning and steatosis grading [35,36]. On the other hand, the histologic specimen is just a small sample (1/50,000) of the whole liver, therefore it cannot be representative of features that likely have a heterogeneous distribution. As for pure fat quantification, it is neither conceivable nor ethical to use liver biopsy to identify and quantify liver fat content in the very large number of individuals with MASLD. In addition, the amount of fat in the liver can change over the course of months so short term follow-up may be required, and serial follow-up evaluation with liver biopsy cannot be justified (cost; risks).

In addition to liver biopsy, liver fat quantification can be achieved using MRI-based methods, including MR spectroscopy (MRS) and MRI-PDFF derived from MR chemical shift imaging (CSI). MRS directly measures signal intensities from fat protons and signal intensities from water protons in the liver on the frequency domain, and thus liver fat fraction can be directly calculated as the ratio of signal intensities from fat protons to the sum of signal intensities from both water and fat protons [37]. Conversely, CSI relies on the difference in resonance frequency between water and fat protons. In human tissue including liver, water protons process slightly faster than fat protons by 3.5 ppm, leading to the oscillation with regular interval [38]. In opposed phase (OP), where vectors from water protons oppose those from fat protons, signal intensities from fat protons are subtracted from the signals of water protons. In contrast, in phase (IP), where vectors from water and fat protons align, signal intensities from fat protons are added to those from water protons. PDFF is determined by calculating the difference in signal intensities between IP and OP. To address intrinsic biases in CSI, multi-echo acquisitions with T2* correction and spectral fat modeling are employed to obtain accurate liver fat quantification [39]. Both MRS and PDFF derived from CSI exhibit excellent diagnostic performance for liver fat quantification and are highly reproducible across different vendors. Consequently, these MRI-based techniques are widely used as noninvasive alternative reference methods to liver biopsy in many clinical trials.

Unlike histology, the MRI-PDFF threshold for detecting liver steatosis slightly vary between studies. The most used is 6% [40].

Both MRI and histology, the reference standards, have distinct approaches: histology arbitrarily counts affected hepatocytes, disregarding the size and distribution of fat droplets within the cells. Conversely, MRI measures relative fat signals but fails to depict the histological distribution. Consequently, these methods should be viewed as complementary rather than directly correlated.

Ultrasound techniques to estimate liver fat

There are three US techniques that are being used to estimate liver fat. These are attenuation coefficient (AC), backscatter coefficient (BSC), and speed of sound (SoS). All these techniques use the "raw data" of US beam to estimate these parameters. The raw data is the US signals that are returned to the transducer. The raw data contains a large amount of information including frequency information, signal strength, as well as other information. Each of these US techniques utilized portion of this raw data to estimate the amount of liver fat. Representative images from each manufacturer are presented in appendix 1 (supplementary material).

The hepatorenal index is the ratio between the US signals backscattered by the liver and the right renal cortex, the latter being the reference. This is performed using the raw US data to remove any correction applied for attenuation to the image. For those to be accurate the renal cortex must be normal. It is not a direct and quantitative measure of liver fat; therefore, it will not be discussed in this document.

Algorithms for the estimate of the attenuation coefficient

The AC is the rate of the amplitude loss of the US beam traveling through tissue. It is frequency dependent. As the US beam traverses tissue energy is lost so the intensity of the US beam decreases. Some tissue (fluid) may not attenuate the US beam; however, other tissues will attenuate it depending on the tissue composition. The change of the US beam amplitude over the depth of a certain frequency is the AC. Fat attenuates the US beam more than normal liver leading to an increased AC. Several modalities can be used to calculate the AC: sound field correction; spectral shift; spectral difference; log difference or hybrid methods. The basic science on this topic can be found elsewhere [2].

Several algorithms to estimate the AC are currently available (Table 1). They include the controlled attenuation parameter (CAP) which estimate the slope of the AC over the distance at a single fixed frequency in decibel/meter (dB/m) and the algorithms available on imaging US systems that calculate the AC in a bandwidth of the US beam; therefore, the values are reported in decibel/centimeter/megahertz (dB/cm/MHz). There could be differences between algorithms from different manufacturers depending on which modality they use to calculate the AC.

The following sections expand on the available evidence for their use in clinical practice.

Table 1
Algorithms currently commercially available for the estimate of liver fat content with ultrasound systems. The manufacturers are listed in alphabetical order

Manufacturer	Algorithm	Name	Unit of measurement
Canon (Japan)	AC	ATI (attenuation imaging)	dB/cm/MHz
Echosens (France)	AC	CAP (controlled attenuation parameter)	dB/m
Esaote (Italy)	AC	QAI (Q-attenuation imaging)	dB/cm/MHz
E-Scopics (France)	AC	ATT (attenuation)	dB/m
	SoS	SOS (speed of sound)	m/s
	BSC	BSC	dB/cm-sr
Fujifilm (Japan)	AC	iATT (attenuation)	dB/cm/MHz
General Electric (USA)	AC	UGAP (ultrasound derived fat fraction)	dB/cm/MHz
Mindray (China)	AC	USAT (ultrasound attenuation)	dB/cm/MHz
Philips (The Netherlands)	AC	ATI (attenuation imaging)	dB/cm/MHz
Samsung (Republic of Korea)	AC	TAI (tissue attenuation imaging)	dB/cm/MHz
	parameter related to BSC	TSI (tissue scattering imaging)	-
	AC + parameter related to BSC	USFF (ultrasound fat fraction)	%
Siemens (Germany)	AC + BSC	UDFF (ultrasound derived fat fraction)	%
SuperSonic Imagine (France)	AC	ATT PLUS (plane-wave ultrasound attenuation)	dB/cm/MHz
	SoS	Ssp PLUS (plane-wave ultrasound speed of sound)	m/s

AC, attenuation coefficient; BSC, backscatter coefficient; dB/cm/MHz, decibel/centimeter/megahertz; dB/m, decibel/meter; m/s, meter/second; sr, steradian; SoS, speed of sound.

Controlled attenuation parameter

The CAP available on the FibroScan system was presented in 2010 as an add-on software tool for the estimation of liver fat content and has been referenced in more than 700 scientific medical publications at the publication of this document. It quantifies the attenuation of the ultrasound tracking impulses during the liver stiffness measurement process and calculates the attenuation slope in dB/m within a range of 100 −400 dB/m. Initially, CAP was only available for the M probe which restricted its use to lean cohorts. After implementation in the XL probe, designed for obese subjects, CAP was extensively evaluated in comparison to liver histology and magnetic resonance-based techniques [1,41]. Recently, the algorithm has been updated including a continuous measurement and an automated withdrawal of unreliable measurements and renamed SMART CAP [42].

Large individual patient data meta-analysis revealed that the accuracy depends on the etiology of liver disease and anthropometric measures such as that high BMI may result in a suboptimal performance for the detection and grading of liver steatosis [43,44]. This can be partially explained by the varying prevalence of steatosis in different cohorts but may also reflect inherent technical limitations of the technology. In clinical practice, CAP has an acceptable accuracy for steatosis estimation in patients with viral hepatitis [45], but its specificity is impaired in cohorts with higher steatosis prevalence, i.e. patients with MASLD [44]. Head-to-head comparison with MRI-PDFF reveals a lower accuracy of CAP [46]. Attempts to improve the accuracy of CAP by adjusting the values to BMI and etiology as well as a combined interpretation with LSM have been proposed but not yet successfully validated [43]. In addition, the application of quality criteria such as the interquartile range (IQR) has been analyzed: Two studies proposed different upper limits for the IQR, i.e., 30% of the median value [47] and 40 dB/m [48]. However, this approach was not validated in a prospective multi-center study and a recent meta-analysis [44,49].

In consequence, a variety of different cut-off values for the detection of steatosis grades has been suggested. A study from the United Kingdom provides the only biopsy-controlled data from a prospective multicenter study including 380 CAP measurements from patients at risk of MASLD [49]: Youden index cutoff values for S≥S1, S≥S2, and S≥S3 were 302 dB/m, 331 dB/m, and 337 dB/m, respectively. For clinical practice, a robust cut-off for the detection of any grade of steatosis is important to establish the diagnosis of MASLD. However, only few patients with a metabolic risk profile and histological exclusion of liver steatosis have been included in the available studies [44]. Therefore, a value of 288 dB/m that was determined in an MRI-PDFF controlled cohort may serve as the best reference available for the detection of steatosis (S >0) [50].

Longitudinal data of CAP in patients with targeted interventions focusing on steatosis reduction mainly derive from cohorts with bariatric intervention or comparable therapies. These data show a significant decline of CAP in responder patients and underline the value of CAP as a bedside tool for repetitive monitoring [51,52]. In a small cohort of individuals with MASLD, a delta-CAP of -46 dB/m has been suggested to identify reduction of steatosis defined by a decline of MRI-PDFF >30% relative to the baseline value in patients aiming for lifestyle modification [53]. Several publications evaluated the value of CAP for the prediction of clinically relevant endpoints [54,55]. Although CAP did not predict liver related endpoints in a large study including patients with advanced chronic liver disease [56], more recent data indicate that CAP may predict the risk of cardiovascular endpoints in patients with type 2 diabetes [57] and HCC development in chronic viral hepatitis B [55].

Besides its role for quantification of liver fat, CAP has been included in algorithms that aim to determine the risk of an “at risk” MASH. The FibroScan-AST (FAST Score) combines LSM, CAP and aspartate-aminotransferase values to identify patients having a high probability of at-risk MASH [58]. This approach has been validated in further cohorts [59,60], but still awaits its clinical inclusion in guideline recommendations.

In conclusion, CAP is a point of care test for estimation of hepatic steatosis. The interpretation of the CAP value requires knowledge of confounding factors, local prevalence, and etiology. The limited specificity in patients with metabolic risk profile demands a careful consideration of CAP with a low threshold for validation by biopsy or MRI-PDFF. CAP has been used to monitor steatosis in patients undergoing therapeutic interventions, however larger studies are needed to validate its use in this setting. Studies with long follow-up intervals are required to determine the prognostic value of CAP in the context of MASLD.

Attenuation coefficient on imaging ultrasound systems

Studies using either liver biopsy or MRI-PDFF as the reference standard have assessed the diagnostic accuracy of AC algorithms implemented on imaging US systems for evaluating hepatic steatosis. Most studies have reported good to excellent performance with area under the receiver operating characteristic curve (AUC) values ranging from 0.74 to 0.97 (Table 2). For instance, AC-Canon (Canon Medical Systems, Japan) exhibited excellent diagnostic performance in detecting various grades of hepatic steatosis within a cohort of 328 biopsy-proven cases [61]. Additionally, in a study involving 1010 participants using MRI-PDFF as the reference standard, it has been reported that AC-GE (GE Healthcare, USA) showed excellent diagnostic performance in detecting different grades of hepatic steatosis [62].

Comparison studies between CAP and other AC algorithms from different manufacturers have also been conducted, indicating comparable [71,72,82,85,88,93] or superior diagnostic performance of AC over CAP in detecting and grading hepatic steatosis [66,70,85,87,96] (Table 3). These studies used either histology or MRI-PDFF as the reference standard.

A recent study has compared the performance of AC-Canon and CAP in a series of patients with type 2 diabetes and MASLD using both MRI-PDFF and histology as reference standard [86]. With MRI- PDFF as reference, the performance of ATI was significantly better than that of the CAP for detecting steatosis (S >0) whereas no differences were observed when histology was the reference (Table 3).

Several studies, that used AC algorithms from different manufacturers and in which histology was used as the reference standard, have reported that the AC values are not influenced by liver fibrosis [61,63,69,97].

In a meta-analysis of 13 studies including 1509 patients in which the AC algorithms from several manufacturers were used, the pooled sensitivity and specificity of the AC were 76% and 84%, respectively, to detect patients with a histopathologic steatosis grade or PDFF S ≥1 and 87% and 79%, respectively, to detect patients with a steatosis grade S ≥2 [98]. The hierarchical summary AUCs for ≥S1 and ≥S2 were 0.83 and 0.91, respectively.

Regarding the reproducibility of AC measurements, most studies have reported good to excellent intra- and inter-reader agreement, with intraclass correlation coefficient (ICC) values exceeding 0.80 (Table 4).

However, certain considerations have arisen in the evaluation of hepatic steatosis using AC. Despite most studies reporting excellent diagnostic performance, the specific cut-off values have shown variation among different studies. For instance, the AC-Canon cut-off value to detect S >0 hepatic steatosis ranged from 0.59 to 0.71 dB/cm/MHz (Table 2), whereas the AC-GE cut-off value ranged from 0.53 to 0.66 dB/cm/MHz (Table 2). This variability may be attributed to differences in the measurement protocol among studies and as well as differences in algorithms by various manufacturers. Heterogeneity in the characteristics of the studied cohorts, inclusion criteria or differences in the prevalence of the disease must also be considered.

Currently, there is no widely accepted consensus regarding several key aspects of measurement, including the size and location of the ROI with respect to the liver capsule, the number of measurements taken, and the chosen examination mode.

Table 2
The diagnostic performance of attenuation coefficient in detecting and grading hepatic steatosis[a]

Technique	Study	Subjects number	Reference standard	S0 vs. S1-S3				S0-S1 vs. S2-S3				S0-S2 vs. S3			
				Cutoff dB/cm/MHz	AUC	Sensitivity (%)	Specificity (%)	Cutoff dB/cm/MHz	AUC	Sensitivity (%)	Specificity (%)	Cutoff dB/cm/MHz	AUC	Sensitivity (%)	Specificity (%)
AC-Canon	Bae [63]	108	Biopsy	0.64	0.84	74.5	77.4	0.70	0.89	86.4	81.4	0.745	0.93	100	82.4
	Bae [64,65]	120	Biopsy	0.63	0.89	80.3	96.3	0.66	0.91	100	73.1				
	Bao [66],[b]	159	MRI-PDFF	0.70	0.94	85.9	94.1	0.79	0.75	87.50	54.37				
	Bulakci [67]	140	MRI-PDFF	0.65	0.94	84.2	92.8	0.74	0.98	93.0	84.4	0.91	0.97	90.0	95.3
	Cassinotto [68]	534	MRI-PDFF	0.65	0.85	77	78	0.70	0.88	85	71	0.71	0.86	81	72
	Dioguardi [69]	101	Biopsy	0.69	0.81	76	86	0.72	0.89	96	74				
	Ferraioli [70]	114	MRI-PDFF	0.63	0.91	80.2	88.9	0.72	0.95	100	78.2				
	Ferraioli [71],[b,c]	72	MRI-PDFF	0.69[b]	0.90[b]	78.6[b]	95.8[b]								
				0.62[c]	0.92[c]	81.1[c]	95.6[c]								
	Jang [72]	57	Biopsy	0.62	0.81	61.5	90.3								
	Jeon [73]	87	MRI-PDFF	0.59	0.76	88.0	62.2	0.65	0.88	85	71.6				
	Lee [74]	102	Biopsy	0.64	0.93	75.0	95.0	0.70	0.88	84.0	76.0	0.73	0.82	86.0	69.0
	Sugimoto [75]	119	Biopsy	0.67	0.88	75.0	100	0.72	0.86	90.0	66.0	0.86	0.79	61.0	85.0
	Tada [76]	148	Biopsy	0.66	0.85	67.8	87.6	0.67	0.91	92.0	83.7	0.68	0.91	100	75.2
	Tada [77]	119	MRI-PDFF	0.63	0.81	67.9	85.7	0.73	0.87	79.3	91.1	0.75	0.94	92.9	88.6
	Torkzaban [78]	66	Biopsy	0.71	0.81	68.0	89.0								
	Yuri [61]	328	Biopsy	0.63	0.82	NA	NA	0.67	0.93	NA	NA	0.70	0.920	NA	NA
	HSu [79]	28	Biopsy	0.69	0.97	100	83.0	0.78	0.99	100	90.0	0.82	0.97	100	85.0
	Kwon [80]	100	MRI-PDFF	0.62	0.91	91.5	80.0	0.72	0.94	93.3	87.1				
	Jang [81]	132	Biopsy	0.62	0.94	85.0	97.0	0.70	0.94	95.0	80.0	0.78	0.94	100	83.0
	Huang [82]	60	Biopsy	0.67	0.97	85.7	100	0.73	0.91	93.8	78.6	0.757	0.766	94.1	60.5
	Bae [83]	102	MRI_PDFF	0.66	0.92	89.5	83.1								
	Chiyanika [84]	15	Biopsy	0.59	0.91	87.5	87.5	0.60	0.97	83.3	90.0	0.63	0.93	100	85.7
	Zhu [85]	130	MRI-PDFF	0.63	0.88	86.5	76.9	0.72	0.86	85.5	71.2				
	Dioguardi Burgio [86]	187	Biopsy	0.59	0.92	95.6	80.0	0.72	0.79	68.9	80.5				
		191	MRI-PDFF	0.61	0.86	93.3	76.9	0.72	0.71	74.2	58.2				
AC-GE	Cassinotto [68]	534	MRI-PDFF	0.66	0.93	84.0	85.0	0.72	0.96	100	80.0	0.78	0.96	100	83.0
	Fujiwara [87]	163	Biopsy	0.53	0.90	81.2	87.1	0.60	0.95	85.7	81.5	0.65	0.959	80.4	90.0
	Imajo [62]	1010	MRI-PDFF	0.65	0.91	86.7	82.0	0.71	0.91	90.6	77.5	0.77	0.894	81.0	82.6
	Kang [88]	87	Biopsy	0.59	0.82	86.8	67.4	0.69	0.80	80.0	84.4				
	Ogino [89]	84	Biopsy	0.60	0.94	86.7	88.9	0.71	0.95	85.7	91.8	0.72	0.88	85.7	80.0
	Tada [90]	126	MRI-PDFF	0.60	0.92	85.5	88.5	0.69	0.87	82.7	81.1	0.694	0.892	96.7	70.8
	Kuroda [91]	582	MRI-PDFF	0.65	0.92	92.0	75.0								
AC-Fujifilm	Tamaki [92]	351	Biopsy	0.62	0.79	72.0	72.0	0.67	0.87	82.0	82.0	0.73	0.96	87.0	89.0
	Koizumi [93]	89	Biopsy	0.68	0.74	55.1	87.7	0.72	0.80	77.8	87.1	0.78	0.96	100	91.1
AC-Samsung	Jeon [94]	173	MRI-PDFF	0.72	0.92	83.0	91.0	0.83	0.91	79.0	91.0	0.86	0.90	100	80.0
	Ronaszeki [95]	101	MRI-PDFF	0.77	0.89	85.2	78.7	0.85	0.93	81.1	89.1				
	Zhu [85]	130	MRI-PDFF	0.91	0.86	74.2	82.1	0.96	0.70	77.4	72.3				

AC, attenuation coefficient; AUC, area under the receiver operating characteristic curve; dB/cm/MHz: decibel/centimeter/megahertz; MRI-PDFF: magnetic resonance imaging derived proton density fat fraction.

[a] For the 95% confidence intervals and other statistical details, please see the cited articles

[b] Utilized ATI-Pen mode

[c] Utilized ATI-Gen mode. Other studies using ATI did not specify their mode.

Table 3
Comparison of the performance of the attenuation coefficient on ultrasound systems with controlled attenuation parameter[a]

Technique	Study	Subjects number	Reference standard	S0 vs S1–S3			S0-S1 vs S2–S3			S0–S2 vs S3		
				AUC	AUC of CAP	*p*-value	AUC	AUC of CAP	*p*-value	AUC	AUC of CAP	*p*-value
AC-Canon	Bae [64,65]	120	Biopsy	0.89	0.83	0.15	0.91	0.90	n.s.			
	Bao [66],[b]	159	MRI-PDFF	0.94	0.79	0.01	0.75	0.57	0.001			
	Ferraioli [70]	114	MRI-PDFF	0.91	0.85	0.14	0.95	0.88	0.04			
	Ferraioli [71],[b, c]	72	MRI-PDFF	0.90[b]	0.85	n.s.						
				0.92 [c]	0.85	n.s.						
	Jang [72]	57	Biopsy	0.81	0.83	0.76						
	Seo [96]	105	Biopsy	0.93	0.93	0.96	0.94	0.94	0.77	0.94	0.87	0.05
	Huang [82]	60	Biopsy	0.97	0.92	0.28	0.91	0.87	0.25	0.77	0.81	0.33
	Zhu [85]	67	MRI-PDFF	0.88	0.87	n.s.	0.86	0.84	n.s.			
	Burgio [86]	187	Biopsy	0.92	0.95	0.64	0.79	0.76	0.61			
		191	MRI-PDFF	0.86	0.69	0.02	0.71	0.69	0.60			
AC-GE	Fujiwara [87]	163	Biopsy	0.90	0.83	0.14	0.95	0.84	0.01	0.96	0.82	0.001
	Kang [88]	87	Biopsy	0.82	0.79	NA	0.80	0.73	NA			
AC-Fujifilm	Koizumi [93]	89	Biopsy	0.74	0.81	0.13	0.80	0.85	0.29	0.96	0.87	0.57
AC-Samsung	Zhu [85]	67	MRI-PDFF	0.86	0.87	n.s.	0.70	0.82	<0.05			

AC, attenuation coefficient; AUC, area under the receiver operating characteristic curve; CAP, controlled attenuation parameter; dB/cm/MHz, decibel/centimeter/megahertz; MRI-PDFF, magnetic resonance imaging derived proton density fat fraction.
[a] For the 95% confidence intervals and other statistical details, please see the cited articles.
[b] Utilized ATI-Pen mode.
[c] Utilized ATI-Gen mode; Other studies using ATI did not specify their mode; n.s., not significant; NA, not available.

Backscatter coefficient

When an US beam propagates through tissue and encounters a spatial variation on a scale smaller than or on the order of an US wavelength local acoustic impedance occurs and a fraction of the incident US energy is scattered in all directions. A portion of that scattered US energy is reflected back to the transducer. This process is called backscatter and is what is used to generate the B-mode image. Fat has a lower density than water leading to an impedance mismatch. Therefore, lipid vacuoles scatter US energy leading to a higher backscatter in fatty livers. A more detailed discussion of the basic science and confounding factors for estimating the BSC for liver fat quantification has been presented previously [102].

Calculation of the BSC requires compensation for the total attenuation of US by all intervening tissues between the body surface and the deepest point in the ROI in the liver. Since AC depends on frequency, attenuation compensation is usually performed by using US spectra. This is discussed in detail elsewhere [102].

The estimation of the BSC alone has been the subject of research studies using the US system in a research mode. These studies reported that BSC was highly correlated with MRI-PDFF with a sensitivity of 87%, a specificity of 91%, and an AUC of 0.95 for detecting steatosis (S >0) [103].

Clinical investigations have measured the normal range of liver BSC between $4\pm2 \times 10^{-4}$ 1/cm-steradian (Sr) at frequencies from 2.25MHz to 3MHz using RF data [104–106]. Using a modified commercial US

Table 4
Inter-observer and intra-observer agreement of attenuation coefficient estimation[a]

Technique	Study	Number of subjects (reproducibility measurement/total)	Reference standard	Interobserver agreement (ICC, CV)	Intraobserver agreement (ICC, CV)	*κ*-value
ATI (Canon)	Bao [66]	159/159	MRI-PDFF		(0.93, -)	
	Bulakci [67]	34/ 140	MRI-PDFF	(0.90, -)	(0.91, -)	
	Ferraioli [70]	30/114	MRI-PDFF	(0.92, -)	Overall; (0.94,-) Rater 1; (0.91,-) Rater 2; (0.98,-)	
	Jang [72]	15/57	Biopsy	(-, 9.6%)		
	Jeon [73]	87/87	MRI-PDFF		Total (0.81, 9.4%) SCD <20 mm (0.83, 7.3%) (n = 72) SCD≥ 20 mm (0.78, 9.8%) (n = 15) BMI <25 (0.86, 8.3%) (n = 47) 25≤BMI <30 (0.89, 7.3%) (n = 33) BMI≥30 (0.56, 11.9%) (n = 7)	
	Yoo [99]	143/143	NA	(0.79, -)	(0.929, 7.1%)	
	Ferraioli [100]	34/34	NA	Intercostal, 2 cm, best image (0.89, -)	Intercostal: (0.92, -)	
	Huang [82]	60/60	Biopsy		(0.98,-)	
	Zhu [85]	130/130	MRI-PDFF		(0.98,-)	
UGAP (GE)	Fujiwara [87]	163/163	Biopsy	(0.84, -)	(0.86, -)	
	Zhao [101]	63	NA	(0.86,-)	15 min interval (0.90,-) Different days (0.91,-)	
ATT (Fujifilm)	Koizumi [93]	89/89	Biopsy			0.91 ± 0.06 (S0 or S≥1)
TAI (Samsung)	Ronaszeki [95]	52/101	MRI-PDFF	TAI (0.95, -)		
	Zhu [85]	130/130	MRI-PDFF		(0.98,-)	

BMI, body mass index; CV, coefficient of variation; ICC, intraclass correlation coefficient; NA, not available; MRI-PDFF, magnetic resonance imaging derived proton density fat fraction; SCD, skin-to-liver capsule distance.
[a] For the 95% confidence intervals, please see the cited articles.

scanner in a study of 101 patients where 93 (92.1%) had MRI-PDFF ≥5% BSC estimated at 3MHz frequency had a coefficient of determination $R^2 = 0.76$, which was higher than that obtained using AC ($R^2 = 0.60$) [107]. By combining the BSC and AC, the Pearson r correlation coefficient compared to MRI-PDFF was 0.87. This combination has been commercialized as US-derived fat fraction (UDFF) and the estimate is given as percentage. A cutoff of 6.34% for detecting steatosis (MRI-PDFF >5%) had 84% sensitivity, 100% specificity and 0.94 AUC [107]. Only the combination of AC and BSC is commercially available.

Some studies have evaluated possible confounding factors. One study found no confounding effect of either liver fibrosis or lobular inflammation [108] or cirrhosis [105]. A minimal correlation with BMI has been observed [109].

A proposal for the development of a standardized protocol for BSC acquisition has been suggested [102]. Presently it is not known if ingestion of food can affect the BSC measurement however there is a theoretical small effect. Currently, it is recommended to follow the protocol for liver stiffness measurement [110,111]. No study has evaluated the appropriate number of acquisitions. Breath holds seem not as critical as in liver stiffness measurements [102].

To conclude, initial studies suggest that the BSC has good reproducibility and correlation to MRI-PDFF. The BSC requires that AC also be obtained, and the combination of both parameters could provide improved accuracy in liver fat quantification. However, the literature is limited, and a better understanding of confounding factors is also needed.

Speed of sound

Conventionally, medical US systems assume a Speed of Sound (SoS) for transmitting and receiving beamforming operations. The assumed SoS is typically held constant, usually at 1540 m/s for the entire image. However, because of this assumption, the ultrasound image quality may have a degradation because the different organs may have different SoSs [112]. The SoS is slower in fatty tissue therefore as fat increases in the liver the SoS will decrease.

The SoS measurements for liver tissue can be based on four techniques: focusing, spatial coherence, compounding, and single-path transmission. The first three selected methods were recently considered the most promising categories for SoS measurements [113,114] A review of the basic science of SoS is available by the AIUM-RSNA QIBA Pulse-Echo Quantitative Ultrasound Initiative [114].

In a review of the literature the hepatic SoS varied from 1470 to 1590 m/s depending on the underlying pathology including fatty livers [113]. Normal liver SoS was approximately 1570 m/s, while fatty livers had lower SoS values. While Bamber and Hill [115], Chen et al. [116] and Hayashi et al. [117] did not report SoS values for S1, S2 and S3 steatosis grades, they reported SoS values of 1547 ± 17.8, 1423 ± 34 and 1556 m/s for fatty liver tissue, respectively [113].

The reproducibility of SoS estimate has been assessed in a study that included 20 normal subjects. The inter-observer ICC was 0.62 whereas the mean intra-observer ICCs were 0.52 and 0.79 [118]. These findings suggest that additional studies are needed regarding the protocol to improve reproducibility.

In a preliminary study on 17 patients using MRI-PDFF as the reference standard, a cut-off value of 1555 m/s was able to differentiate healthy and steatotic livers with an AUC of 0.95 ($p < 0.0001$). The authors also developed a method to correct for the thickness of superficial layers in measuring the SoS in the liver [119].

However, it must be highlighted that the cutoffs for detecting and grading liver steatosis vary largely between published studies and that there is a narrow range of values between no steatosis and severe steatosis [120,121].

There are limited prospective studies with large populations of varying degrees of fatty infiltration. In fact, most studies have just determined a cut-off value for the diagnosis of steatosis and not for grading fatty infiltration. The evidence in literature is very limited. Further studies are needed to understand how the SoS can be used to estimate the degree of liver steatosis.

Methods combining more than one quantitative US technique

The combination of more than one parameter might improve the accuracy in quantifying liver fat content.

As mentioned in the backscatter section above, one manufacturer has a commercially available system that uses the combination of AC and BSC to give the results in % fat as correlated with MRI-PDFF [107].

A study in a small cohort of overweight and obese adolescents and adults has reported that UDFF cutoff of more than 5% had 94.1% sensitivity and 63.6% specificity for diagnosing MRI-PDFF of 5.5% or more [122]. It is worth noting that the percentage obtained with UDFF or MRI-PDFF do not correspond to histological percentages.

One commercially available system combines AC and tissue scatter-distribution imaging (TSI), which is related to the BSC, using artificial intelligence (AI). The technique is called US fat fraction (USFF) [94]. For diagnosing hepatic steatosis (MRI-PDFF ≥5%), the USFF yielded an AUC of 0.97 (95% CI: 0.93−0.99). No large studies are presently published on this technique.

A research system correlating integrated backscatter coefficient, signal-to-noise ratio, and US-guided attenuation parameter (UGAP) using AI has reported an improved discrimination in detecting steatosis (defined by MRI-PDFF >5%) [91]. This study only evaluated this technique to make the diagnosis of steatosis.

Protocol for measurement acquisition

Currently, an algorithm for liver fat quantification, or a combination of them, is available on the US systems from all manufacturers. Most of the studies that have assessed the performance of these tools employed AC measurement and either liver biopsy or MRI-PDFF as reference standard. Generally, these studies report different thresholds for grading steatosis even when using the same algorithm (Table 2). These differences are likely due to the lack of a standardized acquisition protocol.

In this regard, it should be noted that the literature suggests that the measurements of liver fat content are affected by several factors, including, among others, the depth of the region of interest (ROI), the ROI's size, the frequency of the transducer, the scan location [1,2,100,123].

Controlled attenuation parameter (CAP)

The CAP is obtained together with LSM. Therefore, the recommendation for LSM acquisition must be followed. As for specific quality criteria, there are conflicting data in the literature: a study reported a higher accuracy of CAP when the IQR of 10 acquisitions was ≤40 dB/m [48], another study reported that the accuracy improved with and IQR <30 dB/m [50], whereas other studies did not confirm these findings [44,49].

Attenuation coefficient (AC) on imaging ultrasound systems

A study has shown that the highest inter-operator repeatability was observed for measurements obtained in the intercostal space, but it seems that it is not mandatory that the transducer is perpendicular to the liver capsule as recommended for stiffness assessment with the shear wave elastography techniques [100]. The quality of the image should be the highest one, with few vessels and preferably no ligaments. The upper edge of the measurement box must be positioned 2 cm below the liver capsule avoiding the reverberation artifact. The AC value decreases increasing the depth; therefore, results are not the same when obtained at different depths [123,124]. To mitigate differences in values between different algorithms, it is preferable that the length of the measurement box (3 cm is recommended) is the same for all manufacturers [100,123].

If a standalone AC setting is available, it is preferable to avoid the acquisition of liver stiffness and fat quantification at the same time. It is preferable to perform the measurements sequentially rather than at the same time. Indeed, once a good acoustic window is obtained, consecutive AC measurements may take very little time.

The breathing phase does not affect the AC value [101,125,126]; however, the repeatability of AC measurements in different breathing phases has not been investigated yet. A study has shown that AC measurements obtained with free breathing were less repeatable than those obtained while the subject was holding the breath [100]. It has been reported that eating or drinking doesn't affect AC measurement [101,125,127,128].

Table 5 reports the suggested protocol for fat quantification.

A recent study that used histology as reference standard has investigated the optimal number of valid measurements obtained with the AC-Canon in a series of 139 MAFLD patients [97]. It found that there was no significant difference in the mean AC values obtained from one, two, three, five and seven measurements and that the mean AC value of three valid measurements was adequate to guarantee the accuracy of liver steatosis assessment.

As with CAP, when the AC is obtained together with LSM, the standard protocol for LSM acquisition must be followed.

Backscatter coefficient and speed of sound

Currently, there isn't any published study about factors that can affect the measurement of the BSC or the SoS. However, it should be underscored that the measurement of the BSC is dependent and generally combined with that of the AC. Therefore, the protocol used for this latter must be followed to mitigate the variability in the measurement of liver fat content.

Recommendations

1. Noninvasive US-based quantification techniques are more reliable than B-mode US imaging for the detection and quantification of liver fat content.
2. In studies assessing the accuracy of the new algorithms for the estimate of liver fat content, MRI-PDFF should be used as the reference standard.
3. CAP must not be used as a reference standard in studies assessing the accuracy of the new algorithms for fat quantification.
4. CAP has become a point-of-care technique, however its specificity in patients with metabolic risk profile is limited. A value of 288 dB/m, determined in an MRI-PDFF controlled cohort, may serve as the best reference available for the detection of steatosis (S >0).
5. The estimation of liver fat by attenuation coefficient (and attenuation coefficient plus backscatter coefficient) has good initial results; however, a standardized acquisition protocol must be followed to mitigate differences in values between studies.
6. When the attenuation coefficient is obtained together with liver stiffness measurement, the standard protocol for the acquisition of liver stiffness measurement must be followed.
7. Studies with long follow-up intervals are required to determine the prognostic value of US fat quantification in patients with MASLD.
8. Backscatter coefficient and speed of sound have limited evidence, and more evaluation is needed before they can be recommended for routine clinical use.

Table 5
Suggested protocol for attenuation coefficient measurement with ultrasound systems

1	Fasting is not mandatory if the measurement is taken alone[a].
2	Breath-hold.
3	Best quality of the B-mode image, but not necessarily with the transducer perpendicular to the liver capsule.
4	Right intercostal space.
5	Measurement box positioned perpendicular to the transducer.
6	Length of the measurement box 3 cm.
7	Upper edge of the measurement box at 2 cm below the liver capsule.
8	IQR/M ≤ 15%.
9	Median (or mean) value of three to five acquisitions.
10	For a reliable measurement, follow the manufacturer quality criterion when available

IQR/M, interquartile range/median.

[a] In a multiparametric approach for quantitative ultrasound the patients should be in fasting state and the recommended protocol for stiffness assessment must be prioritized.

Conflict of interest

G.F. has received a speaker honorarium from Canon Medical Systems, Fujifilm Healthcare, Mindray Medical Imaging, Philips Ultrasound, Siemens Healthineers. She has served on advisory boards for Philips Healthcare and Siemens Healthineers and her university has received ultrasound equipment grants and unrestricted research grants from Canon Medical Systems, Esaote SpA, Fujifilm Medical Systems, Philips Ultrasound. She receives royalties from Elsevier Publisher.

R.G.B. has received a speaker honorarium from Canon Medical systems, Philips Ultrasound, Siemens Healthineers, Mindray, Samsung Ultrasound, Hologic Ultrasound. He has received research grants from Philips Ultrasound, Canon Ultrasound, Canon MRI, Samsung, Siemens Healthineers, Hologic, Mindray and equipment grants from Canon Medical Systems, Philips Ultrasound, Mindray, Samsung Ultrasound and Siemens Healthineers. He is on the advisory board of Lantheus Medical. He receives royalties from Thieme Publishers and Elsevier Publisher.

A.B. is consultant for Boehringer-Ingelheim and has received speaker honoraria from GE Healthcare and Hologic Ultrasound. She has received research ultrasound equipment support from GE Healthcare.

I.S. has received speaker fees from Siemens Healthineers, General Electric, Samsung Ultrasound, Canon Medical Systems.

V.W.W. served as a consultant or advisory board member for AbbVie, Boehringer Ingelheim, Echosens, Gilead Sciences, Intercept, Inventiva, Novo Nordisk, Pfizer, Sagimet Biosciences, TARGET PharmaSolutions, and Visirna; and a speaker for Abbott, AbbVie, Gilead Sciences, Novo Nordisk, Unilab. He has received a research grant from Gilead Sciences and is a co-founder of Illuminatio Medical Technology.

T.R. received grant support from Abbvie, Boehringer Ingelheim, Gilead, Intercept/Advanz Pharma, MSD, Myr Pharmaceuticals, Philips Healthcare, Pliant, Siemens and W. L. Gore & Associates; speaking honoraria from Abbvie, Gilead, Intercept/Advanz Pharma, Roche, MSD, W. L. Gore & Associates; consulting/advisory board fee from Abbvie, Astra Zeneca, Bayer, Boehringer Ingelheim, Gilead, Intercept/Advanz Pharma, MSD, Resolution Therapeutics, Siemens; and travel support from Abbvie, Boehringer Ingelheim, Dr. Falk Pharma, Gilead and Roche.

T.K. has received speaker honoraria from Echosens, Falk Foundation and Jazz Pharmaceuticals. He has served on advisory boards for Echosens and his university has received ultrasound equipment and unrestricted research grants from Canon Medical Systems and Echosens.

M.T. has received a speaker honorarium from Siemens Healthcare, Echosens, Norgine, Madrigal, Takeda, and Tillotts Pharma. Advisory fee from Boehringer Ingelheim, AstraZeneca, GSK. Co-founder and board member of Evido. Board member for Alcohol & Society (non-governmental organisation).

A.C.C. has received speaker honorarium from Novo Nordisk.

O.T.A. has served as a consultant or adviser to Novo Nordisk, Resonance Health, Norgine and Sun Pharma. He has received research ultrasound equipment support from Canon Medical Systems.

L.C. has served as a consultant for Boston Pharmaceuticals, Echosens, GSK, Madrigal, MSD, Novo Nordisk, Pfizer, Sagimet and Siemens Healthineers; and lecture fees from Echosens, Gilead, Inventiva, Madrigal and Novo Nordisk.

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Data Availability Statement

This guidance was produced by a panel of experts and is based on evidence from the literature. No research unpublished data of the authors was used.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ultrasmedbio.2024.03.014.

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