

World Journal of *Gastroenterology*

World J Gastroenterol 2023 May 7; 29(17): 2515-2703



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INDEXING/ABSTRACTING

The WJG is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports, Index Medicus, MEDLINE, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 edition of Journal Citation Reports® cites the 2021 impact factor (IF) for WJG as 5.374; IF without journal self cites: 5.187; 5-year IF: 5.715; Journal Citation Indicator: 0.84; Ranking: 31 among 93 journals in gastroenterology and hepatology; and Quartile category: Q2. The WJG's CiteScore for 2021 is 8.1 and Scopus CiteScore rank 2021: Gastroenterology is 18/149.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ying-Yi Yuan*; Production Department Director: *Xu Guo*; Editorial Office Director: *Jia-Ru Fan*.

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

PUBLICATION DATE

May 7, 2023

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

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<https://www.wjgnet.com/bpg/GerInfo/287>

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<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Non-invasive evaluation of liver steatosis with imaging modalities: New techniques and applications

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A, A
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Losurdo G, Italy; Tai DI, Taiwan; Uhlmann D, Germany

Received: December 23, 2022

Peer-review started: December 23, 2022

First decision: February 16, 2023

Revised: February 26, 2023

Accepted: April 11, 2023

Article in press: April 11, 2023

Published online: May 7, 2023



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Abstract

In the world, nonalcoholic fatty liver disease (NAFLD) accounts for majority of diffuse hepatic diseases. Notably, substantial liver fat accumulation can trigger and accelerate hepatic fibrosis, thus contributing to disease progression. Moreover, the presence of NAFLD not only puts adverse influences for liver but is also associated with an increased risk of type 2 diabetes and cardiovascular diseases. Therefore, early detection and quantified measurement of hepatic fat content are of great importance. Liver biopsy is currently the most accurate method for the evaluation of hepatic steatosis. However, liver biopsy has several limitations, namely, its invasiveness, sampling error, high cost and moderate intraobserver and interobserver reproducibility. Recently, various quantitative imaging techniques have been developed for the diagnosis and quantified measurement of hepatic fat content, including ultrasound- or magnetic resonance-based methods. These quantitative imaging techniques can provide objective continuous metrics associated with liver fat content and be recorded for comparison when patients receive check-ups to evaluate changes in liver fat content, which is useful for longitudinal follow-up. In this review, we introduce several imaging techniques and describe their diagnostic performance for the diagnosis and quantified measurement of hepatic fat content.

Key Words: Non-alcoholic fatty liver disease; Hepatic steatosis; Imaging techniques; Quantitative evaluation; Ultrasound; Quantitative ultrasound

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Core Tip: Accurate evaluation of the hepatic steatosis is important. The conventional gray scale ultrasound has the limitation of low diagnostic accuracy for mild hepatic steatosis and inability to make quantification evaluations. Quantification imaging techniques including ultrasound-based techniques and magnetic resonance imaging-based techniques can provide objective continuous numbers associated with liver fat content and past records can be found when patients receiving check-ups to evaluate change of liver fat content, which is useful for the longitudinal follow-up to monitor the impact of clinical interventions.

Citation: Zeng KY, Bao WYG, Wang YH, Liao M, Yang J, Huang JY, Lu Q. Non-invasive evaluation of liver steatosis with imaging modalities: New techniques and applications. *World J Gastroenterol* 2023; 29(17): 2534-2550

URL: <https://www.wjgnet.com/1007-9327/full/v29/i17/2534.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v29.i17.2534>

INTRODUCTION

There are several types of chronic liver diseases, but nonalcoholic fatty liver disease (NAFLD) is the broadest state[1,2]. NAFLD represents a wide range of liver abnormalities[3]. Over 25% of general population is influenced by NAFLD, while affected proportion of type 2 diabetes population is 55%-80% [1]. Simple fatty liver may progress to non-alcoholic steatohepatitis (NASH), which is a severe form of fatty liver characterized by inflammation of hepatocyte. This form may result in cirrhosis with portal hypertension or liver dysfunction or even to hepatocellular carcinoma (HCC)[4]. Notably, there is an annual incidence of 0.4 cases of HCC per 1000 population-years among patients with NAFLD, making it the third most common cause of HCC in the United States[5]. A diagnosis of NAFLD is associated with not only adverse effects on the liver, but also an increased risk of type 2 diabetes and cardiovascular disease[6,7]. A study suggested that there was a significant increase in mortality associated with liver-specific diseases or cardiovascular diseases in patients with NAFLD compared to controls[8]. For patients who received hepatectomy, hepatic steatosis can increase incidence of postoperative complications and death[9]. The risk of graft failure for patients undergoing liver transplantation increases when hepatic steatosis exceeds 30%[10].

As NAFLD poses substantial risks of HCC, liver-associated complications and other adverse events to patients, it is of great importance to diagnose and quantify hepatic fat content early[4]. NAFLD is likely to be reversible in its early stage even with simple treatments, for example, lifestyle changes[11]. In addition, the main factor contributing to disease progression in patients with NAFLD is liver fibrosis[1,3]. Abundant liver fat accumulation can trigger and accelerate hepatic fibrosis, thus contributing to disease progression[12,13]. Therefore, in patients with NAFLD, quantitative measurements of liver steatosis could be useful for prognostic assessment and treatment[4]. Although high level of liver fat can lead to fibrosis progression, it is of note that the level of liver fat is not always parallel to the grade of fibrosis. It has been suggested that patients without fibrosis or in the early stages of fibrosis may demonstrate obvious disease progression with high level of liver fat content; however, the fat content decreases when disease progresses to advanced fibrosis or cirrhosis[14-16]. Therefore, when evaluating the value of measuring hepatic steatosis for assessing disease progression and prognosis, the fibrosis status should first be taken into account[17].

When it comes to diagnosing diffuse hepatic disease, liver histopathologic examination is the most precise method. With liver biopsy, quantification of the liver fat level is classified into four grades (grade 0, < 5%; grade 1, 5%-33%; grade 2, 33%-66%; grade 3, > 66%)[18]. Although the use of liver biopsy correctly evaluates liver steatosis, its limitations include its invasiveness, sampling error, which make biopsy impractical for patients who have only simple steatosis[19,20]. Therefore, noninvasive methods to diagnose the presence of steatosis and to monitor changes in hepatic steatosis are needed (Table 1). Conventional gray-scale ultrasound can be applied to diagnose liver steatosis. However, its inability to provide accurate quantification of liver fat has limited its use in the diagnostic pathway of liver steatosis[21]. At present, a number of imaging techniques for the evaluation of hepatic fat content, including MR- and ultrasound-based methods, have been developed. In this review, we summarize the available imaging methods for the quantified measurement of hepatic fat content. In addition, we briefly discuss the clinical performance of these methods.

ULTRASOUND-BASED METHODS TO DIAGNOSE AND QUANTIFY HEPATIC STEATOSIS

Table 2 summarizes published diagnostic utility metrics and optimal cutoff values of quantitative ultrasound methods for quantified measurement of hepatic fat content.

Table 1 Characteristics of imaging techniques for hepatic steatosis evaluation

Techniques	Clinical characteristics	Limitations
CAP	Low cost; High availability; Time-saving Allows simultaneous evaluation of steatosis and fibrosis Moderate to high diagnostic accuracy for detecting and grading steatosis Moderate to high repeatability and reproducibility Well validated	High measurement failure rate Measurement without B-mode ultrasound image The cutoff value for diagnosing steatosis is poorly standardized
ATI, ATT and UGAP	Outperform or have comparable diagnostic accuracy compared with CAP High repeatability and reproducibility Strong correlation with liver histology or MRI-PDFF Low measurement failure rate Measured on B-mode ultrasound images	The measurement may be influenced by liver fibrosis Fairly small number of studies
Att. PLUS	Measurement is obtained at the same time as the sound speed measurement Comparable diagnostic accuracy with CAP	Fairly small number of studies No study comparing this technique with liver histology or MRI-PDFF
TAI and TSI	High diagnostic accuracy for detecting and grading steatosis Strong correlation with MRI-PDFF High repeatability and reproducibility	Fairly small number of studies
BSC	Uses a reference phantom to reduce sources of variability due to ultrasound systems or operators High diagnostic accuracy for detecting and grading steatosis Strong correlation with liver histology or MRI-PDFF High repeatability and reproducibility	Fairly small number of studies
UDFF	Is a combination of both attenuation coefficient and backscatter coefficient UDFF approximates MRI-PDFF	Fairly small number of studies
ASQ and NLV	Moderate to high diagnostic accuracy for detecting and grading steatosis Strong correlation with CAP	Weak correlation with liver histology The correlation with MR-based techniques is controversial The influence of fibrosis on measurement is controversial Fairly small number of studies
SS	Moderate to high diagnostic accuracy for detecting and grading steatosis Strong correlation with CAP	Fairly small number of studies
MRS and MRI-PDFF	High diagnostic accuracy for detecting and grading steatosis Considered as the reference standard	High cost; low availability Time-consuming

CAP: Controlled attenuation parameter; ATI: Attenuation imaging; ATT: Attenuation measurement function; UGAP: Ultrasound-guided attenuation parameter; Att. PLUS: Attenuation plane-wave ultrasound; TAI: Tissue attenuation imaging; TSI: Tissue scatter distribution imaging; BSC: Backscatter coefficient; UDFF: Ultrasound-derived fat fraction; ASQ: Acoustic structure quantification; NLV: Normalized local variance; SS: Speed of sound; MRS: Magnetic resonance spectroscopy; MRI-PDFF: Magnetic resonance imaging-proton density fat fraction.

Conventional gray scale ultrasound

Due to its low price and availability, gray scale ultrasound is a traditional diagnostic method for diagnosing and monitoring liver steatosis[22]. When using this method, fatty infiltration is indicated by the following signs: Hyperechogenicity of the liver parenchyma, liver-to-kidney comparison, ultrasound beam attenuation, and impaired visualization of the intrahepatic structures[23]. However, it is difficult for operators to grade liver steatosis solely based on the gray scale ultrasound[24]. Degree of liver fat content can be classified into 4 grades (normal, mild, moderate, and severe)[22]. For moderate to severe hepatic steatosis, gray scale ultrasound has a high diagnostic accuracy. A meta-analysis enrolling a total of 2815 patients and using hepatic histopathologic results as the golden standard demonstrated that the overall sensitivity and specificity of gray scale ultrasound to distinguish normal liver and moderate steatosis were 85% and 93% [25]. However, gray scale ultrasound has restricted diagnostic performance for mild steatosis[24]. Another limitation is that gray scale ultrasound is based on qualitative visual features, and the intraobserver and interobserver reproducibility vary with different operators[26,27].

Hepatorenal index

To improve the diagnostic performance of using gray scale ultrasound for the measurement of liver content, hepatorenal index (HRI) was developed[28] (Figure 1). This metric calculates the rate of parenchymal echo of the liver and the renal cortex[28]. Previous studies found that HRI had a significant correlation with histologic steatosis[29-31]. Marshall *et al*[32] reported a sensitivity, confirmed by liver biopsy, of 100% with an HRI cutoff of 1.27 for detecting more than 5% steatosis. Borges *et al*[33] reported for diagnosing fatty liver, the cutoff value of 1.24 revealed 93% sensitivity and specificity, but this study only used healthy volunteers as the control group. Stahlschmidt *et al*[34] suggested in livers with advanced fibrosis, HRI should not be used to measure steatosis because fibrosis replaces fat as NAFLD progresses. Similarly, patients suffering from chronic kidney disease may present increased echo of the renal cortex, which makes the HRI unreliable for grading steatosis[35]. Furthermore, Kjaergaard *et al*[36] found that HRI presented a higher incidence of failure (12%) compared to controlled attenuation parameter (CAP, 2%). In addition, it can be challenging to diagnose mild steatosis by HRI[33].

Quantitative ultrasound techniques

Mechanism of quantitative ultrasound techniques: Conventional gray scale ultrasound and HRI cannot provide quantitative information about liver fat content. Essentially, quantitative methods are used to model the relationship between physical properties of hepatic tissue and the echo signals that are scattered by it. The impedance difference of fat vesicles in hepatocytes causes increased scattering magnitudes and signal attenuation. A frequency-dependent analysis of signal attenuation and backscatter is performed on signals returned by tissue[37].

The quantitative ultrasound techniques used for the measurement of hepatic fat quantification included the spectral-based techniques and the techniques based on envelope statistics. Estimation of either attenuation coefficient (AC) or the backscatter coefficient (BSC) is used for spectral based techniques. The AC measures energy loss as ultrasound wave passes through tissue and the BSC measures the returned ultrasound energy when ultrasound wave strikes the microstructure of tissue. Techniques based on the envelope statistics of the backscattered ultrasound include the acoustic structure quantification (ASQ), normalized local variance (NLV), and estimation of sound speed[38]. Techniques according to envelope statistics are relatively novel. Microstructural characteristics of tissues can be determined by the shape and attributes of backscattered ultrasound[38].

Current commercial techniques and their mechanism of hepatic steatosis quantification are presented in Table 3.

CAP: CAP was the initial available technique for quantified measurement of hepatic fat content. Attenuation of the ultrasound beam is applied to generate the CAP amount[39,40]. Typically, two types of probes, the medium probe and the extra-large probe, can be utilized. The choice of optimal probe is automatically controlled according to skin-to-liver capsule distance (SCD). When the SCD exceeds 2.5 cm, the extra-large probe is more effective than the M probe. The CAP is presented in units of decibels per meter (dB/m)[41].

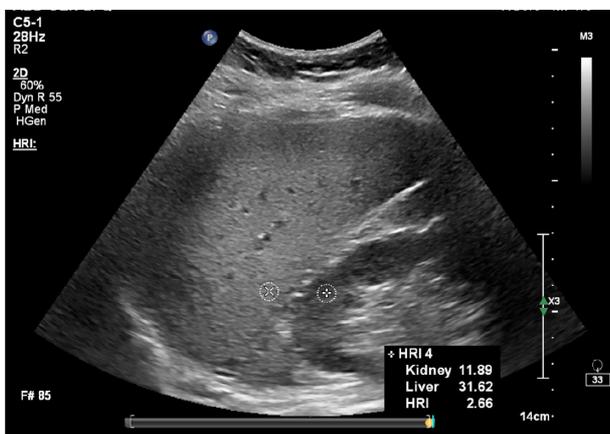
More than 160 studies have discussed the efficacy of CAP as a metric for quantified measurement of liver fat content, and acceptable accuracy was found. The general diagnostic accuracy evaluated by the area under the receiver operating curve (AUROC) of CAP for detecting presence of steatosis has been displayed to range from 0.64 to 0.97[42-44]. A meta-analysis including 19 studies found that CAP had good diagnostic performance with AUROCs of 0.823 for distinguishing steatosis grade > S0, 0.865 for distinguishing steatosis grade > S1, 0.882 for distinguishing steatosis grade > S2. The corresponding optimal cutoff values for > S0, > S1, > S2 were 248, 268 and 280 dB/m. Moreover, they found that there was a potential link between NAFLD, diabetes mellitus, and body mass index with the CAP value[45]. Although the diagnostic utility of CAP for differentiating patients with and without hepatic steatosis has been fully validated, the optimal cutoff value to determine the presence of steatosis varies significantly between studies[17]. A meta-analysis of 2346 participants with different diffused hepatic diseases demonstrated that CAP cutoffs varied according to the etiology of the hepatic diseases,

Table 2 Summary of studies using ultrasound methods to evaluate hepatic steatosis

Ref.	No.	Method	Reference standard	Grade of steatosis	Optimal cutoff value	AUROC
Bae <i>et al</i> [59], 2019	108	ATI	LB	≥ S1	0.64	0.84
				≥ S2	0.70	0.89
				≥ S3	0.75	0.93
Bae <i>et al</i> [60], 2022	120	ATI	LB	≥ S1	0.66	0.91
				≥ S2	0.66	0.91
Tada <i>et al</i> [62], 2019	148	ATI	LB	≥ S1	0.66	0.85
				≥ S2	0.67	0.91
				≥ S3	0.68	0.91
Tada <i>et al</i> [63], 2020	119	ATI	MRI-PDFF	≥ S1	0.63	0.81
				≥ S2	0.73	0.87
				≥ S3	0.75	0.94
Jeon <i>et al</i> [61], 2019	87	ATI	MRI-PDFF	≥ S1	0.59	0.76
Ferraioli <i>et al</i> [65], 2019	129	ATI	MRI-PDFF	≥ S1	0.63	0.91
				≥ S2	0.72	0.95
Ferraioli <i>et al</i> [66], 2021	72	ATI-GEN	MRI-PDFF	≥ S1	0.62	0.92
		ATI-PEN	MRI-PDFF	≥ S1	0.69	0.90
Sugimoto <i>et al</i> [67], 2021	111	ATI	LB	≥ S1	0.67	0.88
				≥ S2	0.72	0.86
				≥ S3	0.86	0.79
Hsu <i>et al</i> [70], 2021	28	ATI	LB	≥ S1	0.69	0.97
				≥ S2	0.78	0.99
				≥ S3	0.82	0.97
Kwon <i>et al</i> [57], 2021	100	ATI	MRI-PDFF	≥ S1	0.62	0.91
				≥ S2	0.72	0.94
Jang <i>et al</i> [58], 2022	57	ATI	LB	≥ S1	0.62	0.81
Koizumi <i>et al</i> [73], 2019	89	ATT	LB	≥ S1	0.68	0.74
				≥ S2	0.72	0.80
				≥ S3	0.78	0.96
Tamaki <i>et al</i> [54], 2018	351	ATT	LB	≥ S1	0.63	0.79
				≥ S2	0.69	0.87
				≥ S3	0.85	0.96
Fujiwara <i>et al</i> [75], 2018	163	UGAP	LB	≥ S1	0.53	0.90
				≥ S2	0.60	0.95
				≥ S3	0.65	0.96
Imajo <i>et al</i> [76], 2022	1010	UGAP	MRI-PDFF	≥ S1	0.65	0.91
				≥ S2	0.71	0.91
				≥ S3	0.77	0.89
Kuroda <i>et al</i> [79], 2021	202	UGAP	LB	≥ S1	0.49	0.89
				≥ S2	0.65	0.91

				≥ S3	0.69	0.92
Tada <i>et al</i> [80], 2019	126	UGAP	MRI-PDFF	≥ S1	0.60	0.92
				≥ S2	0.69	0.87
				≥ S3	0.69	0.89
Jeon <i>et al</i> [83], 2021	120	TAI	MRI-PDFF	≥ S1	0.88	0.86
		TSI	MRI-PDFF	≥ S1	91.2	0.96
Rónaszéki <i>et al</i> [84], 2022	110	TAI	MRI-PDFF	≥ S1	0.59	0.92
		TSI	MRI-PDFF	≥ S1	99.7	0.91
Şendur <i>et al</i> [85], 2023	80	TAI	MRI-PDFF	≥ S1	0.75	0.95
				≥ S2	0.86	0.97
				≥ S3	0.96	0.97
		TSI	MRI-PDFF	≥ S1	92.44	0.96
				≥ S2	96.64	0.91
				≥ S3	99.45	0.94
Lin <i>et al</i> [91], 2015	204	BSC	MRI-PDFF	≥ S1	0.0038	0.98
Dillman <i>et al</i> [94], 2022	56	UDFF	MRI-PDFF	≥ S1	5%	0.90
Labyed <i>et al</i> [37], 2020	101	UDFF	LB	≥ S1	8.1%	0.94
				≥ S2	15.9%	0.88
				≥ S3	16.1%	0.83

AUROC: Area under the receiver operating characteristic curve; LB: Liver biopsy; MRI-PDFF: Magnetic resonance imaging-proton density fat fraction; ATI: Attenuation imaging; ATT: Attenuation measurement function; UGAP: Ultrasound-guided attenuation parameter; TAI: Tissue attenuation imaging; TSI: Tissue scatter distribution imaging; BSC: Backscatter coefficient; UDFF: Ultrasound-derived fat fraction.



DOI: 10.3748/wjg.v29.i17.2534 Copyright ©The Author(s) 2023.

Figure 1 Hepatorenal index. In this case, the result was 2.66, indicating severe hepatic steatosis.

including NAFLD, chronic viral hepatitis, alcoholic liver disease[46].

The CAP value demonstrated a moderate to strong correlation with magnetic resonance (MR)-based techniques for liver steatosis quantification[47,48]. However, compared with MR-based methods, the CAP has inferior diagnostic ability in grading liver steatosis. Diagnostic effectiveness of MR spectroscopy (MRS) over CAP for diagnosing S1 was significantly higher (AUROC, 0.77 *vs* 0.99)[49]. Imajo *et al*[50] demonstrated suboptimal diagnostic performance of CAP compared to MRI-proton density fat fraction (MRI-PDFF) in grading liver steatosis.

However, CAP has the limitation of failure rate up to 7.7%. According to previous reports, an association was found between measurement failure and sex, body mass index, and metabolic syndrome[51]. Use of the extra-large probe can reduce the failure rate because it is designed for patients

Table 3 Summary of techniques for liver fat quantification and their mechanisms

Technique	Mechanism for liver fat quantification	Principle of the techniques
CAP	Spectral based technique (AC)	CAP measures the attenuation of or reduction in the amplitude of the ultrasound waves on their way through the liver
ATI	Spectral based technique (AC)	ATI quantifies the degree of the ultrasound beam attenuation. The attenuation of the ultrasound beam is calculated by analyzing echo signals received by the transducer
ATT	Spectral based technique (AC)	Two ultrasonic waves of different frequencies ($F_0, F_1; F_0 < F_1$) are transmitted to the same beamline and the received signal is obtained. ATT estimates the attenuation coefficient it by calculating the slope of the received signal ratio (F_0/F_1)
UGAP	Spectral based technique (AC)	UGAP compares the measured liver signal and the referential signal (measured on the reference phantom with known attenuation and backscatter coefficients)
Att. PLUS	Spectral based technique (AC)	Att. PLUS measures the decrease in amplitude of ultrasound waves as they propagate throughout the tissue
TAI	Spectral based technique (AC)	TAI is determined based on the attenuation properties of different frequency components in the tissue, and the spectrum of radiofrequency signals provides a downshift of the center frequency according to depth. The TAI parameter indicates the slope of the ultrasound center frequency downshift
BSC	Spectral based technique (BSC)	BSC measures the ultrasound energy returned from the tissue
UDFF	Spectral based technique (BSC)	UDFF is obtained by combining both AC and BSC and the result is presented as the percentage of hepatic steatosis. Reference phantom data is integrated into the ultrasound system and fixed-acquisition region of interest is applied
TSI	Envelope Statistic based technique	The TSI is based on the shape parameter of the Nakagami distribution which reflects the local concentration and arrangement of ultrasound scatterers
ASQ	Envelope Statistic based technique	ASQ measures the FD ratio, which is based on the difference between theoretical and real echo amplitude distributions
NLV	Envelope Statistic based technique	NLV parameter was derived from ASQ, which analyzed ultrasound amplitudes sampled from gray-scale ultrasound images
SS	Envelope Statistic based technique	SS calculates the speed of sound through the liver
SSp.PLUS	Envelope Statistic based technique	SSp.PLUS is a novel technique that allows quantification of the intrahepatic speed of sound which is correlated with the liver fat content

AC: Attenuation coefficient; BSC: Backscatter coefficient; CAP: Controlled attenuation parameter; ATI: Attenuation imaging; ATT: Attenuation measurement function; UGAP: Ultrasound-guided attenuation parameter; Att.PLUS: Attenuation plane-wave ultrasound; TAI: Tissue attenuation imaging; UDF: Ultrasound-derived fat fraction; TSI: Tissue scatter distribution imaging; ASQ: Acoustic structure quantification; NLV: Normalized local variance; SS: Speed of sound; SSp.PLUS: Sound speed plane-wave ultrasound; FD: Focal disturbance.

with obesity[4].

Quantification of attenuation using ultrasound imaging: Several techniques aiming to evaluate the attenuation coefficient applying ultrasound guidance have been exploited, including attenuation imaging (ATI), attenuation measurement function (ATT), and ultrasound guided attenuation parameter (UGAP). CAP has a disadvantage that it lacks the guidance of gray scale ultrasound images in choosing the area for measurement. In contrast, the ATI, ATT, and UGAP techniques are characterized by evaluating liver steatosis on gray scale ultrasonography images with accurate placement of region of interest[17]. When using these techniques, conventional gray scale ultrasound images can be evaluated simultaneously, and the exact region of interest can be placed to avoid the vessels, bile duct, masses or cysts. Therefore, the technical success rate using these methods is high[52-55]. Another advantage of ATI, ATT, and UGAP is that these techniques have high intraobserver and interobserver agreement. A range of 0.81 to 0.98 is found for the intraobserver agreement of ATI, and a range of 0.79 to 0.92 is found for the interobserver agreement. Although there are few studies investigating the topic, the intraobserver and interobserver agreement of UGAP is reported to be 0.86 and 0.84, respectively. In addition, ATI measurements among different operators demonstrated high agreement (intraclass correlation coefficients: 0.91)[17,44,56].

ATI is a kind of two-dimensional attenuation imaging technique (Figure 2)[57,58]. ATI assesses the attenuation of ultrasound beams in a region of interest using color-coded maps in real time. dB/cm/MHz is the unit of measurement for the attenuation coefficient[35]. In addition, to ensure a high technique success rate, the ATI is equipped with a reliability index (R^2), and an R^2 value ≥ 0.80 is considered a reliable measurement[59-61]. In the reported measurements, the cutoff values ranged from 0.63 to 0.69 dB/cm/MHz for detecting $\geq S1$, 0.66-0.72 dB/cm/MHz for detecting $\geq S2$, and 0.68-0.86 dB/cm/MHz for detecting $\geq S3$.

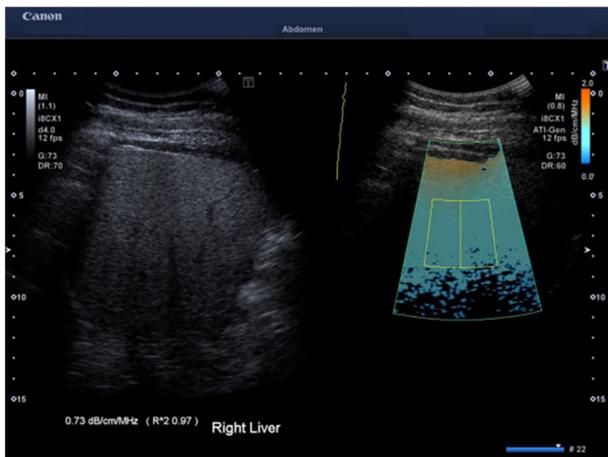


Figure 2 Attenuation imaging technique by Canon with reliability indicator (R^2)[40]. The Gray scale image and the corresponding attenuation imaging image are shown side by side. The attenuation coefficient measurement of the images shown here is 0.73 dB/cm/MHz with an R^2 of 0.97, indicating a valid measurement. Citation: Seneviratne N, Fang C, Sidhu PS. Ultrasound-based hepatic fat quantification: current status and future directions. *Clin Radiol* 2023; 78: 187-200. Copyright© The Author(s) 2023. Published by Elsevier Ltd. The authors have obtained the permission for figure using (Supplementary material).

cm/MHz for detecting = S3. The reported AUROCs were 0.80-0.97 for detecting \geq S1, 0.86-0.99 for detecting \geq S2, and 0.79-0.99 for detecting = S3[59-70]. It has been found that ATI measurements have a significant correlation with histological steatosis grade determined by liver biopsy[59,60,67]. Additionally, in case where MRI-PDFF was applied as the gold standard, the ATI demonstrated positive correlation with it ($r = 0.70-0.83$)[57,65,66]. The ATI also outperformed the CAP in evaluating the grades of hepatic steatosis. A study including 72 consecutive adult patients found that the AUROC for detecting S0 vs S1-S3 of CAP was lower than that of ATI (0.85 vs 0.92, respectively)[66].

ATT is a technique developed by Fujifilm Health Care company (previously Hitachi Medical Systems, Japan) (Figure 3). In ATT, a beamline is connected to an ultrasonic transmitter with two ultrasonic waves of different frequencies (F0, F1) at once. The received signal is obtained, and attenuation coefficients are determined by the slope of the received signal ratio (F0/F1). The results are presented in units of dB/cm/MHz[54,55,71-73]. A study enrolled 351 patients and biopsy specimens were examined quantitatively for fat content. In terms of fat area, ATT had a significant correlation ($r = 0.50$, $P < 0.001$). The cutoff values were 0.62 dB/cm/MHz for $S \geq 1$, 0.67 dB/cm/MHz for $S \geq 2$ and 0.73 dB/cm/MHz for $S \geq 3$ and corresponding AUROCs were 0.79, 0.87 and 0.96[54]. An analysis of 94 patients who received both ATT and CAP examinations when undergoing liver histopathologic examination revealed that ATT exhibited diagnostic accuracy equivalent to that of CAP for grading histological steatosis[73].

With known attenuation and BSC, an ultrasound system uses a phantom method to calculate attenuation coefficients measurement implemented in UGAP (Figure 4). Using this method, the US system's transmitting and receiving beamforming characteristics can be compensated. The result is presented in units of dB/cm/MHz[4,74-76]. Several studies reported good diagnostic efficacy of UGAP for liver fat content quantification applying hepatic histological results as the gold standard, and a positive association was found between UGAP and steatosis percentage (correlation coefficient: 0.78-0.81). The reported AUROCs were 0.89-0.92 for detecting steatosis grade \geq S1, 0.90-0.95 for detecting steatosis grade \geq S2, and 0.88-0.96 for detecting steatosis grade = S3[75,77-79]. Several other studies compared UGAP with MR-based methods, and a significant correlation between MR-based methods and attenuation coefficient values by UGAP was found (correlation coefficient: 0.72-0.77)[76,80]. Imajo *et al*[76] conducted a multicentric study with 1010 patients and reported that UGAP had good diagnostic efficacy for making quantified measurement of liver fat content. In their study, the AUROCs were 0.910 for detecting MRI-PDFF $\geq 5.2\%$, 0.912 for MRI-PDFF $\geq 11.3\%$, and 0.894 for MRI-PDFF $\geq 17.1\%$ [76]. Fujiwara *et al*[75] reported that as compared to CAP, UGAP achieved significantly higher AUROCs for identifying \geq S2 (0.950 vs 0.841) and \geq S3 (0.959 vs 0.817). In addition, they also reported 5.2% of CAP patients had measurement failures, while no UGAP patients did. Tada *et al*[81] reported that there was no effect of liver stiffness on UGAP attenuation coefficient values.

Attenuation plane-wave ultrasound: Attenuation Plane-Wave Ultrasound (Att. PLUS) presents information on ultrasonic beam attenuation through a region of interest. The ultrasound beam attenuation is calculated in a region of interest at a constant depth. The attenuation coefficient results are displayed in units of dB/cm/MHz[56]. The Att. PLUS measurement is combined with the sound speed measurement for each acquisition. It is the median of five measurements taken consecutively that determines the final result[35]. Only one published study regarding this method was found. Popa *et al* [82] carried out a study aiming to assess the clinical value of Att. PLUS of noninvasive measurement of fatty liver with the CAP value considered as control. They reported that the cutoff value to detect S2-S3

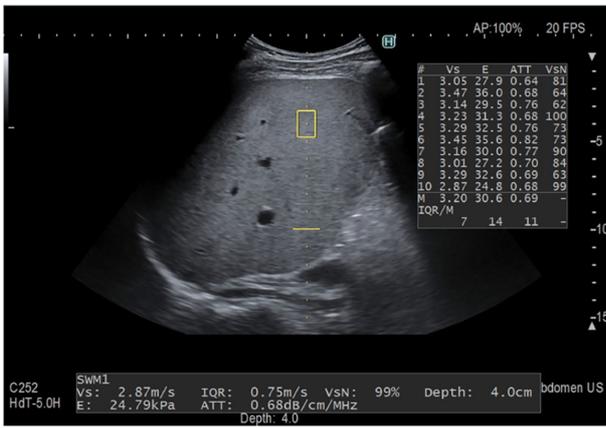


Figure 3 The attenuation measurement function technique was developed by Fujifilm Health Care company[4]. The attenuation coefficient (0.68 dB/cm/MHz) is measured in a fixed area (yellow box) along the same axis as the liver stiffness measurement. Ten acquisitions are performed, and the median value is utilized as the final metric. Citation: Ferraioli G, Berzigotti A, Barr RG, Choi BI, Cui XW, Dong Y, Gilja OH, Lee JY, Lee DH, Moriyasu F, Piscaglia F, Sugimoto K, Wong GL, Wong VW, Dietrich CF. Quantification of Liver Fat Content with Ultrasound: A WFUMB Position Paper. *Ultrasound Med Biol* 2021; 47: 2803-2820. Copyright© The Author(s) 2021. Published by Elsevier Ltd. The authors have obtained the permission for figure using (Supplementary material).

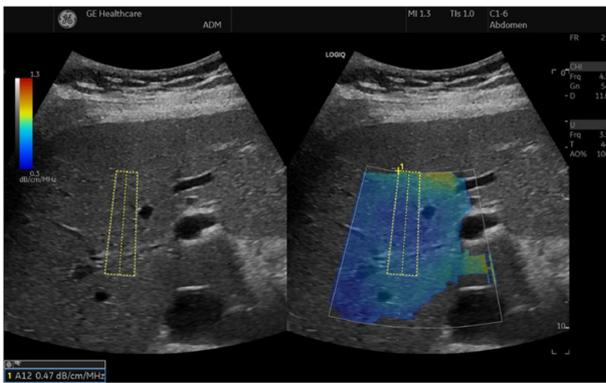


Figure 4 The ultrasound-guided attenuation parameter method implemented in the LOGIQ E9 XDclear 2.0 US scanner[4]. The attenuation coefficient is 0.47 dB/cm/MHz, indicating less than 5% steatosis. Citation: Ferraioli G, Berzigotti A, Barr RG, Choi BI, Cui XW, Dong Y, Gilja OH, Lee JY, Lee DH, Moriyasu F, Piscaglia F, Sugimoto K, Wong GL, Wong VW, Dietrich CF. Quantification of Liver Fat Content with Ultrasound: A WFUMB Position Paper. *Ultrasound Med Biol* 2021; 47: 2803-2820. Copyright© The Author(s) 2021. Published by Elsevier Ltd. The authors have obtained the permission for figure using (Supplementary material).

was 0.5 dB/cm/MHz (sensitivity 53.1%, specificity 82.0%), and the AUROC was 0.72.

Tissue attenuation imaging and tissue scatter distribution imaging: Tissue attenuation imaging (TAI) parameter indicates slope of the ultrasound central frequency downshift along depth, which is able to be utilized to calculate acoustic attenuation. The tissue scatter distribution imaging (TSI) parameter is a measurement of the Nakagami parameters in the region of interest, which reflects the concentration of ultrasound scatterers and their arrangement locally[35,83].

We found three studies comparing TAI and TSI with MRI-PDFF, and these studies revealed that both TAI and TSI revealed correlation with MRI-PDFF[84-86]. Jeon *et al*[86] enrolled 120 patients to assess feasibility of TAI and TSI for hepatic steatosis quantification utilizing MRI-PDFF as the reference. According to MRI-PDFF, the participants were classified into three groups ($\leq 5\%$, $5\%-10\%$, and $\geq 10\%$). They found that both methods had excellent utility for diagnosing and evaluating the degree of hepatic steatosis. For diagnosing fatty quantification of $\geq 5\%$ and $\geq 10\%$, the AUROCs of TAI were 0.861 and 0.835, and those of TSI were 0.964 and 0.935, respectively[86]. Rónaszéki *et al*[84] compared TAI with TSI utilizing MRI-PDFF as gold standard enrolling 101 participants and found that TAI provided better diagnostic performance than TSI for diagnosing $\geq 5\%$ MRI-PDFF (AUROC: 0.89 *vs* 0.87) and $\geq 10\%$ (AUROC: 0.93 *vs* 0.86). TAI and TSI revealed good intra- and interobserver agreement. In TAI, the intra- and interobserver ICCs were reported at 0.994 and 0.975, respectively, while in TSI, they were reported at 0.991 and 0.947[87].

Techniques based on ultrasound BSC: Using the BSC, we can determine amount of ultrasound energy reflected by the tissue. Applying computer algorithm and a reference phantom, the BSC can be

estimated with less changeability resulted from ultrasound systems and operators. The right liver lobe was used to obtain gray scale images, and in the same liver region, a continuous series of 10 frames of transducer signals was captured. Then, in the tissue-imitating reference phantom, which mimics the acoustic properties of human hepatic tissue, consecutive frames were noted without changing scanner settings[35,88-90].

The diagnostic accuracy of the BSC has been evaluated by Lin *et al*[91] by analyzing 204 participants. They found that BSC was positively correlated with MRI-PDFF (Spearman's $\rho = 0.80$; $P < 0.0001$). BSC had an AUROC of 0.98 with a cutoff value of 0.00381/cm-steradian for detecting patients with hepatic steatosis. In addition, when using the optimal BSC cutoff value, in the training group, hepatic steatosis was detected with 93% sensitivity and 97% specificity, while in the validation group, it was detected with 87% sensitivity and 91% specificity[91].

Han *et al*[89,90,92,93] published several studies focusing on the use of the BSC. In a study including 102 participants, they revealed moderate correlation of the BSC with MRI-PDFF (Pearson's $r = 0.58$, $P < 0.001$)[93]. In addition, they enrolled 41 participants to study the repeatability and reproducibility of BSC and found that ICC were 0.87-0.95 for BSC acquired without participant repositioning and 0.69-0.82 with participant repositioning, suggesting that BSC measurement is repeatable and reproducible in patients with NAFLD[89].

Ultrasound-derived fat fraction

The ultrasound-derived fat fraction (UDFF) technique is a coalition of attenuation coefficient and BSC, and a percentage of liver fat content is reported as the result. Data from reference phantoms is integrated into the ultrasound system, and a fixed-acquisition region of interest is utilized[4] (Figure 5). Labyed and Milkowski[37] designed the UDFF method and conducted a study including 101 participants. They found that the UDFF was positively correlated with the MRI-PDFF (Pearson's $r = 0.87$). Using the histology results as the gold standard, the AUROCs of UDFF were 0.94 for detecting $S \geq 1$, 0.88 for $S \geq 2$ and 0.83 for $S = 3$. When using MRI-PDFF to be the gold standard, AUROCs of UDFF were 0.97 for diagnosing MRI-PDFF higher than 5%, 0.95 for diagnosing MRI-PDFF higher than 10% [37]. Similarly, Dillman *et al*[94] reported that liver fat content quantification applying UDFF showed a significant correlation with MRI-PDFF (Spearman's $\rho = 0.82$; $P < 0.001$).

ASQ: Quantifying the acoustic structure of an environment by comparing theoretical and real echo amplitude distributions is referred to as ASQ. In order to compute the theoretical echo amplitude distribution of the hepatic section imaged, the Rayleigh distribution function, assuming that solely ultrasound beam interference from small scattering objects generates the speckle pattern, is applied. However, actual echo amplitude distribution of the liver parenchyma does not follow the Rayleigh distribution. Because ultrasound beams are scattered by small structures, for example the walls of hepatic vessels, resulting in heterogeneity in echo amplitudes[95,96]. However, when diffuse liver diseases cause changes in parenchymal echotexture, ASQ can provide quantitative information by comparing theoretical echo amplitude distribution to a real distribution[97]. Kuroda *et al*[98] tested the ASQ-derived focal disturbance ratio (FD ratio) with 9 Leptin-deficient mice in comparison with histopathological results and found that the FD ratio had significant negative correlations with the fat droplet area (Spearman $r = -0.72$, $P = 0.0017$) and fat droplet size (Spearman $r = -0.98$, $P = 0.0052$), suggesting that the FD ratio can be used to quantify steatosis grade in an animal model and may be a quantitative metric of hepatic steatosis[98]. Karlas *et al*[95] conducted a cohort study to compare ASQ with MRS, and negative correlation was found between FD ratio and MRS (Spearman $r = -0.43$, $P = 0.004$). Similarly, in a prospective study including 36 patients with suspected fatty liver disease, the FD ratio showed a strong, negative correlation with the MRS in 36 patients[99]. Son *et al*[100] also reported FD ratio is comparable to hepatic fat fraction by MRS to make quantified measurement of liver fat content and diagnose liver fat content more than 10% in donor liver patients. Keller *et al*[96] found significant negative correlation between ASQ and steatosis level obtained by histological examination ($r = -0.55$, $P < 0.0001$). Nevertheless, they found no correlation between histologically determined fibrosis stage and any measurements of ASQ.

NLV: The NLV is derived from ASQ and analyzes ultrasound amplitudes sampled from grayscale ultrasound images[4,101]. Bae *et al*[102] assessed the clinical value of the NLV in the measurement of liver fat content in comparison with MRS in 40 male mice using histopathology as the golden standard and found that the AUROCs for diagnosing mild, moderate, and severe hepatic steatosis were 0.953, 0.896, and 0.735, and the NLV value performed similarly to MRS in detecting mild or moderate hepatic steatosis. The same authors also conducted a study with 194 patients to assess the diagnostic efficacy of the NLV for diagnosing and grading liver fat content using liver histopathology as the reference standard. They demonstrated the NLV had excellent diagnostic efficacy in detecting and grading fatty liver with AUROCs of 0.911 for \geq steatosis grade 1, 0.974 for \geq steatosis grade 2, and 0.954 \geq steatosis grade 3[103].

Speed of sound: A speed of sound (SS) estimation is based on the fact that sound speed varies with fat content in soft tissues, and that the relationship between sound speed and liver fat percentage can be

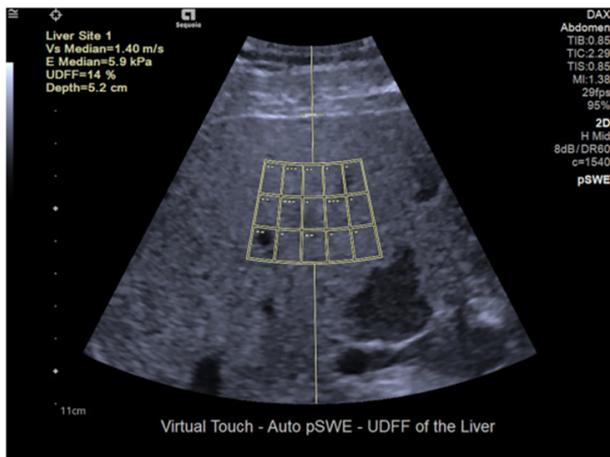


Figure 5 Ultrasound-derived fat fraction method[40]. The ultrasound-derived fat fraction method approximates the magnetic resonance imaging-derived proton density fat fraction and is based on the combination of the attenuation and backscatter coefficient. The method provides both liver stiffness measurement (5.9 kPa in this case) and the percentage of fat accumulation (14% in this case). Citation: Seneviratne N, Fang C, Sidhu PS. Ultrasound-based hepatic fat quantification: current status and future directions. *Clin Radiol* 2023; 78: 187-200. Copyright© The Author(s) 2023. Published by Elsevier Ltd. The authors have obtained the permission for figure using (Supplementary material).

identified[104]. Dioguardi Burgio *et al*[104] carried out a study aiming to explore the value of SS for detecting and quantifying liver steatosis and included 100 patients who underwent both SS and abdominal MR. They found that, in the training cohort, a cut-off value of less than 1.537mm/s led to 87% sensitivity and 95.7% specificity for diagnosing any steatosis with an AUROC of 0.882%. Based on an SS cut-off value of 1.511mm/s, the sensitivity was 100% and specificity was 95.6% for detecting moderate to severe steatosis and the AUROC was 0.989[104].

Sound speed plane-wave ultrasound (SSp.PLUS) is a novel technique for measuring intrahepatic sound speed which is correlated with the liver fat content. The measurement of SSp.PLUS is expressed in m/s[82]. Popa *et al*[82] performed a study with 215 patients to test the value of SSp.PLUS in detecting and grading hepatic fat level applying the CAP value as the gold standard. As a first finding, SSp.PLUS is more closely correlated with CAP values than Att.PLUS: ($r = -0.74$) *vs* ($r = 0.45$). Furthermore, the SSp.PLUS cut-off of less than 1516 m/s indicated 98.36% specificity and 58.74% sensitivity for predicting the presence of significant steatosis (S2-S3)[82].

CONCLUSION

Quantification ultrasound techniques can provide objective continuous number associated with liver fat content and past records can be found when patients receiving check-ups to evaluate change of degree of fatty liver, which is useful for follow-up to monitor the impact of any clinical interventions. Besides, as hepatic steatosis may pose adverse effects to prognosis of patients, quantification of liver fat holds clinical significance. For example, substantial hepatic fat accumulation may contribute to rapid disease progression toward NASH or liver fibrosis[105]. Patients with liver resections are more likely to suffer postoperative complications and die due to liver fat accumulation. Compared with patients without steatosis, those with $\leq 30\%$ steatosis have a significantly increased risk of postoperative complications and patients with $> 30\%$ steatosis have an increased risk of postoperative death[9,106,107]. It is worth to be mentioned that simple steatosis may lead to poor prognosis. A study carried out in a nationwide Swedish cohort from 1966 to 2017 including 10568 patients found that simple steatosis, non-fibrotic NASH, non-cirrhotic fibrosis, and cirrhosis were associated with significant higher hazard ratio for mortality risk compared with controls. The all-cause mortalities of cohorts with simple steatosis, non-fibrotic NASH, non-cirrhotic fibrosis, and cirrhosis were 2.52% person-years, 3.03% person-years, 3.53% person-years, and 7.05% person-years respectively whereas the mortality of population comparators was 1.69% person-years[108]. Association between imaging quantification method and clinical prognosis is another issue. In patients with chronic hepatitis C, CAP value ≤ 221 dB/m is associated with higher risk of HCC and in patients with NAFLD, CAP value ≤ 265 dB/m is associated with higher risk of HCC[109]. Similarly, in another cross-sectional study including 130 patients (HCC) and 54 patients (chronic hepatitis C), the authors reported that CAP value of chronic hepatitis C group was significantly higher than that of HCC group (259.96 dB/m *vs* 209.57 dB/m, $P < 0.001$)[110].

While serving as the conventional reference standard, liver histopathologic test has the limitations of invasiveness, sampling error, and high cost. Issues including availability, cost, accuracy and reliability should be taken into consideration when choosing the optimal noninvasive methods. The further

application of noninvasive methods is desirable for detecting and grading hepatic steatosis at the initial diagnosis and monitoring changes in liver fat content during follow-up after receiving clinical therapies.

MRS and MRI-PDFF are reported to be the most accurate imaging modalities for quantified measurement of liver fat content. However, their low accessibility and high cost make it impossible to use MR-based techniques as repeatable methods to monitor the process of liver steatosis. Therefore, ultrasound-based techniques are more desirable with the advantages of portability and cost-effectiveness. CAP is the first method based on attenuation of the ultrasound beam, and its performance has been validated in several studies. However, the limitations of CAP are nonnegligible in that due to its blindness, it has a high rate of measurement failures because it cannot determine the exact location of the region of interest. UGAP, ATT and ATI have been developed to improve this situation, and these metrics can be used to evaluate degree of fatty liver on gray scale ultrasonography in real-time with a correct region of interest. The CAP measurement also showed suboptimal performance in quantifying liver fat content especially in mild steatosis, which limited its use as a golden standard to evaluate the efficacy of novel imaging methods for liver fat content quantification. In addition, techniques derived from other principles, such as ASQ, TSI and UDFP, have been developed. These techniques are reported to have nice clinical efficacy for liver fat quantification. Nevertheless, studies exploring value of such techniques enrolled a small number of participants. Therefore, future studies enrolling more participants are needed to test the utility of such techniques. Besides, imaging-based techniques may have some limitations. For example, CAP, ATI and MRI-PDFF may be unable to differentiate grade 2 with grade 3 liver steatosis.

Several hepatic steatosis quantification tools are launched by commercial platforms. Larger clinical studies are needed to compare the efficacy among different products. For patients with NAFLD, except for steatosis, inflammation and fibrosis are also significant features which are associated with prognosis. The steatosis measurement is able to be obtained together with the stiffness value by some tools. In this way, comprehensive evaluation of patients with NAFLD can be made. Except for elastography tools, ASQ has also been studied to evaluate liver stiffness. Hepatic steatosis measurement and stiffness measurement, in conjunction with other ultrasound methods, are promising tools for patients with diffuse liver disease to supervise curative effect and disease progression. Developing such a multi-parametric ultrasound modality will require future studies.

ACKNOWLEDGEMENTS

We thank all medical staff and technicians who agreed to participate in this review.

FOOTNOTES

Author contributions: Lu Q conceived and designed the protocol; Zeng KY performed the literature search; Bao WYG and Wang YH selected the studies and extracted relevant information; Liao M, Yang J and Huang JY prepared the figures and tables; Zeng KY wrote the first version of draft; Lu Q critically revised successive drafts of the paper and approved the final version.

Conflict-of-interest statement: The authors have no financial relationships to disclose.

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S-Editor: Yan JP

L-Editor: A

P-Editor: Zhao S

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