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ABOUT COVER

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RESPONSIBLE EDITORS FOR THIS ISSUE

How to select the quantitative magnetic resonance technique for subjects with fatty liver: A systematic review

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Abstract

BACKGROUND

Early quantitative assessment of liver fat content is essential for patients with fatty liver disease. Mounting evidence has shown that magnetic resonance (MR) technique has high accuracy in the quantitative analysis of fatty liver, and is suitable for monitoring the therapeutic effect on fatty liver. However, many packaging methods and postprocessing functions have puzzled radiologists in clinical applications. Therefore, selecting a quantitative MR imaging technique for patients with fatty liver disease remains challenging.

AIM

To provide information for the proper selection of commonly used quantitative MR techniques to quantify fatty liver.

METHODS

We completed a systematic literature review of quantitative MR techniques for detecting fatty liver, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol. Studies were retrieved from PubMed,

Embase, and Cochrane Library databases, and their quality was assessed using the Quality Assessment of Diagnostic Studies criteria. The *Reference Citation Analysis* database (https://www.referencecitationanalysis.com) was used to analyze citation of articles which were included in this review.

RESULTS
Forty studies were included for spectroscopy, two-point Dixon imaging, and multiple-point Dixon imaging comparing liver biopsy to other imaging methods. The advantages and disadvantages of each of the three techniques and their clinical diagnostic performances were analyzed.

CONCLUSION
The proton density fat fraction derived from multiple-point Dixon imaging is a noninvasive method for accurate quantitative measurement of hepatic fat content in the diagnosis and monitoring of fatty liver progression.

Key Words: Fatty liver; Hepatic fat content; ^{1}H-magnetic resonance spectroscopy; Multiple-point Dixon imaging; Two-point Dixon imaging

Core Tip: This study focused on properly selecting commonly used quantitative magnetic resonance (MR) techniques to quantify fatty liver disease. We completed a systematic literature review of quantitative MR techniques for detecting fatty liver, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol. Three techniques including spectroscopy, two-point Dixon imaging, and multiple-point Dixon imaging, were compared. We found that proton density fat fraction derived from multiple-point Dixon imaging is a noninvasive method for accurate quantitative measurement of hepatic fat content. It can be used to diagnose fatty liver disease and monitor disease progression as well as treatment effects.

INTRODUCTION
Fatty liver refers to the excessive accumulation of triglycerides within the cytoplasm of hepatocytes. Increased fat deposition in hepatocytes can cause hepatocyte injury, inflammation, fibrosis, and eventually cirrhosis, with a high risk of liver failure and hepatocellular carcinoma[1]. Therefore, early quantitative assessment of hepatic fat content is essential for patients with fatty liver disease.

Liver biopsy is the gold standard for assessing hepatic fat content[2]. This may increase the chances of sampling error commonly encountered in livers with inhomogeneous fat distribution, because only a small fraction of the entire liver is sampled. Additionally, it can cause complications, such as bleeding, infection, and death. More importantly, this operation cannot be repeated and is not conducive for longitudinal monitoring of disease progression[3].

Ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) are commonly used for noninvasive examination of fatty liver. Ultrasound is easy to perform. Quantitative measurements were performed using the attenuation and backscatter coefficients. However, its accuracy in staging fatty liver is low because the images are blurred by hepatic parenchymal structures and ultrasound beam is attenuated significantly by the fatty liver[4], especially in obese patients[5]. Additionally, ultrasound is highly operator-dependent and has low reproducibility[4]. CT evaluation of fatty liver is based on the absolute CT value of liver parenchyma or relative attenuation difference between liver parenchyma and spleen[6,7]. When the threshold was 42 Hounsfield units, the sensitivity and specificity for grade 2–3 fatty liver were 73% and 100%, respectively[8]. The energy spectrum of fat is similar to that of the liver parenchyma in dual-energy CT examination. Therefore, its accuracy in diagnosing fatty liver is lower than that of conventional CT[6]. Moreover, CT exposes patients to radiation and is thus not advisable for repeated use. Various MR techniques have been developed for the quantitative assessment of signal fat fraction (SFF) and/or proton density fat fraction (PDFF). SFF is defined as the signal from fat divided by the combined signal from fat and water. This is measured using fat-

suppressed techniques or chemical shift–encoded imaging (CSI) and MR spectroscopy (MRS) techniques [9]. This measurement is biased by one or more confounding factors. Once all confounding factors have been addressed, SFF is equivalent to PDFF[10]. PDFF, which can be measured with MRS or CSI, reflects the true fat content in tissue and thus, has become a reliable, accurate, and standardized MR-based biomarker for tissue fat accumulation. Mounting evidence has shown that MR has high accuracy in quantitatively analyzing fatty liver and can be repeated without radiation exposure[11-14]. However, many packaging methods and postprocessing functions have puzzled radiologists in clinical applications. This study compiled widespread data on MR techniques. This study aimed to provide information for properly selecting quantitative MR techniques to visualize the fatty liver.

MATERIALS AND METHODS

Data acquisition
A systematic review of the literature was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[15]. Literature from 1984 to 2021 was searched in PubMed, Embase, and Cochrane Library. The *Reference Citation Analysis* database (https://www. referencecitationanalysis.com) was used to analyze citation of articles which were included in this review. Combined MeSH and free text were used as retrieval strategies (Supplementary Table 1). Only the studies published in English were included. To ensure literature saturation, we scrutinized the reference lists of the included studies. The inclusion criteria were as follows: (1) Studies limited to human participants; (2) Studies related to the principles of MR techniques or systemic review and meta-analysis for measuring hepatic fat content; and (3) Studies involving comparisons of MR techniques with other methods (liver biopsy, ultrasound, or CT) to measure hepatic fat content. Studies conducted on animals, those without full text, review papers, conference proceedings, and case reports were excluded. The studies were independently screened by two authors, and study selection was decided by consensus.

Assessment of study quality
Two authors used the Quality Assessment of Diagnostic Studies (QUADAS)-2 criteria in RevMan 5.4 for judging the risk of bias independently. Each study was given a low, high, or unclear risk of bias (Supplementary material) following QUADAS-2 guidance in the four domains. The signaling question 2 in the first domain was replaced by "Was the study design prospective or retrospective" because a retrospective study had a relatively higher risk of bias[16]. Any disagreements were resolved by a third author.

Data extraction
The following data were extracted: First author, publication year, study design, number of patients, mean age, studied etiology, data on MR techniques such as field strength and scan sequences, comparison, interval between MR methods and comparison, and study outcomes. If a study reported multiple MR methods, the data from the main modality was extracted.

Qualitative synthesis
The principles, main technical factors, advantages, and disadvantages of each method were summarized and evaluated. The results of the studies with an overall low and moderate risk of bias were used to analyze the diagnostic performance of one of the three methods.

RESULTS

Literature search results
Electronic search identified 633 studies. Of these, 467 studies were excluded after reviewing the titles, abstracts, and keywords of each study. Another 52 studies were excluded after reading full-text articles. Of the 114 included studies, 35 were related to MR techniques, and 39 were reviews and meta-analyses. Consequently, 40 studies were used for further analysis, including 20, 9, and 12 studies for spectroscopy two-point Dixon imaging, and multiple-point Dixon imaging compared with other methods, respectively (Figure 1). Detailed data extraction for each study is shown in Tables 1-3.

Quality assessment
The outcomes of risk of bias assessment in the 40 studies are summarized in Figure 2. The overall low risk of bias in the ^{1}H-MRS, two-point Dixon imaging, and multiple-point Dixon imaging groups was 50%, 55.5%, and 33.3%, respectively. Qualitative rather than quantitative synthesis was used in this study because of the high bias of included studies.

Table 1 Studies reporting on the measurement of the hepatic fat content with ¹H-magnetic resonance spectroscopy versus liver biopsy and other imaging methods

Ref.	Year	Study design	Age (year)	N	Etiology	Field strength sequence	Comparison	Interval	Results
Thomsen *et al*[22]	1994		48	14	Fatty liver	1.5 T. STEAM (TE = 34 ms)	Liver biopsy		$r = 0.897$; $P < 0.001$
Longo *et al*[26]	1995		45	29	Diffuse steatosis	1.5 T. PRESS (TE = 50–200 ms)	Liver biopsy		$r = 0.70$
Cowin *et al*[30]	2008		42	12	Steatosis	1.5 T. PRESS (TE = 30 ms)	Liver biopsy	6 wk	$r = 0.928$; $P < 0.0001$
Irwan *et al*[63]	2008	Prospective	47	10	Healthy volunteers	1.5 T. PRESS (TE = 30 ms)	Dual-echo imaging	One measurement session	$r = 0.927$. In the range 1%–10%, the MRI-determined the liver fat contents (corrected algorithm) are systematically higher, on average 4% (range: 2.1%–6.1%) than those obtained with MRS
Kim *et al*[64]	2008	Prospective	15.9 ± 5.3	28	Lean and obese	1.5 TPRESS (TE = 20 ms)	Two-Point Dixon		$r = 0.954$; $P < 0.001$
Borra *et al*[65]	2009	Prospective	62.8 ± 8.3	33	Type 2 diabetes	1.5 T. PRESS (TE = 25 ms)	IP/OP (Dixon)		$r = 0.959$–0.962; $P < 0.001$
Reeder *et al*[66]	2009	Prospective	49.0 ± 12	31	Suspected steatosis and unrelated reasons	1.5 T. PRESS (TE = 25 ms)	IDEAL		$r = 0.83 ± 0.05$; $P < 0.001$. Intercept (1.76 ± 0.76%; $P = 0.03$)
Zhong *et al*[31]	2009		50 ± 12	36	Fatty liver	3.0 T. PRESS (TE = 144 ms)	16-row multislice CT		$r = -0.461$; $P = 0.005$
Hu *et al*[67]	2010			16		3.0 T. PRESS (TE = 23 ms)	IDEAL		Slope = 0.90, intercept = 1.07%; $r^2 = 0.95$, $P < 0.001$
Roldan-Valadez *et al*[68]	2010		35	18	Steatosis	3.0 T	Liver biopsy		$r = 0.876$; $P ≤ 0.001$
Mehta *et al*[32]	2010		39.9	50	Steatosis	1.5 T. PRESS (TE = 135 ms)	Ultrasound		BMI > 30, sensitivity 96%; BMI ≤ 30, sensitivity 64%
Meisamy *et al*[23]	2011	Prospective	40	55		1.5 T. STEAM (TE = 10, 20, 30, 40, and 50 ms)	IDEAL		$r^2 = 0.99$
Georgoff *et al*[69]	2012	Prospective	50.6	52	Steatosis	3.0 T. PRESS (TE = 50 ms)	Liver biopsy	15 ± 9 d	Diagnostic accuracy was (AUC: 0.95; 95%CI: 0.89–1.0)
Kang *et al*[18]	2012	Prospective	54	56	Steatosis	1.5 T. STEAM (TE = 20, 30, 40, 50, and 60 ms)	Liver biopsy	1–28 d	$r = 0.95$
Parente *et al*[70]	2014	Prospective	54 ± 9	73	Nonalcoholic fatty liver disease	3.0 T. PRESS (TE = 40 ms)	Liver biopsy		$r = 0.767$; $P < 0.001$
Bashir *et al*[71]	2015	Prospective	55 ± 13.8	217	Various hepatic diseases	1.5 T. STEAM (TE = 12 ms)	Two-point Dixon		$r = 0.61$; $P < 0.001$
Kim *et al*[57]	2015		52.8 ± 14	42	Various hepatic diseases	3.0 T. STEAM (TE = 12, 24, 36, 48, and 72 ms)	In- and opposed-phase echo pairs		$r = 0.97$
Satkunasingham *et al*[72]	2015	Retrospective	57.8 (12–83)	156	Various hepatic diseases	3.0 T. STEAM (TE = 12, 24, 36, 48, and 72 ms)	MRI-PDFF		$r = 0.977$; $P < 0.001$
Rastogi *et al*[73]	2016	Retrospective	32.5	73	Steatosis	3.0 T. STEAM (TE = 15, 20, 25, 30, and 35	Biopsy and surgery	≤ 20 d	MRS correlated well with the histopathology results ($r = 0.882$). An accuracy of 96%

					ms)			and sensitivity of 94%
Kramer *et al*[6]	2017	Prospective	57 ± 5	50	Various hepatic diseases	1.5 T. STEAM (TE = 10, 20, 30, 40, and 50 ms)	PDFF	r^2 = 0.992; slope, 0.974; intercept, –0.943

MRS: Magnetic resonance spectroscopy; PDFF: Proton density fat fraction; TE: Echo time; BMI: Body mass index; CT: Computed tomography; Blank: No information; PRESS: Point-resolved spectroscopy; STEAM: Stimulated-echo acquisition mode.

Table 2 Studies reporting on the measurement of the hepatic fat content with in-phase and out-of-phase imaging versus liver biopsy and other imaging methods

Ref.	Year	Study design	Age (year)	N	Etiology	Field strength sequence	Comparison	Interval	Results
Fishbein e*t al*[35]	2005		47 ± 10	38	Various hepatic diseases	1.5 T. IP/OP (Dixon)	Biopsy	2 wk	r = 0.773, P < 0.001; Macrovesicular steatosis: r = 0.920, mixed steatosis: r = 0.605, P = 0.05
Kalra *et al* [74]	2009	Prospective	41 ± 9.2	10	Nonalcoholic fatty liver disease	1.5 T. IP/OP (Dixon)	Biopsy		Provides data on fat infiltration without information of hepatic fibrosis
Mennesson *et al*[41]	2009	Prospective	52.5	40	Various hepatic diseases	1.5 T. IP/OP (Dixon)	Biopsy	Same day	r = 0.852; P < 0.0001
Fischer *et al* [37]	2010	Prospective	66 ± 12	23	Various hepatic diseases	1.5 T IP/OP (Dixon)	Biopsy and surgery	≤ 10 d	r = 0.92; P < 0.0001
Pacifico *et al* [75]	2011	Case–control	7-16	25	Nonalcoholicfatty liver disease	1.5 T. Two-point Dixon	Biopsy	1–7 d	r = 0.883; P < 0.0001
Guaraldi *et al*[76]	2012	Observational pilot		16		1.5 T. IP/OP (Dixon)	Biopsy		r = 0.88; P < 0.0001
Koelblinger *et al*[77]	2012	Prospective	60.5	35	Various hepatic diseases	3.0 T. IP/OP (Dixon)	Biopsy		Uncorrected: r = 0.67, P < 0.001. Spleen correction: r = 0.85, P < 0.001
Rastogi *et al* [73]	2016	Retrospective	32.5	73	Steatosis	3.0 T. IP/OP (Dixon)	Biopsy and surgery	≤ 20 d	Dual-echo MRI correlated well with the histopathology results (r = 0.871). An accuracy of 95% and sensitivity of 97%
Bhat *et al*[78]	2017	Prospective	46	30	Steatosis	1.5 T. Two-point DIXON	Biopsy	1 wk	Good correlation between the MR estimation of liver fat and histological grading. 90% of patients had a fat content of less than 10%. The maximal fat content of 28% was observed in one patient

MRI: Magnetic resonance imaging; Blank: No information.

Findings of three MR methods

^{1}H-MRS-principle: ^{1}H-MRS measures the chemical composition of tissues. A signal from a region of interest (ROI) is Fourier transformed into an MR spectrum that displays various metabolites with unique frequencies. Triglycerides are composed of three fatty acid chains connected to a glycerol backbone; hence, at least six peaks can be resolved in the MRS spectrum. The water proton yields a single peak whose position in the spectrum may vary slightly depending on the temperature[17]. Liver SFF can be calculated as follows: $A_{fat}/(A_{fat} + A_{water}) \times 100\%$, where A_{fat} is the summation of lipid peak areas and A_{water} is the area under the water peak[18]. After T1 and T2 relaxation effects are corrected, spectroscopy-derived PDFF can be corrected[19,20].

Main technical factors-single-voxel technique *vs* multi-voxel technique: ^{1}H-MRS spectra can be obtained using single-voxel or multiple-voxel techniques. The single-voxel technique for sampling a voxel of interest with a high signal-to-noise ratio (SNR) is commonly applied in hepatic MRS measurements[19].

Main technical factors-PRESS *vs* stimulated-echo acquisition mode: The most commonly used techniques for ^{1}H-MRS are point-resolved spectroscopy (PRESS) and stimulated-echo acquisition mode (STEAM). PRESS is a spin-echo technique with a longer minimal echo time (TE) that allows for better

Table 3 Studies reporting on the measurement of the hepatic fat content with multiple-point Dixon imaging versus liver biopsy and other imaging methods

Ref.	Year	Study design	Age (year)	N	Etiology	Field strength sequence	Comparison	Interval	Results
Noureddin *et al*[79]	2013	Randomized		50	Nonalcoholic fatty liver disease	MRI-PDFF	MRS	0 and 24 wk	$r^2 = 0.98$; $P < 0.0001$
Idilman *et al* [28]	2013	Prospective	44.7 ± 13.1	70	Nonalcoholic fatty liver disease	1.5 T. IDEAL-IQ	Biopsy	14.5 d (0–259)	$r = 0.820$; The correlation of PDFF in mild hepatic steatosis was found to be better than that of moderate or severe steatosis ($r = 0.835$ and $r = 0.402$, respectively; $P = 0.003$)
Deng *et al* [51]	2014	Prospective	3–16	10	Nonalcoholic fatty liver disease	1.5 T. Multi-point Dixon	Biopsy		$r = 0.90$; $P = 0.0004$
Kukuk *et al* [59]	2015		51.7 ± 15.2	59	Liver disorders	3.0 T. Six echo-mDixon	Biopsy	≤ 6 wk	$r = 0.967$, $P < 0.001$. Slightly a higher hepatic fat contents than q Histo (mean difference 2.1% for 6E-mDixon and 1.9% for MRS)
Rehm *et al* [52]	2015	Prospective	13.3 ± 2 (11–22)	132	Healthy females	3.0 T. Multi-echo Dixon	STEAM (TE = 10, 15, 20, 25, and 30 ms)		$r = 0.96$
Schwimmer *et al*[80]	2015	Prospective	14	174	No steatosis and nonalcoholic fatty liver disease	3.0 T. Multi-echo Dixon	Biopsy	57 ± 51 d	$r = 0.725$; $P < 0.01$
Idilman *et al* [55]	2016	Retrospective	41.7 ± 14.6	19	Nonalcoholic fatty liver disease	1.5 T. DEAL-IQ	Biopsy		$r = 0.743$; $P < 0.001$
Hetterich *et al*[39]	2016	Prospective	57.2 ± 9.4	215		3.0 T. STEAM (TE = 12, 24, 36, 48, and 72 ms)	Multi-echo Dixon		$r = 0.96$; $P = 0.001$
Middleton *et al*[81]	2017	Randomized	51 ± 11	113	Nonalcoholic steatohepatitis	1.5 T or 3.0 T. Six echo-mDixon	Biopsy	51 d	$r = 0.80$; $P < 0.001$
Kang *et al* [46]	2018	Prospective	47.3 ± 14.9	29	NAFLD (34). Alcoholic liver disease (13). Liver cirrhosis (9)	3.0 T. mDIXON-Quant sequence	Biopsy	Same day	$r = 0.809$; $P < 0.001$
Pickhardt *et al*[82]	2018	Retrospective	54 ± 12	221		1.5 T or 3.0 T. MRI-PDFF	CT	0–158 mo	$r = 0.88$ (≤ 1 mo) substantially worsened with increasing time
Guo *et al*[83]	2020	PProspective	52.6 (22–83)	400	Healthy adults and older adults	3.0 T mDixon-Quant sequence	CT	Same day	$r = 0.79$; $P < 0.001$

MRS: Magnetic resonance spectroscopy; PDFF: Proton density fat fraction; TE: Echo time; BMI: Body mass index; CT: Computed tomography; Blank: No information; PRESS: Point-resolved spectroscopy; STEAM: Stimulated-echo acquisition mode.

visualization of metabolites with long T2 relaxation times. However, STEAM applies a 90°–90°–90° pulse and provides a shorter TE that is suitable for metabolites with short T2 relaxation times. PRESS has a higher SNR and is relatively insensitive to patient motion compared to STEAM, whereas STEAM is less affected by J-coupling and is generally preferred[21].

Main technical factors-correcting T1 and T2 effects: T1 and T2 values affect fat content measurement. In general, T1 relaxation times cause no trouble because the TR of MRS is much longer than the longest T1 of fat[22,23]. However, different T2 relaxation times may be problematic[24]. Both PRESS and STEAM sequences have a TE delay, causing spin-spin relaxation and decrease the signal[25]. Multiple spectroscopic acquisitions with different TEs are required to correct T2 values. If the spectra are acquired at a single TE, the sequence must use minimal TE to reduce T2 effects. Therefore, STEAM with shorter TE is recommended.

Main technical factors-ROI: The ROI was placed at the center of the right hepatic lobe to avoid vascular structures, bile ducts, and the liver edge[19].
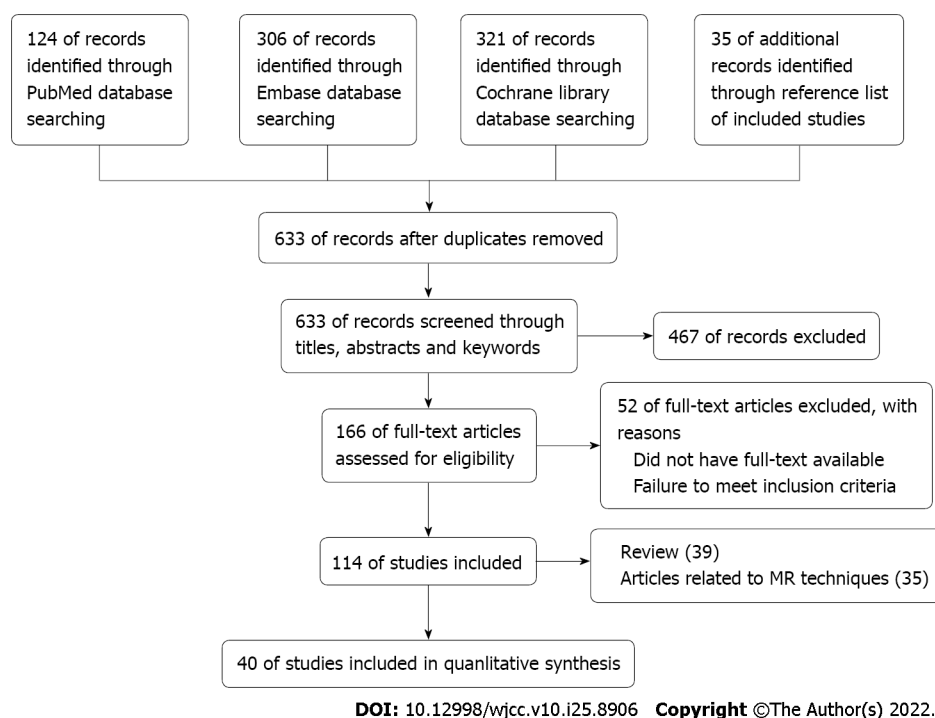
Figure 1 Flowchart of the study selection. MR: Magnetic resonance.

Main technical factors-advantages: ^{1}H-MRS is an alternative to liver biopsy. It can accurately quantify fat content with high intra- or inter-individual reproducibility[26] and is not affected by hepatic iron deposition, inflammation, and fibrosis[18].

^{1}H-MRS is a noninvasive method for assessing hepatic lipid composition. Higher indices of hepatic fatty acid saturation and lower indices of unsaturation were observed in patients with obesity-related metabolic disease[27].

Main technical factors-disadvantages: ^{1}H-MRS requires technical expertise for its acquisition and analysis[28]. ^{1}H-MRS introduced sampling errors, especially in the liver with nonhomogeneous fat distribution, because fat is measured in the ROI rather than in the entire liver[29].

Hepatic fat showed multiple peaks on MR spectroscopy. The main lipid peak is at approximately 0.9–2.75 ppm and two unsolved lipid resonances at 4.2 and 5.3 ppm overlapping with the water peak, leading to quantification errors[19].

Diagnostic performance-^{1}H-MRS *vs* liver biopsy: Five studies with an overall low risk of bias were used to evaluate the diagnostic performance of ^{1}H-MRS[22,26,30-32]. These studies showed that ^{1}H-MRS strongly correlated with the degree of hepatic steatosis on liver biopsy ($r = 0.767–0.959$). The sensitivity and specificity for ^{1}H-MRS diagnosis of hepatic fat content of 5% or more were 94.4% and 89.5%, respectively[18].

Diagnostic performance-^{1}H-MRS *vs* other imaging methods: ^{1}H-MRS is considered the gold standard for other imaging methods to quantify hepatic fat content. One study[32] demonstrated that ultrasound detected liver fat in 82% of cases, measurable by ^{1}H-MRS. Zhong *et al*[31] compared CT with ^{1}H-MRS to quantitatively assess hepatic fat content and found that ^{1}H-MRS correlated with the CT liver/spleen ratio ($r = –0.461$).

Two-point Dixon technique

Principle: Two-point Dixon technique produces in-phase (IP) and out-of-phase (OP) images using two acquisitions[33,34]. The signal intensity (SI) on IP images is the sum of water and fat signals within a voxel, whereas that on OP images is the difference between water and fat signals. Thus, SFF can be calculated using the following formula: $SFF = [(SI_{IP} – SI_{OP})/2SI_{IP}] \times 100$, where SI_{IP} is the SI in a voxel on the IP image and SI_{OP} is the SI on the OP image[35].

Main technical factors-SE *vs* gradient-recalled echo: Gradient-recalled echo (GRE) is routinely used for hepatic fat estimation. Since the GRE sequence is susceptible to the motion and paramagnetic effects of iron, Dixon used the SE sequence instead of the GRE sequence for CSI. A three-point Dixon method, which introduced a third echo to correct phase errors, was required to overcome long scan time and sensitivity to magnetic field inhomogeneities[34,36].
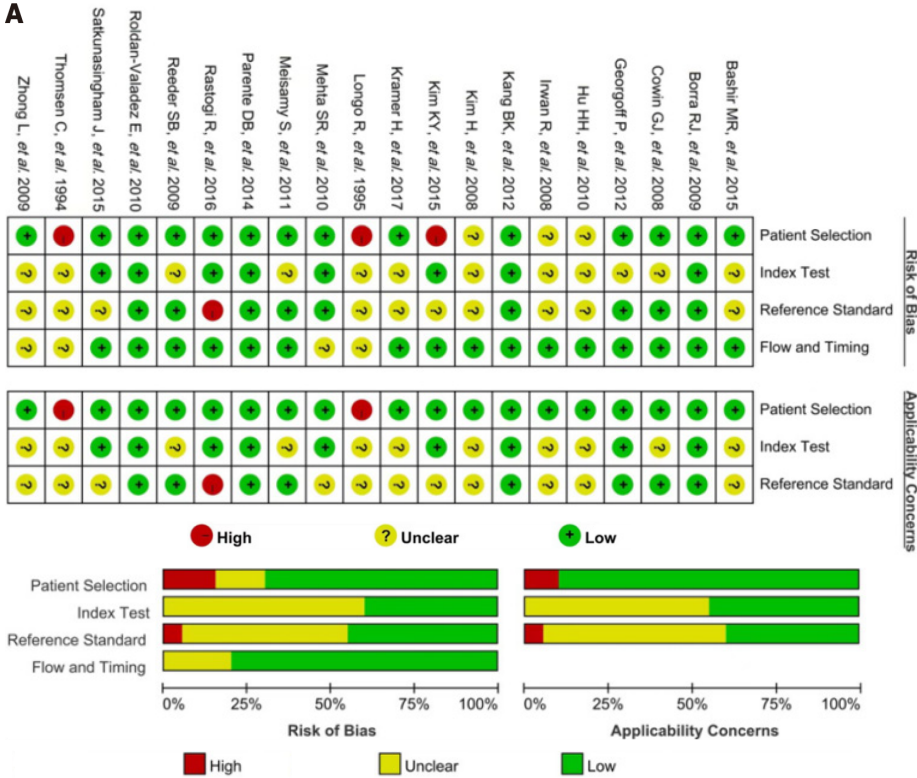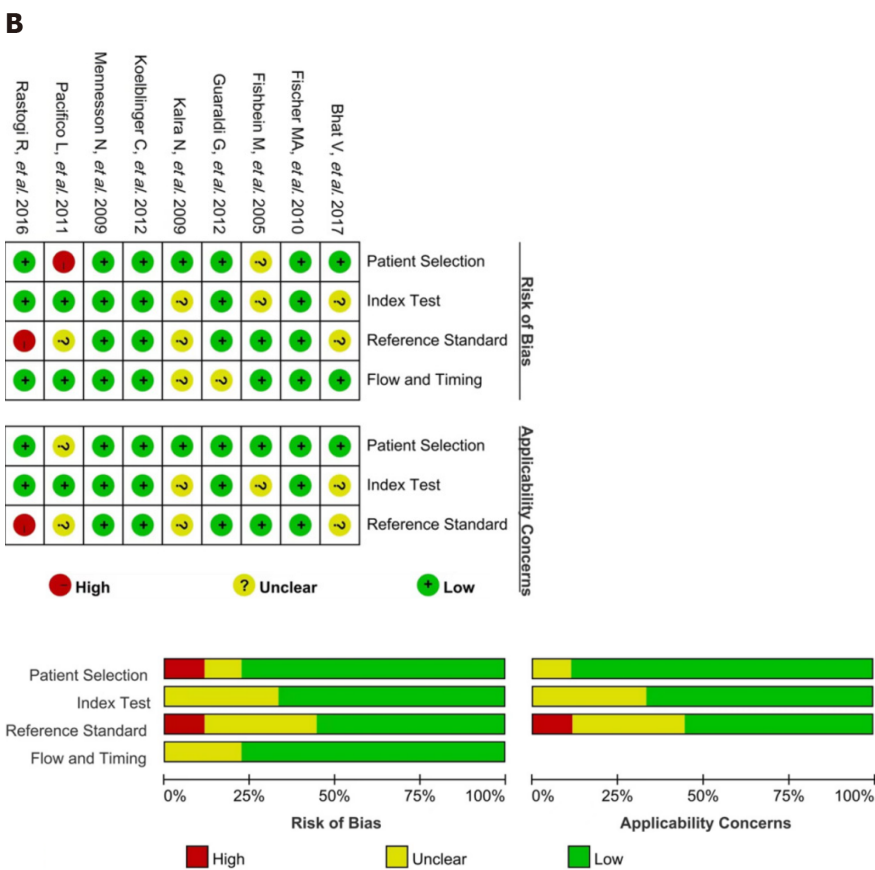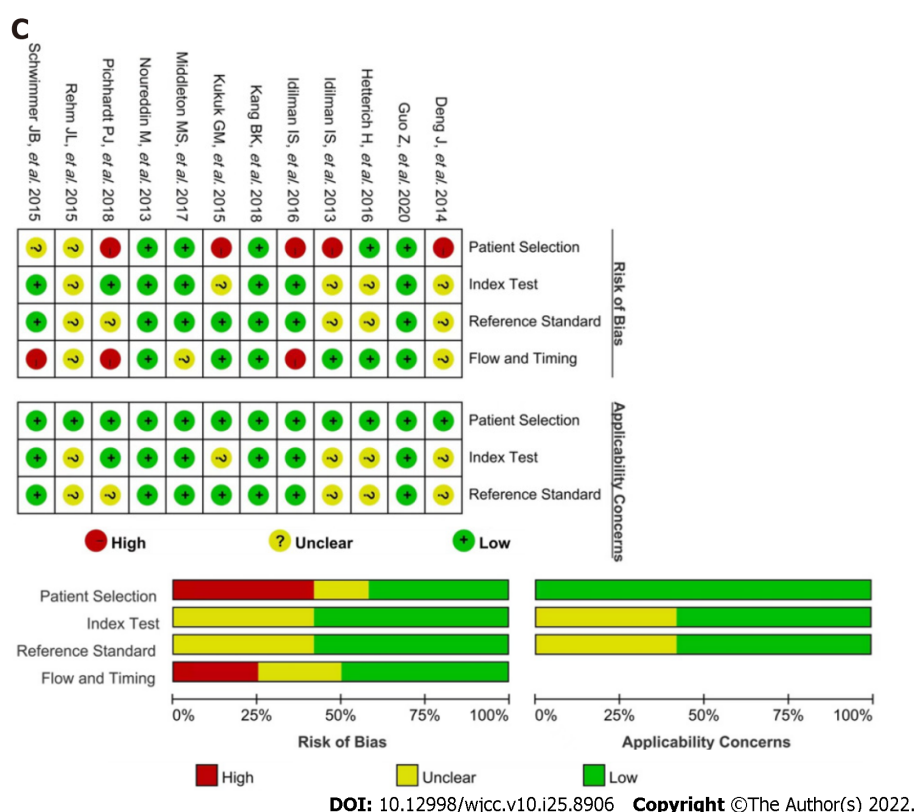
Figure 2 Risk-of-bias and applicability concerns graph. A: Studies for [1]H-magnetic resonance spectroscopy *vs* liver biology and other imaging methods in measuring hepatic fat content; B: Studies for in-phase and out-of-phase imaging *vs* liver biology and other imaging methods in measuring hepatic fat content; C: Studies for multiple-point Dixon imaging *vs* liver biology and other imaging methods in measuring hepatic fat content.

Main technical factors-2D *vs* 3D: IP and OP images are typically obtained in 2D acquisitions with multiple breath-holds for nonvolumetric quantification of hepatic fat. The 3D GRE sequence provided volumetric coverage of the liver but increased the post-processing time[37].

Main technical factors-ROI: ROIs were drawn at anatomically matched locations on the hepatic parenchyma on paired sequences, using a co-registration tool to exclude vessels, bile ducts, motion artifacts, and partial volume effects. Two of the 12 circular ROIs were placed in the right liver and two in the left liver above, below, and at the level of the porta hepatis[38].

Main technical factors-advantages: This technique could be used with all types of MR scanners (0.5T-3T). Both IP and OP images were acquired in the same breath-hold, and all imaging parameters, except TE, were similar. Therefore, the SI differences between the two images were based only on parallel, opposing water, and fat protons. The quality of the images was not affected by phase-related effects owing to amplitude imaging without phase information[33].

Main technical factors-disadvantages: The IP and OP images contained T1, T2, and T2*. These estimate the hepatic fat content inaccurately, especially for the liver with a fat content lower than 5%[38,39]. Because the liver SFF is within the dynamic range of 0%–50%[18], when the hepatic fat content was > 50%, the dominant constituent in a voxel is ambiguous on IP and OP images. This require phase-sensitive processing or a dual flip angle (20°and 70°) for removal[40].

The SFF derived from the IP and OP images assumes that water and fat have a single resonance frequency. In fact, this was not true for fat. Therefore, SFF based on IP and OP images is intrinsically incorrect[33].

Diagnostic performance: The sensitivity and specificity of SFF for diagnosing hepatic fat content > 20% are 96% and 93%, respectively[41]. However, a sensitivity of 89% and specificity of 82% were observed for an SFF of 1.8%[37].

Multiple-point Dixon technique

Principle: Multiple-point Dixon acquires data from more than three echoes and provides images with both the magnitude and phase information of the echoes. This method addresses many confounding factors and yields accurate PDFF measurements. Simultaneously, transverse relaxation rate maps for

measuring the iron content are also obtained[33,34,40]. The whole-liver PDFF was measured by averaging PDFF values from multiple regions in different parts of the liver. However, an optimal ROI-based sampling strategy has not yet been established[42].

Main technical factors-correcting T1 and T2* effects: In general, a long TR or a low flip angle in spoiled GRE acquisitions is used to minimize T1 bias. Echoes were acquired at three or more nominally OP and IP TEs to minimize T2* interference, especially the IDEAL-IQ sequence using a 6-echo 3-point Dixon method[28,33].

Main technical factors-noise and eddy: The noise bias originated from the skewed noise distribution in areas with a low signal during the magnitude operation. It significantly affects low-fat regions and makes the diagnosis of mild steatosis difficult. Noise bias can be mitigated using a hybrid complex/magnitude reconstruction[43].

Eddy currents were generated during rapid gradient switches at multiple TEs, which led to a phase shift and adversely affected the complex-based PDFF. This can be addressed by acquiring additional calibration data[44].

Main technical factors-fat spectral complexity: The fat spectrum consisted of multiple peaks that interfered with each other, as well as water, and made the PDFF incorrect. Multiple spectral models are required to address these multifrequency effects[45].

Main technical factors-ROI: It is recommended to select one to three ROIs *per* Couinaud segment, with the first ROI in each segment as centrally as possible and the remaining two on the same slice. ROI placement on the source images must avoid vessels, artifacts, and the edge of the liver.

Main technical factors-advantages: Multipoint Dixon imaging can be completed within a single breath-hold[46]. MRI-PDFF calculation used both the phase and magnitude data of the MR signal to measure the fat concentration in the range of 0%–100%[47]. The field strength and imaging manufacturer had negligible effects on the measurements[48].

Main technical factors-disadvantages: The accuracy of MRI-PDFF measurements is affected by fibrosis and severe steatosis[49]. The correlation between liver biopsy findings and MRI-PDFF was weaker in patients with moderate or severe hepatic steatosis than in those with milder forms[50].

Diagnostic performance: The sensitivity and specificity of MRI-PDFF were 83% and 89% for LS ≥ G2, and 79% and 89% for LS = G3, respectively[12]. An excellent correlation (r = 0.96–0.984)[28,51,52] with ^{1}H-MRS has also been shown and confirmed by a previous meta-analysis (r = 0.96)[48].

DISCUSSION

MR techniques have emerged as reliable tools for the noninvasive estimation of hepatic fat content. This systematic review compared three common MR techniques: ^{1}H-MRS, two-point Dixon imaging, and multiple-point Dixon imaging. These techniques have the same basic physical principles based on the chemical shift between the main peak of fat and that of water[33].

Before 2012, many studies used ^{1}H-MRS and two-point Dixon imaging to measure hepatic fat content. The liver SFF calculated from ^{1}H-MRS was not affected by iron deposition, fibrosis, or coexisting pathology, and provided accurate quantification of liver fat[19,53], especially MRS-PDFF[20]. Therefore, ^{1}H-MRS is commonly used as a reference for other imaging techniques to measure hepatic fat content. However, expensive and complex post-processing procedures as well as only providing accurate data of liver fat content from small parenchymal regions, especially single-voxel ^{1}H-MRS, hampered its widespread clinical application. Moreover, ^{1}H-MRS is not available at every institution. Chemical shift MR imaging can visualize the regional distribution of intrahepatic lipids. The IP and OP images derived from the two-point Dixon technique are simple approaches. This technique requires several data sets with different TEs to calculate the fat content, which contains T1 and T2* effects; therefore, it evaluates the hepatic fat content inaccurately, especially for livers with less than 5% fat[39]. Springer[54] used additional individual time-consuming T1 and T2* measurements to correct the measured intrahepatic lipids; however, most measurements are not applicable in time-restricted examination protocols. This method also measures liver fat concentration within the dynamic range of 0%–50%[18].

Aside from measuring the liver fat concentration in the range of 0%–100%, the PDFF derived from multiple-point Dixon imaging mitigates confounding factors, such as T1, T2*, lipid spectral complex, noise, and eddy current, and has been successfully applied to quantify liver fat. It has been extensively used for detecting and grading hepatic steatosis, especially for differentiating moderate/severe steatosis from mild/no hepatic steatosis[55] accurately. This is due to its good correlation with histopathology and ^{1}H-MRS measurements[12,56] as well as the shorter acquisition time compared with MRS[3,10,12,28,57]. Concurrent with PDFF acquisition, an R2* (1/T2*) map might also be formed, which could measure the iron concentration in the liver[58]. Additionally, PDFF was independent of field strength,

scanner platform, and specific scanning parameters. However, this method yields a slightly higher hepatic fat content than liver histology[59] and the accuracy of measurements could be affected by fibrosis and severe steatosis. It lacked the power to detect the changes in non-alcoholic fatty liver disease (NAFLD) such as inflammation or fibrosis[13,47].

Recent studies have also shown that MR elastography and T1-T2 mapping can be useful in detecting hepatic inflammatory and fibrotic changes[13,60,61]. Therefore, the multiparametric MRI protocol may be helpful in liver tissue characterization and in risk stratification and therapeutic management of patients with NAFLD.

How do we choose each technique in daily practice? For epidemiological studies, MR and CT are unsuitable because of the expensive and time-consuming nature of MR and radiation damage from CT. Here, ultrasound is preferred. For clinical studies, especially follow-up or assessment of treatment efficacy, two-point Dixon and multiple-point Dixon imaging are preferred because of their subjective and robust characteristics. However, CT can be selected for shorter follow-up in primary or secondary care where there is no MR machine. MRS is the most accurate noninvasive technique and is a good standard in research studies, although its accuracy depends on expertise and the result is difficult to explain. Multiparametric MRI protocols, including MR elastography and T1-T2 mapping may be useful for stratification and therapeutic management of patients with NAFLD.

This study has several limitations. First, this review may have potential publication bias because gray literature and non-English language literature were not retrieved. Second, the overall moderate and high risks of bias in the ^{1}H-MRS, two-point Dixon imaging, and multiple-point Dixon imaging groups were 50%, 45.5%, and 66.7%, respectively. Therefore, qualitative methods other than quantitative synthesis were used. The diagnostic accuracy of each method requires further investigation through a meta-analysis. Third, less commonly used methods for quantitative analysis of hepatic fat content were not included in this review. These include fat-selective imaging with spectral-spatial excitation, which requires a homogenous static magnetic field for optimal spectral-spatial excitation and is relatively sensitive to breathing artifacts[54,62].

CONCLUSION

PDFF derived from multiple-point Dixon imaging is a noninvasive method that provides an accurate, quantitative measurement of hepatic fat content. It can be used clinically to diagnose fatty liver and follow-up the progression of the disease and treatment effect.

ARTICLE HIGHLIGHTS

Research background

Fatty liver can cause hepatocyte injury, inflammation, fibrosis, and eventually cirrhosis, with a high risk for liver failure and hepatocellular carcinoma. Early quantitative assessment of liver fat content is essential for patients with fatty liver disease.

Research motivation

Mounting evidence has shown that magnetic resonance (MR) technique has high accuracy in the quantitative analysis of fatty liver disease. However, many packaging methods and postprocessing functions have puzzled radiologists in clinical applications. Hence, selecting quantitative MR imaging (MRI) for patients with fatty liver disease is challenging.

Research objectives

To provide information for the proper selection of commonly used quantitative MR techniques to quantify fatty liver.

Research methods

A systematic review of the literature from 1983 to May 2021 using PubMed, Embase, and Cochrane Library was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Research results

A total of 114 articles were included, including 35 articles on MR techniques for measurement of hepatic fat content, 39 articles on reviews and meta-analysis, and 40 studies for further qualitative analysis. Because the overall moderate and high risk of bias in the 40 studies was approximately 50.0%, qualitative synthesis other than quantitative synthesis was used in this systematic review. The principle, main technical factors, advantages, and disadvantages of ^{1}H-MR spectroscopy, two-point Dixon

imaging, and multiple-point Dixon imaging, as well as their clinical diagnostic performance were summarized and analyzed.

Research conclusions

Proton density fat fraction (PDFF) derived from multiple-point Dixon imaging is a noninvasive method that provides an accurate, quantitative measurement of hepatic fat content.

Research perspectives

The accuracy of the PDFF derived from multiple-point Dixon imaging can be affected by fibrosis and severe steatosis. Therefore, the multiparametric MRI protocol might be helpful in liver tissue character-ization and thereby in the risk stratification and therapeutic management of patients with non-alcoholic fatty liver disease.

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FOOTNOTES

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