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MAGNETIC RESONANCE

Diagnostic value of MRI-PDFF for hepatic steatosis in patients with non-alcoholic fatty liver disease: a meta-analysis

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Abstract

Objective To systematically review studies about the diagnostic accuracy of magnetic resonance imaging proton density fat fraction (MRI-PDFF) in the classification of hepatic steatosis grade in patients with non-alcoholic fatty liver disease (NAFLD).

Methods Areas under the summary receiver operating characteristic curves (AUROC), sensitivity, specificity, overall diagnostic odds ratio (DOR), diagnostic score, positive likelihood ratio (+LR), and negative likelihood ratio (−LR) for MRI-PDFF in classification of steatosis grades 0 vs. 1–3, 0–1 vs. 2–3, and 0–2 vs. 3 were compared and analyzed.

Results A total of 6 studies were included in this meta-analysis ($n = 635$). The summary AUROC values of MRI-PDFF for classifying steatosis grades 0 vs. 1–3, 0–1 vs. 2–3, and 0–2 vs. 3 were 0.98, 0.91, and 0.90, respectively. Pooled sensitivity and specificity of MRI-PDFF for classifying steatosis grades 0 vs. 1–3, 0–1 vs. 2–3, and 0–2 vs. 3 were 0.93 and 0.94, 0.74 and 0.90, and 0.74 and 0.87, respectively. Summary +LR and −LR of MRI-PDFF for classifying steatosis grades 0 vs. 1–3, 0–1 vs. 2–3, and 0–2 vs. 3 were 16.21 (95%CI, 4.72–55.67) and 0.08 (95%CI, 0.04–0.15), 7.19 (95%CI, 5.04–10.26) and 0.29 (95%CI, 0.22–0.38), and 5.89 (95%CI, 4.27–8.13) and 0.29 (95%CI, 0.21–0.41), respectively.

Conclusions Our meta-analysis suggests that MRI-PDFF has excellent diagnostic value for assessment of hepatic fat content and classification of histologic steatosis in patients with NAFLD.

Key Points

- *MRI-PDFF has significant diagnostic value for hepatic steatosis in patients with NAFLD.*
- *MRI-PDFF may be used to classify grade of hepatic steatosis with high sensitivity and specificity.*

Keywords NAFLD · Magnetic resonance imaging · Meta-analysis

Jiulian Gu and Shousheng Liu contributed equally to this work.

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Abbreviations

95%CI	95% confidence interval
ARFI	Acoustic radiation force impulse
AUROC	Areas under summary receiver operating characteristic curves
BMI	Body mass index
CAP	Controlled attenuation parameter
CRN	Clinical Research Network
DOR	diagnostic odds ratio
ElastPQ	Elastography point quantification
HCC	Hepatocellular carcinoma
LR	Likelihood ratio
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
PDFF	Proton density fat fraction
pSWE	Point shear wave elastography

QUADAS	Quality assessment of diagnostic accuracy studies
ROC	Receiver operating characteristic
TE	Transient elastography

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease affecting approximately 20–30% of adults and 10% of adolescents in western developed countries [1–3]. The condition is common in the Middle East, with a prevalence of 24.8% in Saudi Arabia and 23.7% in the United Arab Emirates [4]. NAFLD ranges from non-alcoholic fatty liver (NAFL) which is characterized as simple benign hepatic steatosis to non-alcoholic steatohepatitis (NASH), whose histologic features are macrovesicular steatosis, hepatocellular ballooning, lobular inflammation, and pericellular fibrosis. NASH can progress to the more severe fibrosis that is defined as the accumulation of extracellular matrix proteins in the liver interstitial space, cirrhosis (characterized as the histological development of regenerative nodules surrounded by fibrous bands), and even the hepatocellular carcinoma (HCC) [5–9]. Biopsy remains the diagnostic gold standard for NAFLD. However, biopsy is invasive in nature and operator dependent. These characteristics, in addition to the relatively small portion of tissue biopsied, limit its utility as a population-screening tool for longitudinal clinical trials or clinical monitoring in early-stage disease [10–12]. Accurate and non-invasive methods for the clinical assessment of NAFLD are therefore urgently needed.

Hepatic steatosis is a significant feature of NAFLD and characterized as the excessive accumulation of triglyceride in the hepatocytes [13]. Steatosis is graded as 0, 1, 2, and 3 according to the hepatocellular fat proportion (< 5%, 5–33%, 33–66%, and > 66%) by the standardized NASH CRN histologic scoring system for NAFLD [14, 15]. In addition, hepatic steatosis combined with inflammation, steatohepatitis, liver cell injury (ballooning degeneration), and various degrees of fibrosis is the histological characteristic of NASH [16]. Computed tomography provides only a semi-quantitative estimate of liver fat content and is inconvenient to evaluate the fat content of whole liver [11]. Controlled attenuation parameter (CAP), derived from transient elastography, may be associated with severe fat accumulation. However, the accuracy of CAP is significantly decreased when body mass index (BMI) > 28 kg/m^2 [17, 18]. Magnetic resonance imaging proton density fat fraction (MRI-PDFF) is an accurate and highly sensitive method for the measurement of steatosis throughout the liver. This technique can accurately detect even 5% microscopic steatosis [19–22]. One study conducted by Bannas et al validated the accuracy of MRI-PDFF in determining the concentration of triglycerides in ex vivo human livers [23]. In a single-center study, Tang et al showed that PDFF was associated with histologic steatosis grade of 0 vs. 1; in this context, PDFF demonstrated a sensitivity of 68% and specificity of 98% [24]. Recently, MRI-PDFF had been used as a reference to evaluate the accuracy of conventional ultrasonography in the assessment of hepatic steatosis [25]. Loomba et al also used MRI-PDFF as the diagnostic reference of hepatic steatosis in investigating the effects of GS-0976 on hepatic steatosis [26]. Some researchers have used MRI-PDFF to measure fat content in other organs and tissues such as the pancreas, kidney, and bone marrow of NAFLD patients [27–29]. The diagnostic value of MRI-PDFF was also validated in animal models such as fish and mice [30, 31].

Although MRI-PDFF had been used to evaluate hepatic steatosis in some studies, the number of patients included in such studies has been relatively small, and the overall performance of MRI-PDFF in grading histologic steatosis in NAFLD was inconsistent. Therefore, we conducted this meta-analysis to evaluate the diagnostic accuracy of MRI-PDFF in histologic grading of steatosis in patients with NAFLD.

Materials and methods

Search strategy

The aim of our study was to identify published studies that investigated the diagnostic accuracy of MRI-PDFF in the assessment of hepatic steatosis and classification of steatosis grades 0 vs. 1–3, 0–1 vs. 2–3, and 0–2 vs. 3. A systematic literature search was performed in PubMed, EMBASE, and the Cochrane library until September 2018. The search terms used in this search were as follows: MRI-PDFF, MRI-based proton density fat fraction, Non-alcoholic fatty liver disease, nonalcoholic fatty liver disease, fatty liver, nonalcoholic, non-alcoholic fatty livers, nonalcoholic fatty liver, nonalcoholic steatohepatitis, and steatohepatitis. Only articles written in English were included.

Selection and exclusion criteria

Studies were included if they met the following inclusion criteria: (1) The study assessed the diagnostic value of MRI-PDFF for the prediction and classification of steatosis grade in NAFLD patients. Studies could also be included while the data for NAFLD was available even if the patients have combined other liver diseases. (2) Pathological examination was used as the reference standard for assessing the grade of steatosis. (3) Information included in the studies should be able to construct at least one 2 × 2 table to test the performance of MRI-PDFF for steatosis grade with the threshold. (4) The study included at least 30 patients. (5) The study must be full-text articles to achieve adequate data. Review articles, case

reports, and conference abstracts were excluded because of insufficient/inadequate data.

Grading of hepatic steatosis

All the studies included in this meta-analysis defined hepatic steatosis grade as 0, 1, 2, and 3 which are corresponding to the steatosis affecting < 5%, 5–33%, 33–66%, and > 66% by the standardized NASH CRN histologic scoring system for NAFLD [14]. In each included study, images of the entire liver were obtained using a standard torso-phased array coil centered over the liver. Parameters were selected to correct for or avoid confounding factors such as T1 bias, T2* decay, or multi-frequency interference. The differences of sensitivity, specificity, ROC plot, and diagnostic odds ratio (DOR) values between each grade were compared, respectively. So, we summarized the overall sensitivity, specificity, ROC plot, and DOR values of each grade in this meta-analysis.

Data extraction and quality assessment

Two investigators (Gu and Liu) independently carried out data extraction and evaluated the study eligibility and quality. Consensuses regarding the differences of opinion were reached after discussion or by consultation with another investigator. For each study, author, year of publication, region where the study was performed, and methodology were recorded. The detailed information of MRI devices in the 6 studies was also recorded. The following data related to the diagnostic value of MRI-PDFF were extracted: threshold for classification of steatosis stage, sensitivity, specificity, and ROC values. Moreover, histological scoring system and average liver biopsy length were also included. Quality Assessment of Diagnostic Accuracy Studies (QUADAS) questionnaire was used to assess the quality of the studies included in our study [32].

Statistical analysis and data synthesis

Available data were used to construct 2 × 2 tables for each included study. Areas under the summary receiver operating characteristic curves (AUROC), summary sensitivity and specificity, +LR, and −LR were calculated with Meta-Disc software (version 1.4). Stata 12.0 software (StataCorp) was used to evaluate the overall diagnostic performance of MRI-PDFF in distinguishing stages of hepatic steatosis. Besides, the summary DOR was also used to examine the diagnostic accuracy of MRI-PDFF; data were presented with 95%CI. When the AUROC is 100%, the diagnostic tool was defined as perfect, greater than 90% as excellent, and greater than 80% as good. In addition, a 0.5 value was automatically added to all cells with 0 for adjustment. The heterogeneity of accuracy estimates across studies was explored with the I^2 statistic. Values of $I^2 > 50\%$ were considered to represent substantial heterogeneity. To detect the possible publication bias, a linear regression analysis of asymmetry funnel plot visualized on a Deeks plot was conducted.

Results

Study characteristics

A total of 80 studies were yielded with the search strategies as described above. After removing duplications ($n = 2$), 78 records remained for evaluation. In all, 72 studies were excluded for the following reasons: relevant to treatment, review and only abstract, animal studies, other human organs or tissues, insufficient data, or failure to use biopsy as the reference standard (Fig. 1). The final dataset for the meta-analysis comprised 6 studies [15, 24, 33–36].

The main features of the 6 studies included in this meta-analysis were shown in Table 1, and a total of 635 patients

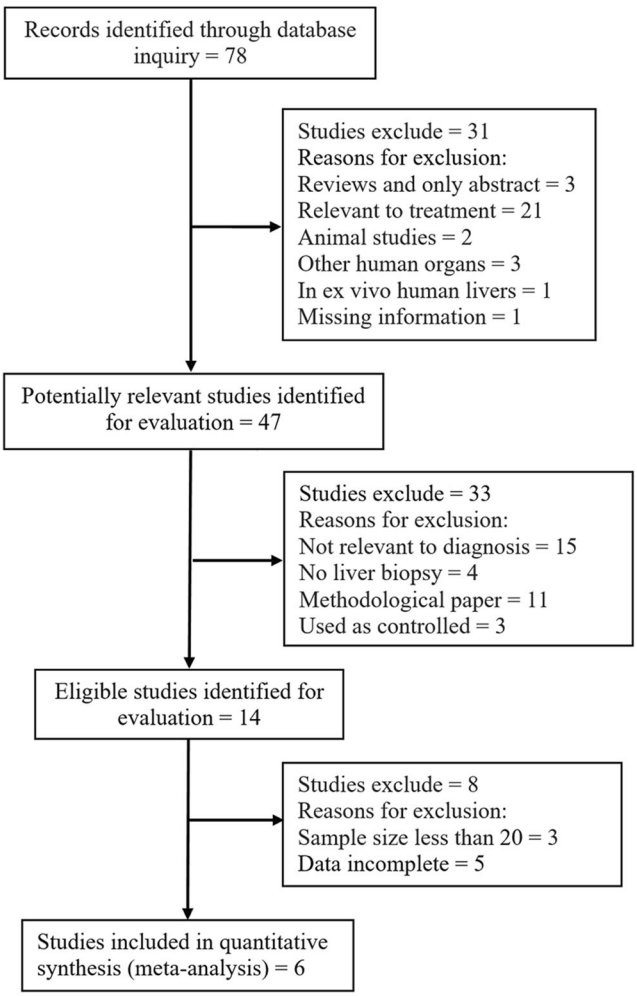

Fig. 1 The study demonstration

Table 1 Features of the 6 studies included in this meta-analysis

Author, year, region	Study/center description	Number	Adults/ children	Interval between biopsy and MRI PDFF	Median/mean age (year) (% male)	Etiology	Liver biopsy scoring system	Blind	Liver biopsy Median length	Steatosis stage			
										0	1	2	3
Charlie et al, 2017, USA	Prospective, tertiary center	104	A	42 days	50.8 ± 14.6 (43.3%)	NAFLD	NASH Clinical Research Network Histologic Scoring System	Yes	Unclear	9	49	29	16
Michael et al, 2018, USA	Prospective, multicenter	110	C	Mean 61 days	13 ± 3 (70.9%)	NAFLD	NASH CRN histologic NAFLD scoring system	Yes	Unclear	0	19 (17%)	31 (28%)	60 (55%)
Michael et al, 2017, USA	Prospective, multicenter	113	A	51 days	51 ± 11 (38%)	NASH	NASH CRN histologic NAFLD scoring system	Yes	–	0	38	44	31
Kento et al, 2016, Japan	Cross-sectional	142	A	< 6 months	57.5 ± 14.6 (57%)	NAFLD+ NASH	NASH CRN histologic NAFLD scoring system	Yes	> 20 mm in length and/or with > 10 portal tracts	0	59	59	24
Tang et al, 2015, USA	Prospective, cross-sectional, single-center	89	A	< 6 months (from 0 to 173 days) (median, 35 days)	51.0 ± 13.0 (43%)	NAFLD	NASH CRN histologic NAFLD scoring system	Yes	–	6	39	30	14
Tang et al, 2013, USA	prospective, cross-sectional, single-site study	77	12 A + 65 C	0 to 173 days (median, 11 days)	14 (8–61) (79.2%)	NAFLD	NASH CRN histologic NAFLD scoring system	Yes	15.6 ± 5.9 mm	5 (6.5%)	26 (33.8%)	27 (35.1%)	19 (24.7%)

Table 2 Quality assessment of included studies

Author, year, region	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14
	Spectrum composition	Selection criteria	Appropriate reference standard	Disease progression bias	Partial verification bias	Differential verification bias	Incorporation bias	Test execution details	Reference execution details	Test review bias	Diagnostic review bias	Clinical review bias	Intermediate results	Withdrawals
1. Charlie C. Park, 2017, USA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
2. Michael S. Iddleton, 2017, USA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Michael S, 2017, USA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Kento Imajo, 2016, Japan	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
5. An Tang, 2015, USA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. An Tang, 2013, USA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

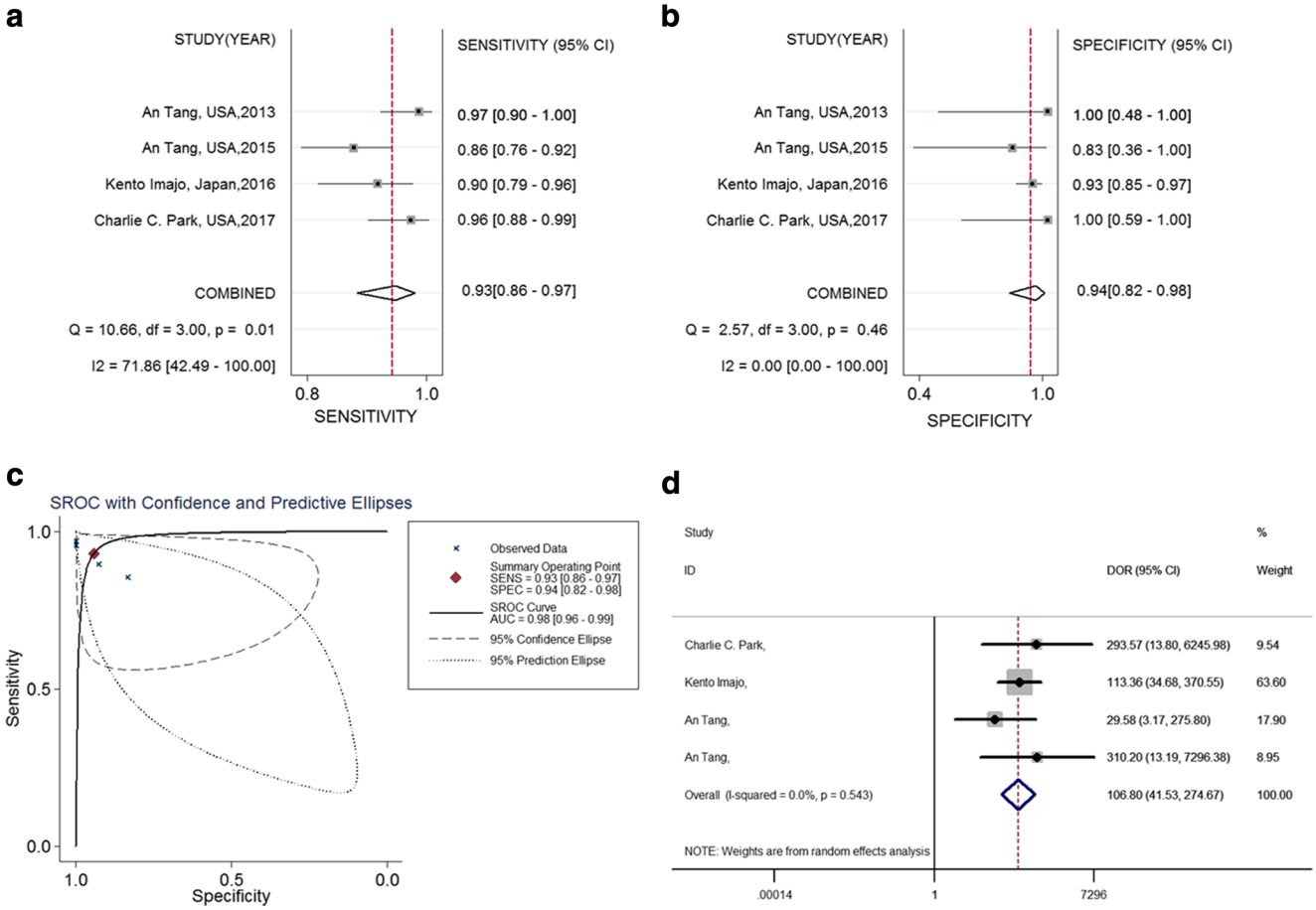

Fig. 2 Summary sensitivity, specificity, ROC plot, and DOR values of the MRI PDFF for the classification of steatosis 0 vs. 1–3. **a**, **b** The pooled sensitivity and specificity were 0.93 (0.86–0.97) and 0.94 (0.82–0.98), respectively. **c** The summary AUROC value was 0.98 (0.96–0.99). **d** The overall DOR is 106.80 (95%CI: 41.53–274.67)

(median age 41.35 years; 53.6% male) were included. Among the 6 studies included, the overall prevalence of steatosis stage 0, 1, 2, or 3 was 3.15% (range, 0–8.65%), 36.22% (range, 17.27–47.12%), 34.65% (range, 27.88–41.55%), and 25.83% (range, 15.38–54.55%), respectively. The Nonalcoholic Steatohepatitis Clinical Research Network Scoring System was used to assess steatosis grade in all 6 studies. Besides, the methodological quality of the included studies was excellent according to the QUADAS scale which evaluated by the two investigators (Gu and Liu) (Table 2). The

Table 3 Summary sensitivities and specificities of the MRI PDFF at various thresholds for the classification of histologic steatosis

	Thresholds (%)	Number of studies (patients)	Summary sensitivity	Summary specificity
0 vs. 1–3	3.71	1 (104)	0.96	1
	5.20	1 (142)	0.90	0.93
	6.40	2 (166)	0.91	0.91
0–1 vs. 2–3	13.03	1 (104)	0.80	0.83
	17.50	1 (110)	0.74	0.90
	16.30	1 (113)	0.83	0.90
	11.30	1 (142)	0.79	0.84
	17.40	2 (166)	0.62	0.93
0–2 vs. 3	16.37	1 (104)	0.82	0.84
	23.30	1 (110)	0.60	0.90
	21.70	1 (113)	0.84	0.90
	17.10	1 (142)	0.74	0.81
	22.10	2 (166)	0.70	0.92

Table 4 Summary sensitivity, specificity, and ROC plot of the MRI-PDFF in detecting liver fat content

	Number of studies (patients)	Summary sensitivity (95%CI)	Summary specificity (95%CI)	Summary +LR (95%CI)	Summary −LR (95%CI)	Summary AUROC	Summary DOR (95%CI)	Diagnostic score (95%CI)
0 vs. 1–3	4 (412)	0.93 (0.86–0.97)	0.94 (0.82–0.98)	16.21 (4.72–55.67)	0.08 (0.04–0.15)	0.98	106.80 (41.53–274.67)	5.38 (3.69–7.06)
0–1 vs. 2–3	4 (635)	0.74 (0.66–0.80)	0.90 (0.85–0.93)	7.19 (5.04–10.26)	0.29 (0.22–0.38)	0.91	25.19 (15.13–41.95)	3.21 (2.73–3.69)
0–2 vs. 3	4 (635)	0.75 (0.64–0.82)	0.87 (0.83–0.91)	5.89 (4.27–8.13)	0.29 (0.21–0.41)	0.90	20.21 (12.17–33.56)	3.00 (2.48–3.51)

detailed information of MRI devices in the 6 studies was summarized in supplementary Table 1.

Diagnostic accuracy of MRI-PDFF for classification of steatosis 0 vs. 1–3

The performance of MRI-PDFF for the classification of steatosis 0 vs. 1–3 was examined in a total of 4 studies (412 patients). The average prevalence of steatosis 1–3 in these studies was 95.15% (from 91.35 to 100%). The summary AUROC values using MRI-PDFF for classification of steatosis 0 vs. 1–3 was 0.98 (0.96–0.99) (Fig. 2). The diagnostic score of MRI-PDFF was 5.38 (3.69–7.06); the overall DOR of MRI-PDFF is 106.80 (95%CI, 41.53–274.67). No significant heterogeneity was observed in the analysis of steatosis 0 vs. 1–3 ($Q = 0.007$, $I^2 = 0$). The sensitivity and specificity of MRI-PDFF for the identification of steatosis 1–3, at various thresholds, are presented in Table 3. The pooled sensitivity and specificity of the 4 studies using MRI-PDFF for the classification of hepatic steatosis is 0.93 (0.88–0.95) and 0.94 (0.82–0.98), respectively (Table 4). Besides, the summary +LR is 16.21 (95%CI, 4.72–55.67) ($Q = 2.32$, $I^2 = 0$), and the summary −LR is 0.08 (95%CI, 0.04–0.15) ($Q = 9.41$, $I^2 = 68.13$) (Table 4).

Diagnostic accuracy of MRI-PDFF for classification of steatosis 0–1 vs. 2–3

The performance of MRI-PDFF for the classification of steatosis 0–1 vs. 2–3 was examined in all 6 included studies (635 patients). The average prevalence of steatosis 0–1 in these studies was 39.37% (range, 17.27–55.77%), and the average prevalence of steatosis 2–3 in these studies was 60.47% (range, 43.27–82.73%). The summary AUROC values using MRI-PDFF for classification of steatosis 0–1 vs. 2–3 was 0.91 (0.88–0.93) (Fig. 3); the overall DOR of MRI-PDFF was 25.19 (95%CI, 15.13–41.95), and the diagnostic score of MRI-PDFF was 3.21 (2.73–3.69). The analysis of steatosis 0 vs. 1–3 revealed no significant heterogeneity ($Q = 2.102$, $I^2 = 4.86$). The pooled sensitivity and specificity of the 6 studies using MRI-PDFF for the identification of steatosis is 0.74 (95%CI, 0.66–0.80) and 0.90 (95%CI, 0.85–0.93). Besides, the summary +LR is 7.19 (95%CI, 5.04–10.26) ($Q = 3.62$, $I^2 = 0$), and the summary −LR is 0.29 (95%CI, 0.22–0.38) ($Q = 8.8$, $I^2 = 43.2$) (Table 4).

Diagnostic accuracy of MRI-PDFF for classification of steatosis 0–2 vs. 3

The performance of MRI-PDFF for the classification of steatosis 0–2 vs. 3 was examined in all 6 studies (635 patients). In these studies, the average prevalence of steatosis 0–2 was 74.02% (range, 45.45–84.27%); the average

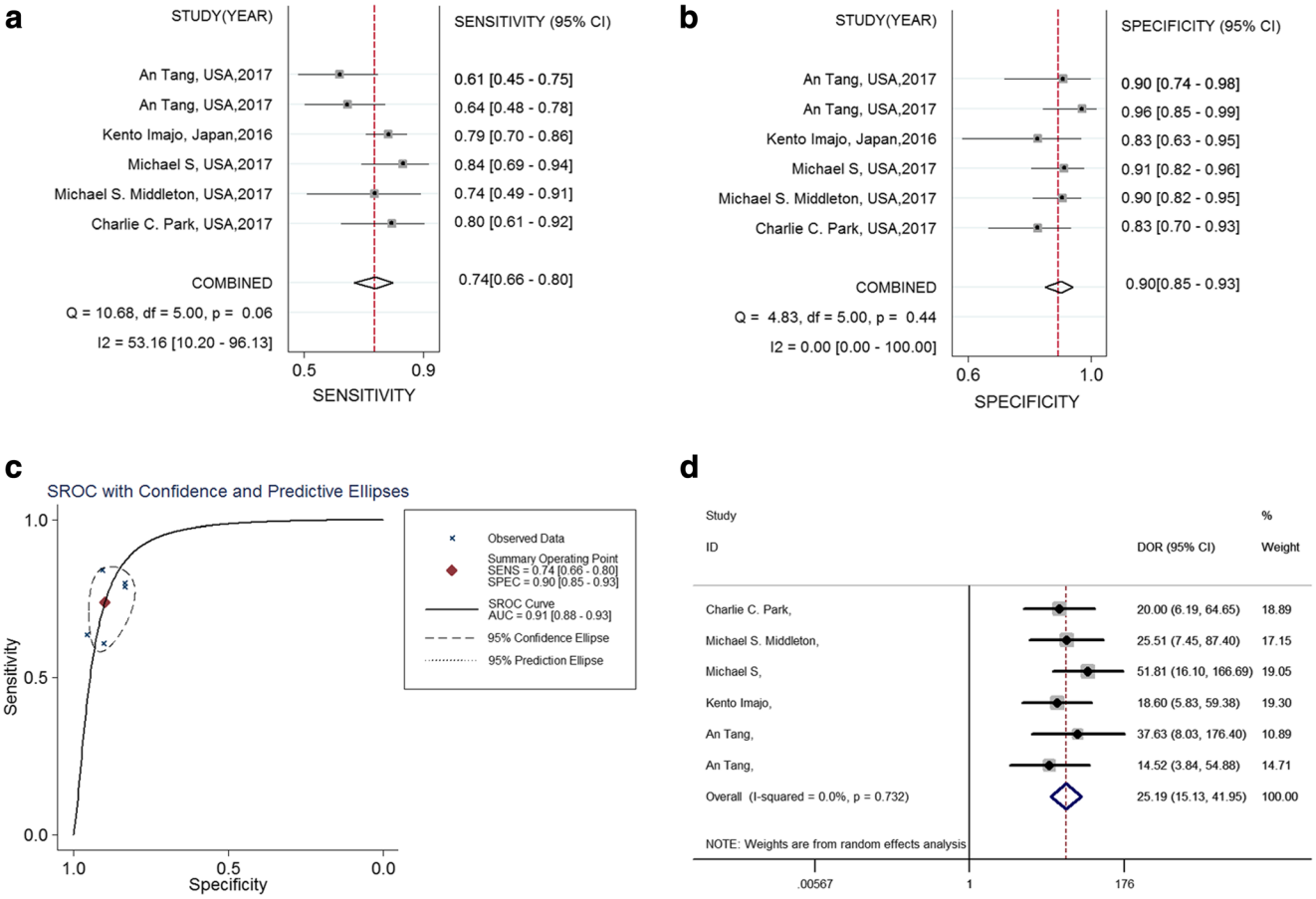

Fig. 3 Summary sensitivity, specificity, ROC plot, and DOR values of MRI PDFF for the classification of steatosis 0–1 vs. 2–3. **a**, **b** The pooled sensitivity and specificity were 0.74 (0.66–0.80) and 0.90 (0.85–0.93), respectively. **c** The summary AUROC value was 0.91 (0.88–0.93). **d** The overall DOR is 25.19 (95%CI: 15.13–41.95)

prevalence of steatosis 3 was 25.83% (range, 15.38–54.55%). The summary AUROC values using MRI-PDFF for classification of steatosis 0–2 vs. 3 was 0.90 (0.87–0.92) (Fig. 4). The overall DOR for MRI-PDFF is 20.21 (12.17–33.56), and the diagnostic score for MRI-PDFF was 3.00 (2.48–3.51). Analysis of steatosis 0–2 vs. 3 revealed no significant heterogeneity ($Q = 2.12$, $I^2 = 5.51$). The pooled sensitivity and specificity of these 6 studies using MRI PDFF for the identification of steatosis is 0.74 (0.64–0.82) and 0.87 (0.83–0.91) (Table 3). Besides, the summary +LR is 5.89 (95%CI, 4.27–8.13) ($Q = 5.25$, $I^2 = 0$), and the summary −LR is 0.29 (95%CI, 0.21–0.41) ($Q = 9.53$, $I^2 = 47.54$) (Table 4).

Discussion

This meta-analysis included 6 original articles (635 patients) with sufficient data for an investigation of the diagnostic performance of MRI-PDFF in the classification of steatosis. In these studies, hepatic steatosis of all the patients was evaluated by liver biopsy. The AUROC values of MRI-PDFF methods in different stages of steatosis were evaluated; the summary AUROC values of MRI-PDFF for the classification of steatosis grades 0 vs. 1–3, 0–1 vs. 2–3, and 0–2 vs. 3 were 0.98, 0.91, and 0.90, respectively. No heterogeneity was observed in all the analysis, indicating that the data extracted from the 6 studies were comparable. The overall DOR at each steatosis grade was > 1, suggesting that MRI-PDFF may be used to accurately stage hepatic steatosis. The sensitivity and specificity of MRI-PDFF under the cutoff values corresponding to various grades of steatosis showed that a higher cutoff value was associated with more severe hepatic steatosis. The higher pooled sensitivities and specificities and the summary +LR and −LR of MRI-PDFF for hepatic steatosis grade indicated a high veracity of the diagnostic results.

NAFLD is a prevalent chronic liver disease that may progress to cirrhosis and/or hepatocellular carcinoma. The representative feature of NAFLD is hepatic fat accumulation, which is associated with obesity and other metabolic diseases and may interfere with liver transplantation [37–39]. Because no effective therapies and medicines are available at present, patients with NAFLD require an early diagnosis to begin the appropriate dietary modifications. Biopsy as the golden standard for identifying the hepatic steatosis, limited by the defect

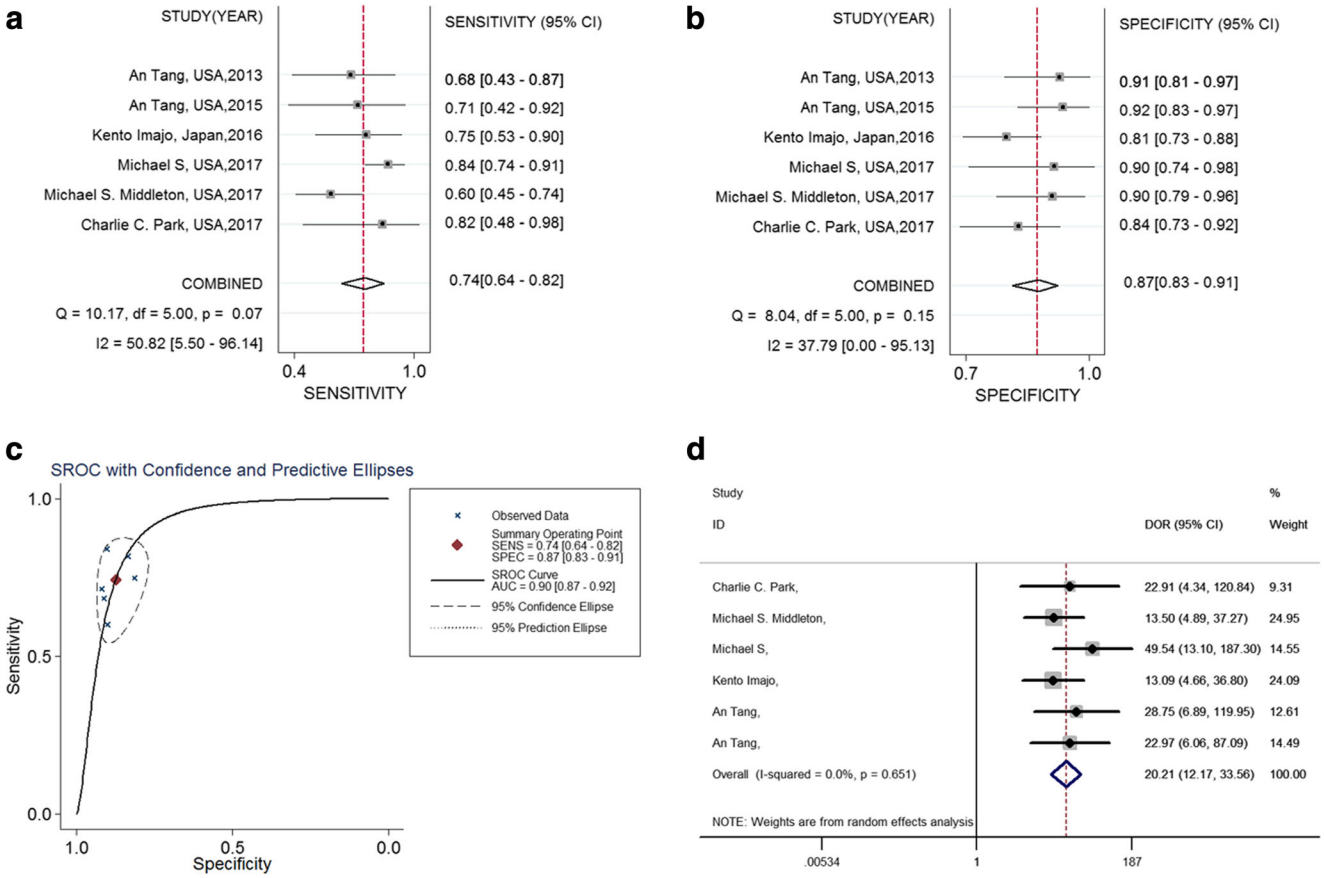

Fig. 4 Summary sensitivity, specificity, ROC plot, and DOR values of the MRI PDFF for the classification of steatosis 0-2 vs. 3. **a**, **b** The pooled sensitivity and specificity were 0.74 (0.64–0.82) and 0.87 (0.83–0.91), respectively. **c** The summary AUROC value was 0.90 (0.87–0.92). **d** The overall DOR is 20.21 (95%CI: 12.17–33.56)

such as invasive, easy to sample error, and operator dependent [11, 40]. With the emergence of numerous studies referred to the non-invasive methods for the detection of hepatic steatosis in NAFLD patients, MRI-PDFF received more attention due to the high accuracy for evaluation of steatosis grade. Previous studies have shown that MRI-PDFF was superior to TE technology in quantifying liver fat content in NAFLD patients; one of the advantages of MRI-PDFF is the larger measured area of liver and reduced sampling variability [11, 15, 41]. In addition, the 3-Tesla magnetic resonance imaging had been used to measure the liver iron concentration, which is tightly associated with the pathological conditions of the liver [42]. Compared with MRI-PDFF, ^{1}H MR spectroscopy (MRS) requires sophisticated processing after diagnosis. Furthermore, common MRI scanners may not have the capability for MRS [43–45]. In our study, the summary AUROC values of MRI-PDFF in the classification of steatosis grades 0 vs. 1–3, 0–1 vs. 2–3, and 0–2 vs. 3 were significantly higher, similar to the previous individual study which was conducted by Charlie et al [15]. In addition, we found that the overall sensitivity and specificity were decreased with the increased liver fat content, which implied the lower accuracy of MRI-PDFF in patients with severe hepatic steatosis. Noureddin et al found that MRI-PDFF was more sensitive than histological examination in detecting small changes in liver fat content [46]. This finding is in line with the results of our meta-analysis.

Although MRI-PDFF exhibits higher accuracy in diagnosing hepatic steatosis in most cases, the application of MRI-PDFF in patients with NASH, fibrosis, inflammation that induced by the injured steatotic hepatocytes, and who were too obese to fit into the MRI scanner was limited accordingly [47]. Another non-invasive diagnostic method, acoustic radiation force impulse (ARFI), has several advantages over transient elastography (TE), including greater accuracy, and has been used in the diagnostic of liver steatosis, fibrosis, and liver stiffness [48–50]. Elastography point quantification (ElastPQ) is an ARFI-based point shear wave elastography (pSWE) technique that had been used in the diagnosis of fibrosis and liver stiffness [51–55]. In view of the significant diagnostic value of ARFI and ElastPQ in NASH, fibrosis, and liver stiffness, more attention should be paid to the utility of MRI-PDFF, ARFI, and ElastPQ in the diagnosis of different grades of NAFLD.

Our meta-analysis had several limitations. First, the number of studies that met our inclusion criteria was relatively small. The number of patients who underwent MRI-PDFF

for the classification of hepatic steatosis grade with liver biopsy as a reference standard was relatively small. This may have decreased the diagnostic accuracy of MRI-PDFF. Secondly, we did not compare children and adults in terms of the diagnostic accuracy of MRI-PDFF in predicting hepatic steatosis grade because of insufficient data. Thirdly, hepatic iron content was a confounding factor which may have affected the likelihood of diagnosis with hepatic steatosis [56, 57]. However, it was not possible to examine the influence of hepatic iron in the classification of hepatic steatosis because of insufficient data. Finally, because this meta-analysis included only studies written in English, language bias and publication bias may have influenced the results.

In summary, our meta-analysis suggests that MRI-PDFF is an accurate non-invasive diagnostic method for the classification of hepatic steatosis grade in patients with NAFLD. Future studies should focus on improving MRI-PDFF sufficiently for this technique to replace invasive methods of detection.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Yongning Xin.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry Qing Zhang as an expert in statistics and radiology, who worked at Qingdao Municipal Hospital, gave us much guidance of statistics and biometry.

Informed consent Written informed consent was not required for this study because this study was a meta-analysis.

Ethical approval Institutional Review Board approval was not required because this study was a meta-analysis.

Methodology
- Retrospective
- Multicenter study

References

1. Loomba R, Sanyal AJ (2013) The global NAFLD epidemic. Nat Rev Gastroenterol Hepatol 10:686–690
2. Bellentani S, Scaglioni F, Marino M, Bedogni G (2010) Epidemiology of non-alcoholic fatty liver disease. Dig Dis 28:155–161
3. Schwimmer JB, Deutsch R, Kahen T, Lavine JE, Stanley C, Behling C (2006) Prevalence of fatty liver in children and adolescents. Pediatrics 118:1388–1393
4. Alswat K, Aljumah AA, Sanai FM et al (2018) Nonalcoholic fatty liver disease burden - Saudi Arabia and United Arab Emirates, 2017–2030. Saudi J Gastroenterol 24:211–219
5. Rinella ME (2015) Nonalcoholic fatty liver disease: a systematic review. Jama 313:2263–2273
6. Alexander J, Torbenson M, Wu TT, Yeh MM (2013) Non-alcoholic fatty liver disease contributes to hepatocarcinogenesis in non-cirrhotic liver: a clinical and pathological study. J Gastroenterol Hepatol 28:848–854
7. Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R (2015) Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. Clin Gastroenterol Hepatol 13:643–654 e641–649; quiz e639–640
8. Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ (2018) Mechanisms of NAFLD development and therapeutic strategies. Nat Med 24:908–922
9. Schuppan D, Afdhal NH (2008) Liver cirrhosis. Lancet 371:838–851
10. Cadranel JF (2002) [Good clinical practice guidelines for fine needle aspiration biopsy of the liver: past, present and future]. Gastroenterol Clin Biol 26:823–824
11. Bonekamp S, Tang A, Mashhood A et al (2014) Spatial distribution of MRI-determined hepatic proton density fat fraction in adults with nonalcoholic fatty liver disease. J Magn Reson Imaging 39:1525–1532
12. Merriman RB, Ferrell LD, Patti MG et al (2006) Correlation of paired liver biopsies in morbidly obese patients with suspected nonalcoholic fatty liver disease. Hepatology 44:874–880
13. Idilman IS, Ozdeniz I, Karcaaltincaba M (2016) Hepatic steatosis: etiology, patterns, and quantification. Semin Ultrasound CT MR 37:501–510
14. Kleiner DE, Brunt EM, Van Natta M et al (2005) Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 41:1313–1321
15. Park CC, Nguyen P, Hernandez C et al (2017) Magnetic resonance elastography vs transient elastography in detection of fibrosis and noninvasive measurement of steatosis in patients with biopsy-proven nonalcoholic fatty liver disease. Gastroenterology 152:598–607 e592
16. Hashimoto E, Taniai M, Tokushige K (2013) Characteristics and diagnosis of NAFLD/NASH. J Gastroenterol Hepatol 28(Suppl 4):64–70
17. Alisi A, Pinzani M, Nobili V (2009) Diagnostic power of fibroscan in predicting liver fibrosis in nonalcoholic fatty liver disease. Hepatology 50:2048–2049 author reply 2049-2050
18. Chan WK, Nik Mustapha NR, Mahadeva S (2014) Controlled attenuation parameter for the detection and quantification of hepatic steatosis in nonalcoholic fatty liver disease. J Gastroenterol Hepatol 29:1470–1476
19. Schwimmer JB, Middleton MS, Deutsch R, Lavine JE (2005) A phase 2 clinical trial of metformin as a treatment for non-diabetic paediatric non-alcoholic steatohepatitis. Aliment Pharmacol Ther 21:871–879
20. Reeder SB, Hu HH, Sirlin CB (2012) Proton density fat-fraction: a standardized MR-based biomarker of tissue fat concentration. J Magn Reson Imaging 36:1011–1014
21. Reeder SB (2013) Emerging quantitative magnetic resonance imaging biomarkers of hepatic steatosis. Hepatology 58:1877–1880
22. Le TA, Chen J, Changchien C et al (2012) Effect of colesevelam on liver fat quantified by magnetic resonance in nonalcoholic steatohepatitis: a randomized controlled trial. Hepatology 56:922–932
23. Bannas P, Kramer H, Hernando D et al (2015) Quantitative magnetic resonance imaging of hepatic steatosis: validation in ex vivo human livers. Hepatology 62:1444–1455

24. Tang A, Tan J, Sun M et al (2013) Nonalcoholic fatty liver disease: MR imaging of liver proton density fat fraction to assess hepatic steatosis. Radiology 267:422–431
25. Kim M, Kang BK, Jun DW (2018) Comparison of conventional sonographic signs and magnetic resonance imaging proton density fat fraction for assessment of hepatic steatosis. Sci Rep 8:7759
26. Loomba R, Kayali Z, Noureddin M et al (2018) GS-0976 reduces hepatic steatosis and fibrosis markers in patients with nonalcoholic fatty liver disease. Gastroenterology
27. Patel NS, Peterson MR, Lin GY et al (2013) Insulin resistance increases MRI-estimated pancreatic fat in nonalcoholic fatty liver disease and normal controls. Gastroenterol Res Pract 2013:498296
28. Idilman IS, Tuzun A, Savas B et al (2015) Quantification of liver, pancreas, kidney, and vertebral body MRI-PDFF in non-alcoholic fatty liver disease. Abdom Imaging 40:1512–1519
29. Yu NY, Wolfson T, Middleton MS et al (2017) Bone marrow fat content is correlated with hepatic fat content in paediatric non-alcoholic fatty liver disease. Clin Radiol 72:425.e429–425.e414
30. Runge JH, Bakker PJ, Gaemers IC et al (2014) Measuring liver triglyceride content in mice: non-invasive magnetic resonance methods as an alternative to histopathology. MAGMA 27:317–327
31. Ueno T, Suzuki H, Hiraishi M, Amano H, Fukuyama H, Sugimoto N (2016) In vivo magnetic resonance microscopy and hypothermic anaesthesia of a disease model in Medaka. Sci Rep 6:27188
32. Schueler S, Schuetz GM, Dewey M (2012) The revised QUADAS-2 tool. Ann Intern Med 156:323 author reply 323-324
33. Imajo K, Kessoku T, Honda Y et al (2016) Magnetic resonance imaging more accurately classifies steatosis and fibrosis in patients with nonalcoholic fatty liver disease than transient elastography. Gastroenterology 150:626–637.e627
34. Middleton MS, Van Natta ML, Heba ER et al (2017) Diagnostic accuracy of magnetic resonance imaging hepatic proton density fat fraction in pediatric nonalcoholic fatty liver disease. Hepatology 67: 858–872
35. Middleton MS, Heba ER, Hooker CA et al (2017) Agreement between magnetic resonance imaging proton density fat fraction measurements and pathologist-assigned steatosis grades of liver biopsies from adults with nonalcoholic steatohepatitis. Gastroenterology 153:753–761
36. Tang A, Desai A, Hamilton G et al (2015) Accuracy of MR imaging-estimated proton density fat fraction for classification of dichotomized histologic steatosis grades in nonalcoholic fatty liver disease. Radiology 274:416–425
37. Vernon G, Baranova A, Younossi ZM (2011) Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther 34:274–285
38. Adams LA, Lindor KD (2007) Nonalcoholic fatty liver disease. Ann Epidemiol 17:863–869
39. Kim SH, Lee JM, Han JK et al (2006) Hepatic macrosteatosis: predicting appropriateness of liver donation by using MR imaging–correlation with histopathologic findings. Radiology 240:116–129
40. Fernandez-Salazar L, Velayos B, Aller R, Lozano F, Garrote JA, Gonzalez JM (2011) Percutaneous liver biopsy: patients' point of view. Scand J Gastroenterol 46:727–731
41. Ratziu V, Charlotte F, Heurtier A et al (2005) Sampling variability of liver biopsy in nonalcoholic fatty liver disease. Gastroenterology 128:1898–1906
42. d'Assignies G, Paisant A, Bardou-Jacquet E et al (2018) Non-invasive measurement of liver iron concentration using 3-Tesla magnetic resonance imaging: validation against biopsy. Eur Radiol 28:2022–2030
43. Reeder SB, Cruite I, Hamilton G, Sirlin CB (2011) Quantitative assessment of liver fat with magnetic resonance imaging and spectroscopy. J Magn Reson Imaging 34:729–749
44. Yokoo T, Shiehmorteza M, Hamilton G et al (2011) Estimation of hepatic proton-density fat fraction by using MR imaging at 3.0 T. Radiology 258:749–759
45. Di Martino M, Pacifico L, Bezzi M et al (2016) Comparison of magnetic resonance spectroscopy, proton density fat fraction and histological analysis in the quantification of liver steatosis in children and adolescents. World J Gastroenterol 22:8812–8819
46. Noureddin M, Lam J, Peterson MR et al (2013) Utility of magnetic resonance imaging versus histology for quantifying changes in liver fat in nonalcoholic fatty liver disease trials. Hepatology 58:1930–1940
47. Caussy C, Reeder SB, Sirlin CB, Loomba R (2018) Noninvasive, quantitative assessment of liver fat by MRI-PDFF as an endpoint in NASH trials. Hepatology 68:763–772
48. Friedrich-Rust M, Romen D, Vermehren J et al (2012) Acoustic radiation force impulse-imaging and transient elastography for non-invasive assessment of liver fibrosis and steatosis in NAFLD. Eur J Radiol 81:e325–e331
49. Cassinotto C, Boursier J, de Ledinghen V et al (2016) Liver stiffness in nonalcoholic fatty liver disease: a comparison of supersonic shear imaging, FibroScan, and ARFI with liver biopsy. Hepatology 63: 1817–1827
50. Woo H, Lee JY, Yoon JH, Kim W, Cho B, Choi BI (2015) Comparison of the reliability of acoustic radiation force impulse imaging and supersonic shear imaging in measurement of liver stiffness. Radiology 277:881–886
51. Ferraioli G, Tinelli C, Lissandrin R et al (2014) Point shear wave elastography method for assessing liver stiffness. World J Gastroenterol 20:4787–4796
52. Ma JJ, Ding H, Mao F, Sun HC, Xu C, Wang WP (2014) Assessment of liver fibrosis with elastography point quantification technique in chronic hepatitis B virus patients: a comparison with liver pathological results. J Gastroenterol Hepatol 29:814–819
53. Fraquelli M, Baccarin A, Casazza G et al (2016) Liver stiffness measurement reliability and main determinants of point shear-wave elastography in patients with chronic liver disease. Aliment Pharmacol Ther 44:356–365
54. Conti F, Serra C, Vukotic R et al (2017) Accuracy of elastography point quantification and steatosis influence on assessing liver fibrosis in patients with chronic hepatitis C. Liver Int 37:187–195
55. Mare R, Sporea I, Lupusoru R et al (2017) The value of ElastPQ for the evaluation of liver stiffness in patients with B and C chronic hepatopathies. Ultrasonics 77:144–151
56. Idilman IS, Aniktar H, Idilman R et al (2013) Hepatic steatosis: quantification by proton density fat fraction with MR imaging versus liver biopsy. Radiology 267:767–775
57. McPherson S, Jonsson JR, Cowin GJ et al (2009) Magnetic resonance imaging and spectroscopy accurately estimate the severity of steatosis provided the stage of fibrosis is considered. J Hepatol 51: 389–397