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Comparison of sonographic hepatorenal ratio and the degree of hepatic steatosis in magnetic resonance imaging-proton density fat fraction

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Keywords

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Abstract

Objectives: Conventional ultrasonography can provide only semi-quantitative assessment of hepatic steatosis. The aim of this study was to assess sonographic hepatorenal ratio to quantify the severity of fatty liver. **Methods:** We performed a retrospective analysis of 179 patients with various liver diseases who underwent abdominal magnetic resonance imaging and ultrasonography on the same day. The hepatorenal ratio was calculated by the ratio between the mean echo intensity in regions of interests of the liver and regions of interests of the right renal cortex. Magnetic resonance imaging-proton density fat fraction was used as standard reference for steatosis grading. The effect of fibrosis measured by magnetic resonance elastography on the degree of correlation was also assessed. **Results:** The hepatorenal ratio was highly correlated with magnetic resonance imaging-proton density fat fraction (Spearman's coefficient = 0.83) ($p < 0.001$). High correlation of hepatorenal ratio with magnetic resonance imaging-proton density fat fraction was observed in patients with less than stage 2 fibrosis ($p < 0.001$), whereas moderate correlation of hepatorenal ratio with magnetic resonance imaging-proton density fat fraction was found in patients with \geq stage 2 fibrosis or higher ($p < 0.001$). The hepatorenal ratio cutoff point for prediction of grade 1 hepatic steatosis was 1.18 with sensitivity of 90.0% and specificity of 80.0%. The hepatorenal ratio cutoff point for prediction of grade 2 and grade 3 hepatic steatosis was 1.55 and 1.60, respectively, with sensitivity greater than 90% and specificity greater than 80%. **Conclusions:** The hepatorenal ratio could become an effective quantitative tool for hepatic steatosis alternative to magnetic resonance imaging-proton density fat fraction. Application should be careful in the group of patients with stage 2 liver fibrosis or higher.

Introduction

Hepatic steatosis is a condition of excessive intrahepatocytic accumulation of fat. Steatosis is the hallmark of non-alcoholic fatty liver disease (NAFLD) and also occurs in patients with alcohol abuse, viral hepatitis, HIV and those receiving certain pharmacological treatment^(1,2). NAFLD is the most common chronic liver disease affecting approximately 30% of the general population^(2,3). Steatosis can progress to liver fibrosis and, eventually, cirrhosis, and it can also worsen the course of disease in patients with viral hepatitis^(4,5).

A quantitative tool for assessment and monitoring of hepatic steatosis is needed in clinical practice. Liver biopsy still remains the gold standard for the assessment of liver fat⁽⁶⁾. However, its routine clinical use is limited due to its invasiveness with a small potential risk of life-threatening complications, sampling errors and inter-observer variability^(7–9).

Noninvasive imaging techniques, including MR spectroscopy (¹H-MRS) and magnetic resonance imaging-proton density fat fraction (MRI-PDF), can accurately measure

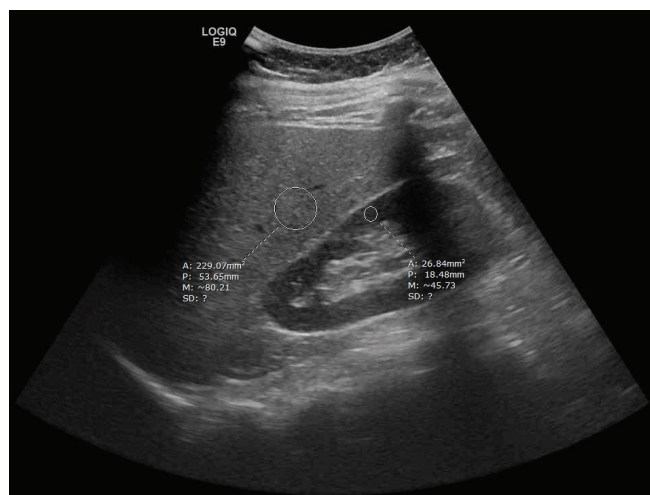


Fig. 1. The hepatic and right renal ROIs were selected at the same depth along the focusing area near the center of the image to avoid image distortion effects and beam attenuation

hepatic fat. ¹H MRS is accepted as the noninvasive reference standard for liver fat quantification⁽¹⁰⁾.

PDFF measured by MRI is a direct measure of the fraction of mobile triglyceride protons relative to those in water⁽¹⁰⁾. MRI-PDFF proved to have excellent agreement with ¹H-MRS^(11–15) and to be closely correlated with liver histology^(14,16,17), as well as has been recently considered as a standardized MR biomarker of steatosis used in clinical practice and research. Despite the accuracy of the MR techniques, their use is restricted due to high operational cost and considerable time consumption.

Ultrasonography (US) is often the first imaging modality used to detect hepatic steatosis. However, conventional ultrasonography can provide only qualitative or semi-quantitative assessment based on liver echogenicity, vessel visibility, and beam attenuation. Overall sensitivity and specificity of ultrasonography previously reported were about 60–94% and 66–97%, respectively⁽¹⁸⁾. Prior studies have investigated sonographic parameters in an attempt to overcome subjectivity and qualitative limitations, such as hepatic-renal differences⁽¹⁹⁾ and hepatorenal (HR) ratio^(20–25). The diagnostic value of the HR ratio varies among studies depending on different standard references and study populations; therefore further validation for clinical application is still needed. Moreover, a direct comparison between sonographic HR ratio and MRI-PDFF has not been performed yet.

The aim of this study was to evaluate the sonographic HR ratio for the diagnosis and quantification of hepatic steatosis using MRI-PDFF as reference.

Materials and methods

The study was approved by the Institutional Review Board. No informed consent was required due to the retrospective nature of the study.

Subjects

Patients aged ≥ 18 years with various liver diseases who had undergone abdominal MR imaging and ultrasonography on the same day at King Chulalongkorn Memorial Hospital (KCMH) between January 2016 and December 2017 were assessed retrospectively. All images were reviewed using Picture Archiving and Communication System (PACS; Fujifilm Synapse, Tokyo, Japan).

Exclusion criteria

All patients meeting at least one of the following criteria were excluded: 1.) Patients whose liver or the right kidney was not clearly visualized on the same US image or ectopic right kidney or inadequate area of each organ to be sampled 2.) Patients whose renal echogenicity was altered by atrophy, numerous cortical cysts/masses, renal cortical scarring or hydronephrosis of the right kidney 3.) Patients with abnormal serum creatinine > 1.3 mg/dL⁽²²⁾ 4.) Patients with focal lesions in the right hepatic lobe causing distortion of liver echotexture or heterogeneous fat distribution in the liver.

Ultrasonographic examination

All participants underwent upper abdominal examination with ultrasonography in B-mode (GE logiq E9 with a 1–6 MHz Broad-spectrum convex transducer) by board-certified radiologists. Various image parameters were adjusted for each examination. All images were transmitted to a Picture Archiving and Communication System (PACS; Fujifilm Synapse, Tokyo, Japan).

Ultrasound image analysis

All ultrasound image analyses were performed by two independent operators, using a region of interest (ROI) tool on standard workstation from DICOM images on PACS without using extra-image analysis software.

The first operator was a radiologist with more than 8 years of experience in advance abdominal imaging, and the second operator was a radiology resident. Both of them were blinded to patients' clinical details. The hepatic and right renal ROIs were selected at the same depth along the focusing area near the center of the image to avoid image distortion effects and beam attenuation. An ROI in the liver parenchyma of 200–250 mm² was selected, excluding blood vessels, bile ducts or focal liver lesions. An ROI of the right renal cortex of 20–30 mm² was selected, excluding large vessels, renal sinus, masses or cysts. Portions of ROIs affected by artifacts were also excluded (Fig. 1).

The sonographic HR ratio was calculated by dividing the mean echo intensity of the pixels within the selected hepatic ROI by those within the selected ROIs of the right renal cortex.

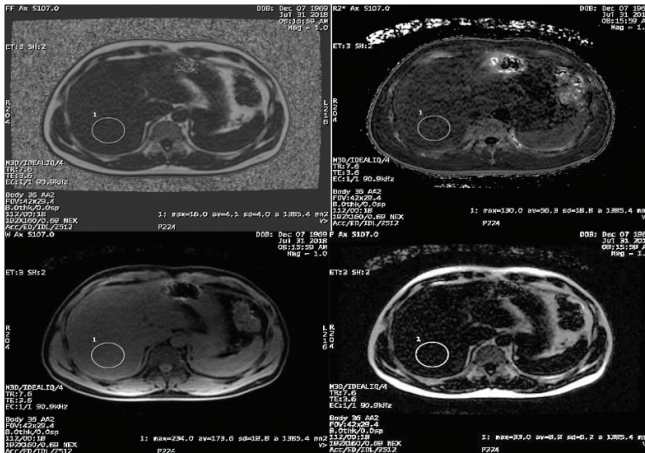


Fig. 2. The images were processed by using the software provided by the manufacturer (IDEAL-IQ; GE Healthcare) which created water, fat, R2* maps and PDFF parametric map representing fat mapping of the entire liver. ROI was placed in hepatic segment VI

MRI examinations were performed using 3T GE Discovery MR750w. All participants underwent PDFF examination using complex-based, chemical shift-based, water and fat separation technique with low-flip angle, T1-weighted, 2D multiple-echo, spoiled gradient-echo sequence. The images were processed by using the software provided by the manufacturer (IDEAL-IQ; GE Healthcare) which created water, fat, R2* maps and PDFF parametric map representing fat mapping of the entire liver (Fig. 2). This technique provided correction of confounding factors on MR signal intensity, such as T1 bias, T2* decay, spectral complexity of fat, noise bias, and eddy currents⁽⁶⁾. (Detailed imaging parameters are as follows: TR7.6/TE3.6, flip angle 4°, bandwidth 90.91 Hz/pixel, number of excitations, 0.5; field of view 42 cm; section thickness, 8 mm; intersection gap, 0, matrix 192×160. We acquired data sets with eight different echo times that ranged from 1.25 to 11.83 msec.)

MR elastography (MRE) was also performed in all individuals with 60-Hz vibrations applied to the abdominal wall using a pneumatic actuator (MR-Touch; GE Healthcare), with two-dimensional gradient-echo MR elastography sequence and the direct inversion algorithm, previously described elsewhere⁽²⁶⁾. (Detailed imaging parameters were as follows: TR/TE, 1000.3/63 ms; bandwidth 250 Hz/pixel; field-of-view (FOV), 38 cm; matrix, 64 × 64; NEX, 2; slice thickness, 7.0 mm with a 2.5-mm intersection gap.)

PDFF measured by MRI image processing

The radiology resident (the second operator), who was blinded to the patients' clinical details, manually performed circular ROI measurements in the hepatic segment VI on the PDFF parametric map to obtain fat fraction percentage using a work station provided by the manufacturer: AW4.4; GE healthcare. ROIs were selected to be >400 mm² avoiding major blood vessels, intrahepatic bile ducts, focal lesions and the lateral margin of the liver.

Other data

MRI imaging was reviewed using PACS; Fujifilm Synapse, Tokyo, Japan. Liver stiffness values (kPa) were recorded. All MRE image analyses were performed by radiology residents and the quality was approved by advanced abdominal imaging radiologists.

Medical data records of each patient were obtained from hospital information system (HIS) and laboratory record. Baseline demographic, physical and biochemical data of the study participants included age, sex, weight, height, body mass index (BMI), alcohol use, hepatic viral profile, total bilirubin, albumin, SGPT, ALP, total cholesterol, low density lipoprotein (LDL) and triglycerides.

Statistical analysis

All statistical analyses were performed using Stata version 14.0. For descriptive analyses, categorical variables were reported in numbers and percentages.

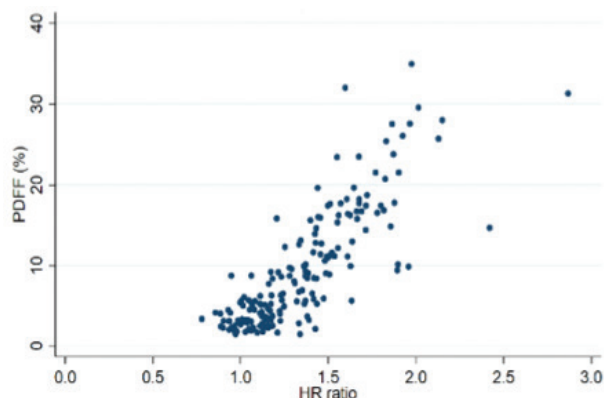
Continuous variables were reported as means (SD) and ranges or medians and interquartile ranges (IQR). The Student's t-test and Mann-Whitney U-test were applied for the comparison of variables in different categories. Kruskal-Wallis H test was used for the assessment of differences in HR ratio between different grades of steatosis. After a positive Kruskal-Wallis H test (p -value <0.05), a post-hoc analysis was used to perform pairwise comparisons between subgroups.

Spearman's correlation was used for the assessment of a correlation between continuous variables. The diagnostic performance of HR compared with MRI-PDFF was assessed by using receiver operating characteristic (ROC) curve. We determined the optimal HR ratio cutoff points for the diagnosis and grading of hepatic steatosis, as well as the sensitivity and specificity for each cutoff point. The HR ratios for statistical analysis were performed by the first operator who was more experienced in the field. The HR ratio interobserver agreement was determined using intraclass correlation coefficient (ICC) (p -values <0.05 were statistically significant and all tests were two tailed.)

Reference standard for optimal threshold value of MRI-PDFF

Currently, there are still no exact standardized fat fraction cutoff values for normal and abnormal liver fat.

We determined hepatic steatosis at PDFF $\geq 5.56\%$, which is a common threshold to distinguish normal from abnormal. This threshold was derived from a large MR spectroscopy study performed by Szczepaniak *et al.* in 2349 participants of the Dallas Heart Study⁽³⁾. Using this threshold, MRI-PDFF accuracy was close to 100% for the detection of steatosis compared with MRS⁽¹³⁾.



Spearman's correlation coefficient = 0.830, $P < 0.001$

Fig. 3. Spearman's correlation between HR ratio and fat fraction quantified by MRI-PDFF 3T ($N = 179$)

We classified liver steatosis according to previous study by Middleton *et al.*, as follows: Grade 2: PDFF $\geq 16.3\%$ and Grade 3: PDFF $\geq 21.7\%$ ⁽²⁷⁾.

According to the suggested guidelines for the interpretation of liver stiffness with MR elastography at 60 Hz⁽²⁶⁾, we determined abnormal increased liver stiffness at ≥ 2.9 kilopascals (kPa) and performed staging of liver fibrosis as follows: normal or chronic inflammation: < 2.9 kPa, stage 1–2 fibrosis: 2.9–3.5 kPa, stage 2–3 fibrosis: 3.5–4.0 kPa, stage 3–4 fibrosis: 4.0–5.0 kPa and stage 4 fibrosis/cirrhosis: ≥ 5.0 kPa.

Results

A total of 179 patients were included in this study (82 males and 97 females; mean age of 53 years; range: 23–77 years). The indications for abdominal MR imaging included non-alcoholic fatty liver disease ($n = 97$), hepatitis C virus (HCV) infection ($n = 59$), psoriasis on methotrexate treatment ($n = 4$), HBV and HCV coinfection ($n = 2$), post liver transplantation with HCV infection ($n = 2$), post liver transplantation ($n = 2$), patients treated with chemotherapy ($n = 1$), unexplained elevation of liver enzymes ($n = 1$) and unknown etiology ($n = 11$).

Hepatic fat content by MRI-PDFF ranged from 1.5 to 35.0%. Based on the diagnostic criteria for steatosis, 75 patients had no steatosis (75/179, 42%) and 104 patients had steatosis (104/179, 58%). Grade 1 ($\geq 5.56\%$ and $< 16.3\%$), grade 2 ($\geq 16.3\%$ and $< 21.7\%$) and grade 3 ($\geq 21.7\%$) steatosis was found in 71 (40%), 20 (11%) and 13 (7%) patients, respectively. The median age of patients without steatosis was 58 years, and the median age of patients with steatosis was 51 years; the difference was statistically significant ($p = 0.007$). BMI was statistically significantly higher in the steatosis group than non-steatosis group (26.9 ± 3.4 vs. 23.7 ± 3.5 kg/m²; p -value < 0.001). The patients in the steatosis group had elevated triglyceride and SGPT levels compared with the non-steatosis group ($p < 0.05$). There was no significant difference in total cholesterol, low density lipoprotein (LDL), albumin, TB or ALP between these

Tab. 1. Demographic data of the 179 patients in the study sample

Characteristics	Non-steatosis group (N = 75)	Steatosis group (N = 104)	p-value
Age (y), median (IQR)	58 (49–64)	51 (41–60)	0.007
BMI (kg/m ²), mean (SD)	23.7 (3.5)	26.9 (3.4)	<0.001
TC, mean (SD)	189.9 (41.0)	201.8 (40.6)	0.111
TG, median (IQR)	117 (82–141)	137 (97–187)	0.033
LDL (mg/dL), mean (SD)	113.7 (38.4)	121.2 (38.5)	0.11
Albumin, median (IQR)	4.1 (3.8–4.3)	4.2 (4.0–4.4)	0.059
TB, median (IQR)	0.78 (0.56–1.30)	0.73 (0.57–0.94)	0.884
SGPT, median (IQR)	32.5 (19–55)	45 (29–64)	0.033
ALP, median (IQR)	79.0 (61–101)	77 (61–88)	0.557
HR ratio, median (IQR)	1.11 (1.01–1.18)	1.49 (1.34–1.68)	<0.001

Abbreviations: SD – standard deviation, IQR – interquartile range, LDL – low-density lipoprotein, TG – serum triglyceride, BMI – body mass index (kg/m²), SGPT – serum glutamate-pyruvate transaminase, ALP – alkaline phosphatase, HR ratio – hepatorenal ratio

Tab. 2. Correlation between hepatorenal ratio and MRI-PDFF by liver stiffness ($n = 179$)

Liver stiffness by MRE (kPa)	N	Spearman's correlation coefficient	p-value
< 2.5	87	0.874	< 0.001
2.5–2.8	18	0.849	< 0.001
2.9–3.4	26	0.832	< 0.001
≥ 3.5 –5	48	0.591	< 0.001

two groups. Demographic data of the 179 patients in the study sample are summarized in Tab. 1.

The HR ratio was significantly highly correlated with MRI-PDFF (Spearman's correlation coefficient = 0.83) ($p < 0.001$) (Fig. 3). In subgroup analysis, there was a higher correlation between HR ratio and MRI-PDFF in patients with normal liver stiffness ($n = 105$) than those with increased liver stiffness ($n = 74$) (Spearman's correlation coefficient = 0.87 vs. 0.69, respectively, $p = 0.0017$). High correlation of HR ratio with MRI-PDFF was observed

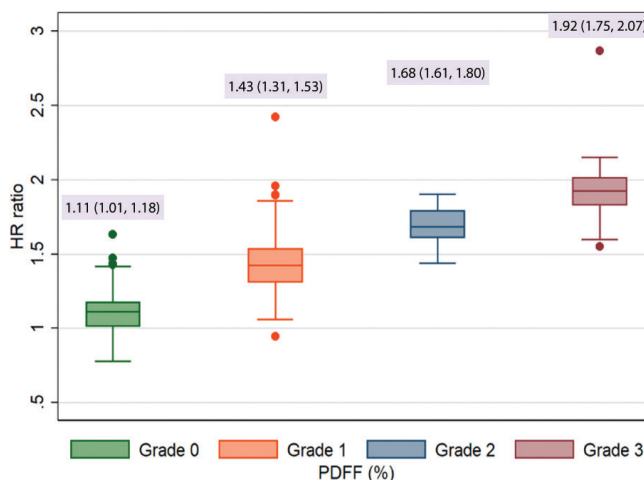


Fig. 4. Distribution of hepatorenal ratio in patients according to categories of steatosis; none, grade 1, grade 2 and grade 3 steatosis

All patients, N=179

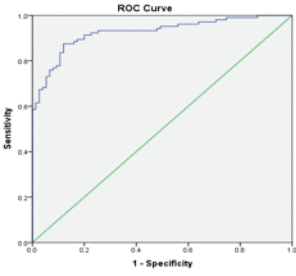
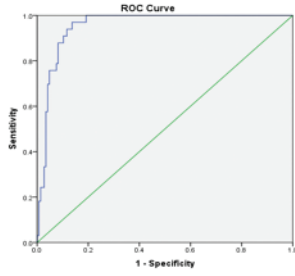
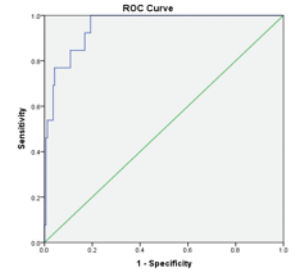
	PDFF \geq 5.56%	PDFF \geq 16.3%	PDFF \geq 21.7%
ROC			
HR ratio cut off point	\geq 1.18	\geq 1.55	\geq 1.60
Sensitivity	90.0%	90.9%	92.3%
Specificity	80.0%	89.7%	83.1%

Fig. 5. ROC curve of sensitivity (true-positive fraction) plotted against 1-specificity (false-positive fraction) of hepatorenal ratio for the diagnosis of different levels of steatosis quantified by MRI-PDFF

in patients with less than stage 2 fibrosis, whereas moderate correlation of HR ratio with MRI-PDFF was found in patients with stage 2 fibrosis or higher (Tab. 2).

The median of HR ratio was 1.31 (1.10–1.55), and the range was 0.78–2.87. There was a significant difference in the median of HR ratio between patients with steatosis and those without, i.e. 1.49 (1.34–1.68) vs. 1.11 (1.01–1.18) ($p < 0.001$), respectively. Higher HR ratio corresponded with higher PDFF. There were also significant differences in the median HR ratio among sub-groups ($p < 0.001$) except for between grade 2 and 3 steatosis, which was marginally significant ($p = 0.05$) (Fig. 4).

ROC analysis and the HR ratio cutoff points

The appropriate HR ratio cutoff points were selected on the basis of the sensitivity and specificity, using the ROC analysis. The optimal cutoff for the HR ratio to define steatosis

at MRI-PDFF \geq 5.56% was a value equal to or greater than 1.18, with a sensitivity of 90.0% (95% CI, 83.0–95.3%), specificity of 80.0% (95% CI, 69.2–88.4%) and AUC 92.6 (95% CI, 88.8–96.4%), PPV 86.2% (95% CI, 79.9–90.8%) and NPV 85.7% (95% CI, 76.7–91.6%).

The optimal HR ratio cutoff point for prediction of grade 2 hepatic steatosis \geq 16.3% was 1.55, with sensitivity of 90.9% (95% CI, 75.7–98.1%) and specificity of 89.7% (95% CI, 83.6–94.1%), AUC 95% (95% CI, 92.4–98.2%), PPV 66.7% (95% CI 55.0–76.6%) and NPV 97.7% (95% CI, 93.7–99.2%). The optimal HR ratio cutoff point for the prediction of grade 3 hepatic steatosis \geq 21.7% was 1.60, with sensitivity of 92.3% (95% CI, 64.0–99.8%) and specificity of 83.1% (95% CI, 76.6–88.5%), AUC 95% (95% CI, 91.1–99.2%), PPV 30.0% (95% CI, 22.8–38.4%), NPV 99.3% (95% CI, 95.5–99.9%) (Fig. 5).

Interobserver reliability

The reproducibility of HR ratios was assessed by intraclass correlation coefficient (ICC), showing a high correlation between two independent operators (ICC = 0.882, $p < 0.001$) (Fig. 6).

Discussion

Nowadays, ultrasonography is usually the most initial modality to assess hepatic steatosis. The diagnosis of hepatic steatosis on ultrasonography involves subjective evaluation of increased liver echogenicity, portal vein blurring, beam attenuation and poor visualization of diaphragm. Prior studies found that abnormal hepatorenal echogenicity was the most sensitive among other sonographic signs in the diagnosis of hepatic steatosis^(18,28). Sonographic parameters for quantitative assessment of hepatic steatosis,

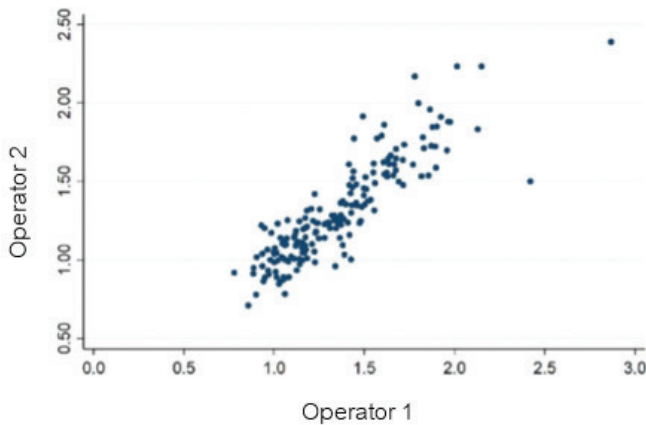


Fig. 6. Hepatorenal ratio interobserver reliability. Intraclass correlation coefficient = 0.882, $p < 0.001$. Spearman's correlation coefficient = 0.889, $p < 0.001$

including HR ratio, have been previously investigated. Prior studies have reported high correlation between sonographic HR ratio and histologic steatosis among patients with various liver diseases ($r = 0.71-0.82$)^(20,22) and also in patients with NAFLD ($r = 0.80$)⁽²³⁾. There was also a high correlation between sonographic HR ratio and ¹H-MRS in patients with NAFLD ($r = 0.89-0.95$)^(24,25). Therefore, HR ratio may offer a potentially useful quantitative tool for hepatic steatosis.

The previously reported HR cutoff ratios are varied, depending on the characteristics of the target population, standard reference and the selected threshold. For example, Webb *et al.*⁽²⁰⁾ and Marshall *et al.*⁽²²⁾ reported HR ratio cutoff value using specialized software at 1.49 and 1.28, respectively, for identifying more than 5% of fat from biopsy in patients with various liver diseases. Shiralkar⁽²⁹⁾ investigated the same patients included in the study by Marshall *et al.*, and found that the HR ratio can be accurately calculated from PACS without specialized software yielding a cutoff point at 1.34. Borges *et al.*⁽²³⁾ reported a cutoff ratio at 1.24 in patients with only NAFLD using the same threshold from biopsy. Mancini *et al.*⁽²²⁾ and Martin-Rodriguez⁽²⁴⁾ investigated HR ratio in patients with NAFLD for the prediction of ¹H-MRS of at least 5%, yielding the best HR ratio cutoff point at 2.2 and 1.28, respectively. However, there is no perfect agreement in the percentage of fat from liver biopsy and MR techniques since they measure different aspects of hepatic steatosis. Also, a direct comparison between sonographic HR ratio and MRI-PDFF has not been performed yet.

In this study, we assessed sonographic HR ratio to predict the degree of fat content measured by MRI-PDFF in patients with liver disease of varying etiology. We calculated HR ratio using standard workstation without additional software because we attempted to keep the method simple so as to be easily applied and repeated. In this study, we measured PDFF on parametric maps at hepatic segment VI because the sonographic HR ratios were calculated in this segment.

Our study revealed a high correlation between sonographic HR ratio and percentage fat fraction measured by MRI-PDFF. We found that HR ratio could provide diagnosis of small fat content as low as PDFF of 5.56% with good accuracy. In our population, the HR cutoff ratio for predicting hepatic steatosis at 1.18 yielded sensitivity of 90.0% and specificity of 80.0%. Our study shared similar

findings with the study by Kim *et al.*⁽²⁸⁾ which correlated conventional ultrasonography signs with the MRI-PDFF. They found that PDFF was 2.6% (S.D. \pm 1.22) in subjects without any signs of hepatic steatosis, while PDFF was 5.4% (S.D. \pm 3.35) when abnormal hepatorenal echoes were present. Abnormal hepatorenal echoes yielded 96.6% sensitivity, 74.8% specificity and 87.5% AUC for detecting 6.4% PDFF.

Interference of liver fibrosis in liver parenchymal echogenicity had been previously investigated. Some studies^(18,30) showed

that bright liver echogenicity significantly correlated with steatosis, but not fibrosis. Borges *et al.*⁽²³⁾ also reported that HR ratio was more strongly correlated with steatosis than fibrosis on liver biopsy. On the other hand, Perez *et al.* showed that US was inaccurate for diagnosing hepatic steatosis in patients with chronic liver disease due to the higher probability of hepatic fibrosis or inflammation in these patients, causing echogenic alteration seen in US⁽³¹⁾. Stiffness value measured by MRE is now the most accurate noninvasive method for the detection of liver fibrosis⁽²⁶⁾. In our study, we found a reduced correlation between HR ratio and MRI-PDFF in patients with \geq stage 2 fibrosis. Therefore, the HR ratio should be used carefully in this group of patients.

Nowadays, liver fibrosis can be assessed not only with MRE, but also with ultrasound elastography (UE), providing comprehensive one-time assessment of liver steatosis and fibrosis. However, confounding of steatosis grade on the fibrosis estimation of UE is controversial and still under investigated^(32,33).

Limitations of this study include its retrospective design. Also, this study had no histologic evaluation, which is the gold standard of quantification of hepatic steatosis. Furthermore, the result may be affected by selection bias since the study population who underwent MRI and US at our institution were not representative of the general population. Also, sonographic HR ratio could be assessed only in patients who had adequate sample area of each organ on ultrasonographic image and without focal lesions or diseases of the liver and the right kidney, which may alter their echogenicity. Due to the nature of heterogeneous distribution of hepatic steatosis, it might lead to sampling errors, which can occur whatever method is used. The population in our study was heterogeneous due to the broad etiologies of liver disease that can be responsible for liver steatosis. However, we believe that the population might be more representative of the general population rather than focused on patients with NAFLD only.

Further validation is needed, including future study in larger populations and evaluation of HR ratio in the detection of subtle change of fat content for follow-up study.

Conclusion

In conclusion, the sonographic HR ratio was highly correlated with PDFF measured by MRI, easily applicable using standard workstation without additional software, and also reproducible. It could become an effective tool for quantitative evaluation of hepatic steatosis alternative to MRI-PDFF.

Conflict of interest

Authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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