



# Accuracy of ultrasonography in the assessment of liver fat compared with MRI



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## ARTICLE INFORMATION

### Article history:

Received 3 October 2018

Accepted 26 February 2019

**AIM:** To investigate the accuracy of ultrasonography in the assessment of hepatic steatosis using magnetic resonance imaging (MRI) as standard of reference and to explore the influence of additional hepatic iron overload.

**MATERIAL AND METHODS:** A total of 2,783 volunteers (1,442 women, 1,341 men; mean age, 52.3±13.8 years) underwent confounder-corrected chemical-shift-encoded MRI of the liver at 1.5 T. Proton-density fat fraction (PDFF) and transverse relaxation rate (R2\*) were calculated to estimate hepatic steatosis and liver iron overload, respectively. In addition, the presence of hepatic steatosis was assessed by B-mode ultrasonography. The sensitivity, specificity, and accuracy of hepatic ultrasonography were determined for different degrees of hepatic steatosis and different amounts of liver iron.

**RESULTS:** MRI revealed hepatic steatosis in 40% of participants (n=1,112), which was mild in 68.9% (n=766), moderate in 26.7% (n=297), and severe in 4.4% (n=49) of patients. Ultrasonography detected hepatic steatosis in 37.8% (n=1,052), corresponding to 74.5% sensitivity and 86.6% specificity. The sensitivity of ultrasound increased with the amount of hepatic fat present and was 65.1%, 95%, and 96% for low, moderate, and high fat content; whereas the specificity was constantly high at 86.6%. The diagnostic accuracy of ultrasound for detection of hepatic steatosis did not vary significantly with the amount of liver iron present.

**CONCLUSION:** Ultrasonography is an excellent tool to assess hepatic steatosis in the clinical setting with some limitations in patients with a low liver fat content. The detection of hepatic steatosis by ultrasonography is not influenced by liver iron.

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## Introduction

Metabolic syndrome is common in the general population.<sup>1</sup> Insulin resistance is part of metabolic syndrome and results in excessive ectopic fat storage especially in the visceral organs. In particular, the liver shows very fast

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ectopic fat storage. According to the image method used for the assessment of hepatic steatosis, the prevalence of hepatic steatosis ranges from 17% to 40% in adults<sup>2</sup> and nearly 10% in children and adolescents.<sup>3</sup> Steatosis of the liver is of high clinical relevance: the disease was shown to be an independent risk factor for cardiovascular disease,<sup>4,5</sup> is associated with and possibly causes type 2 diabetes,<sup>6,7</sup> and is related to malignant tumours, especially those of the gastrointestinal system.<sup>8</sup> Furthermore, liver steatosis can progress to steatohepatitis, liver fibrosis,<sup>9</sup> and consequently, to an irreversible stage of liver cirrhosis. Early detection and treatment of liver steatosis would be helpful in preventing its sequelae.

Histopathology is considered the current clinical reference standard for diagnosing and grading hepatic steatosis; however, liver biopsy is an invasive procedure and has inherent complications. Furthermore, histological slides evaluate only a small part of the liver and just offer a two-dimensional assessment of steatosis.<sup>10</sup> Therefore, reliable imaging techniques are warranted to detect liver steatosis. The demands on radiological imaging are very high and approaches should be simple, accurate, widely available, and cost-effective.

Magnetic resonance imaging (MRI), especially the proton-density fat fraction (PDFF) determined from chemical-shift-encoded MRI or spectroscopy, allows accurate quantification of liver fat content and has become a well-accepted approach for the detection of liver steatosis.<sup>11</sup> PDFF is currently the non-invasive standard of reference for the assessment of liver fat content in diagnosing hepatic steatosis. In addition, in the setting of PDFF measurement, MRI is also able to quantify liver iron content using the transverse relaxation rate,  $R2^*$ .<sup>14</sup> Disadvantages of MRI include the lack of general availability and high costs.

Ultrasonography is commonly used to detect liver steatosis<sup>12</sup> and has the advantage of being cost-effective, simple, and widely available. Nevertheless, the accuracy and reliability of ultrasonography in the assessment of hepatic steatosis are critically discussed.<sup>13</sup> In addition, to the best of authors' knowledge, no study has been published that investigated liver iron content as potential confounder for the sonographic detection of hepatic steatosis.

Because ultrasound is widely used as a first-line clinical technique to detect hepatic steatosis, the purpose of the present study was to investigate its diagnostic accuracy in the assessment of fatty liver in comparison to MRI as the reference standard in volunteers with different degrees of hepatic steatosis. In addition, liver enzymes and hepatic iron concentrations were investigated as potential confounders affecting the assessment of hepatic steatosis by ultrasound.

## Material and methods

### Study population

Patients were selected from the database of the Study of Health in Pomerania (SHIP), a population-based study in

Northeast Germany. SHIP was approved by the local ethics committee of Greifswald University Medicine, Germany. Written informed consent was obtained for each patient. Parts of this study, especially findings regarding the epidemiology of hepatic steatosis and liver iron overload, have already been published elsewhere.<sup>14</sup>

This study included 2,783 participants with a mean age of  $52.3 \pm 13.8$  years, among them 1,442 women and 1,341 men. The participants had a mean body mass index of  $27.6 \pm 4.4$  kg/m<sup>2</sup>. An inclusion criterion for this project was the attendance of MRI examination and abdominal ultrasonography in the setting of SHIP.<sup>15</sup>

### Ultrasonography examination and liver enzymes

Standardised ultrasonography of the upper abdominal organs, carotid arteries, and heart is part of the imaging examinations performed in the population-based SHIP study. Ultrasonography was performed by certified examiners using a transportable B-mode ultrasound device (vivid I; GE-Healthcare, Waukesha, WI, USA) with a 2.5 Mhz transducer. The examiners used a two-point scale to assess the presence of hepatic steatosis: (0) no steatosis and 1 steatosis. Hepatic steatosis was defined as a bright liver pattern in comparison to the renal cortex.<sup>15</sup> Other features, such as liver size and pattern of steatosis, were completely ignored. The examiners were unaware of any information on participants, such as medical history.

Serum alanine aminotransferase (ALT), aspartate transferase (AST), and  $\gamma$ -glutamyl transpeptidase (GGT) concentrations were measured photometrically (Hitachi 704; Roche, Mannheim, Germany).

### MRI

MRI was performed at 1.5 T (Avanto, Siemens Healthcare, Erlangen, Germany) and included a three-echo chemical-shift-encoded sequence with water/fat separation of the upper abdominal organs. The three-dimensional (3D) gradient-echo sequence was acquired during a 19-second breath-hold using the following image parameters: 11 ms repetition time (TR); 2.4/4.8/9.6 ms echo times ( $TE_1/TE_2/TE_3$ ), 10° flip angle, one averages,  $\pm 1065$  Hz/pixel bandwidth,  $224 \times 168 \times 64$  matrix,  $410 \times 308$  mm field of view, parallel imaging (GRAPPA) effective acceleration factor=1.8, 3 mm section thickness, and 56 sections. Potential confounders affecting liver fat quantification such as T1 bias, T2\* decay, multi-spectral complexity of fat, and noise bias were corrected for by post-processing. T2\* correction information was used for quantification of liver iron. General post-processing of MRI datasets generated two parametric maps: an PDFF map and  $R2^*$  map for detecting liver fat and liver iron, respectively.<sup>14,16,17</sup> PDFF and  $R2^*$  are well-accepted techniques and reference standards for the assessment of hepatic steatosis and liver iron overload.<sup>18–20</sup>

Images were analysed by a certified observer with >10 years of experience in abdominal MRI, especially liver imaging. The observer was unaware of the results of

ultrasound. PDFF and R2\* values were measured using Osirix version 4.6 (Pixameo SARL, Bern, Switzerland). First, a representative section in the middle position was selected. Second, a region of interest (ROI) was placed in the liver in this section, avoiding artefacts and large vessels, especially the central portal vein.

Based on a previous study dealing with the histopathological calibration of PDFF, patients were divided into two groups: hepatic steatosis and healthy.<sup>16</sup> The hepatic steatosis group was subdivided into three groups according to the amount of fat: low fat content (PDFF >5.1–14%), moderate fat content (PDFF >14–28%), and high fat content (PDFF >28%).<sup>16</sup> In addition, patients were also grouped according to their liver iron content (no iron versus iron content) using a cut-off of R2\* <41/second.<sup>16</sup>

### Statistical analysis

Hepatic steatosis detection by ultrasonography was compared with PDFF as the reference standard. Based on the true positive (TP), false positive (FP), true negative (TN), and false negative (FN) values between these two different methods, the sensitivity, specificity, positive (PPV) and negative predictive value (NPV) were calculated as follows:

$$\begin{aligned} \text{Sensitivity} &= \text{TP}/(\text{TP}+\text{FN}) \\ \text{Specificity} &= \text{TN}/(\text{TN}+\text{FP}) \\ \text{PPV} &= \text{TP}/(\text{TP}+\text{FP}) \\ \text{NPV} &= \text{TN}/(\text{TN}+\text{FN}) \end{aligned}$$

The diagnostic performance of ultrasonography was determined for the whole study population and for three subgroups with different grades of hepatic steatosis.

The MRI-derived liver fat content was used as predictor of the sonographic detection of hepatic steatosis in a logistic regression model. Based on the individual risk of sonographic hepatic steatosis derived from this model, a receiver operating characteristic (ROC) analysis was performed, and the area under the curve (AUC) was calculated. The best cut-off for predicting sonographic hepatic steatosis from the amount of liver fat seen on MRI was identified by

maximising the Youden index, which is defined as sensitivity + specificity – 1.

In a second logistic regression model, liver fat and liver iron derived from MRI were used as predictors of hepatic steatosis on ultrasound. The predictive performance of this model was compared with that of the model using only liver fat as a predictor by comparing the AUCs derived from the two models using a chi-squared test.

For predicting the effect of liver enzyme levels on hepatic steatosis from MRI, receiver operating characteristic (ROC) analysis was performed and the areas under the ROC curves (AUCs) were calculated. The optimal cut-offs were found by maximising the Youden index. For these cut-offs, the sensitivity, specificity, PPV and NPV were calculated for each liver enzyme separately and the combination of all three enzymes. Furthermore, the three liver enzymes were combined with hepatic steatosis on ultrasound (1 if all liver enzymes and hepatic steatosis were positive; 0 if at least one of the liver enzymes or sonographic hepatic steatosis was negative) as predictor of hepatic steatosis on MRI, and the sensitivity, specificity, PPV and NPV were again determined.

In all analyses,  $p < 0.05$  was considered to indicate statistically significant differences. Statistical analysis was performed using Stata 14.2 (Stata Corporation, College Station, TX, USA).

### Results

MRI revealed hepatic steatosis in 40% of the participants (1,112/2,783), while ultrasonography identified hepatic steatosis in 37.8% (1,052/2,783). In a total of 828 individuals (29.8%), hepatic steatosis was diagnosed by both MRI and ultrasound. Sonographically, the number of FNs was 284 (10.2%) and the number of FPs was 224 (8.1%), resulting in 74.5% sensitivity and 86.6% specificity of ultrasound compared with MRI (Table 1).

Hepatic steatosis identified by MRI was mild in 766 patients (68.9%), moderate in 297 patients (26.7%), and high in 49 patients (4.4%). The sensitivity of ultrasound increased with the amount of liver fat: from 65.1% when the amount

**Table 1**

Diagnostic performance of ultrasonography in the detection of hepatic steatosis in comparison to MRI as the reference standard for the whole study population and stratified by amount of hepatic fat.

	All patients	Patients selected by grade of liver fat content		
	Hepatic steatosis versus healthy	Mild hepatic steatosis versus healthy	Moderate hepatic steatosis versus healthy	High hepatic steatosis versus healthy
<i>n</i>	2,783	2,437	1,968	1,720
Sensitivity (%)	74.5 (72.8; 76.1)	65.1 (63.3; 67)	95 (94; 96)	96 (95; 96.9)
Specificity (%)	86.6 (85.3; 87.9)	86.6 (85.2; 88)	86.6 (85.1; 88.1)	86.6 (85; 88.2)
True positive	828 (29.8%)	499 (20.5%)	282 (14.3%)	47 (2.3%)
True negative	1,447 (52%)	1,447 (59.4%)	1,447 (73.5%)	1,447 (84.1%)
False positive	224 (8.1%)	224 (9.2%)	224 (11.4%)	224 (13%)
False negative	284 (10.2%)	267 (11%)	15 (0.8%)	2 (0.1%)
PPV	78.7 (77.2; 80.2)	69 (67.2; 70.9)	55.7 (53.5; 57.9)	17.3 (15.6; 19.1)
NPV	83.6 (82.2; 85)	84.4 (83; 85.9)	99 (98.5; 99.4)	99.9 (99.7; 100)

Data in parentheses are 95% confidence intervals.

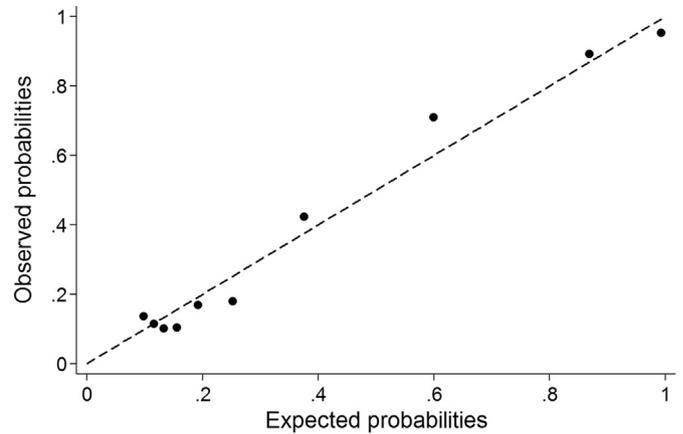
PPV, positive predictive value; NPV, negative predictive value.

small was to 95% and 95.9% for moderate and high amounts. The specificity was constant at 86.6% for all degrees of hepatic steatosis. Examples of ultrasonography in selected participants compared with MRI are shown in Fig 1.

The AUC for the prediction of hepatic steatosis on ultrasound from liver fat detected by MRI was 0.8607 (95% confidence interval [CI]=0.8448–0.8766). The calibration plot showed good agreement between the expected probabilities from the model and the actually observed probabilities (Fig 2). The best cut-off for liver fat on MRI to discriminate between individuals with and without hepatic steatosis on ultrasound was 5.6%. For this cut-off, a sensitivity of 77.4%, specificity of 85.5%, PPV of 76% and NPV of 86.5% was identified.

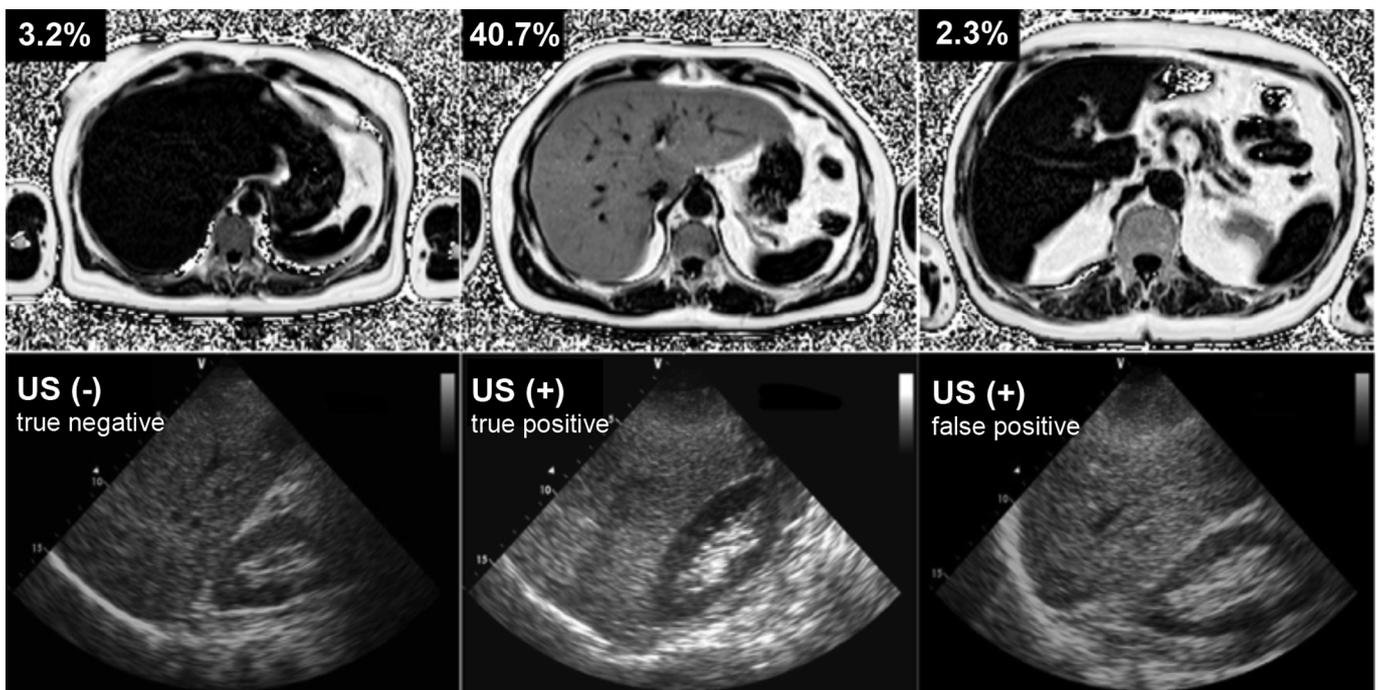
Based on R2\* mapping, MRI demonstrated a liver iron overload in 12.8% of participants (356 patients). The AUC for predicting hepatic steatosis on ultrasound from liver iron on MRI was 0.61 (95% CI=0.59–0.63). Adding liver iron to the prediction model already including liver fat did not improve the AUC significantly (AUC=0.8615, 95% CI=0.8457–0.8773,  $p=0.324$ ). Fig 3 demonstrates MRI (PDFF maps, R2\* maps) and corresponding ultrasound images in selected volunteers with and without hepatic steatosis, respectively, iron overload. Fig 4 shows ROC curves for the two prediction models explaining hepatic steatosis at ultrasound based on either MRI liver fat only or MRI liver fat and MRI liver iron. Adding MRI liver iron did not significantly improve the prediction of the model, demonstrating that assessment of liver fat is unaffected by the presence of liver iron.

Furthermore, the additional value of liver enzyme measurement for the detection of hepatic steatosis by

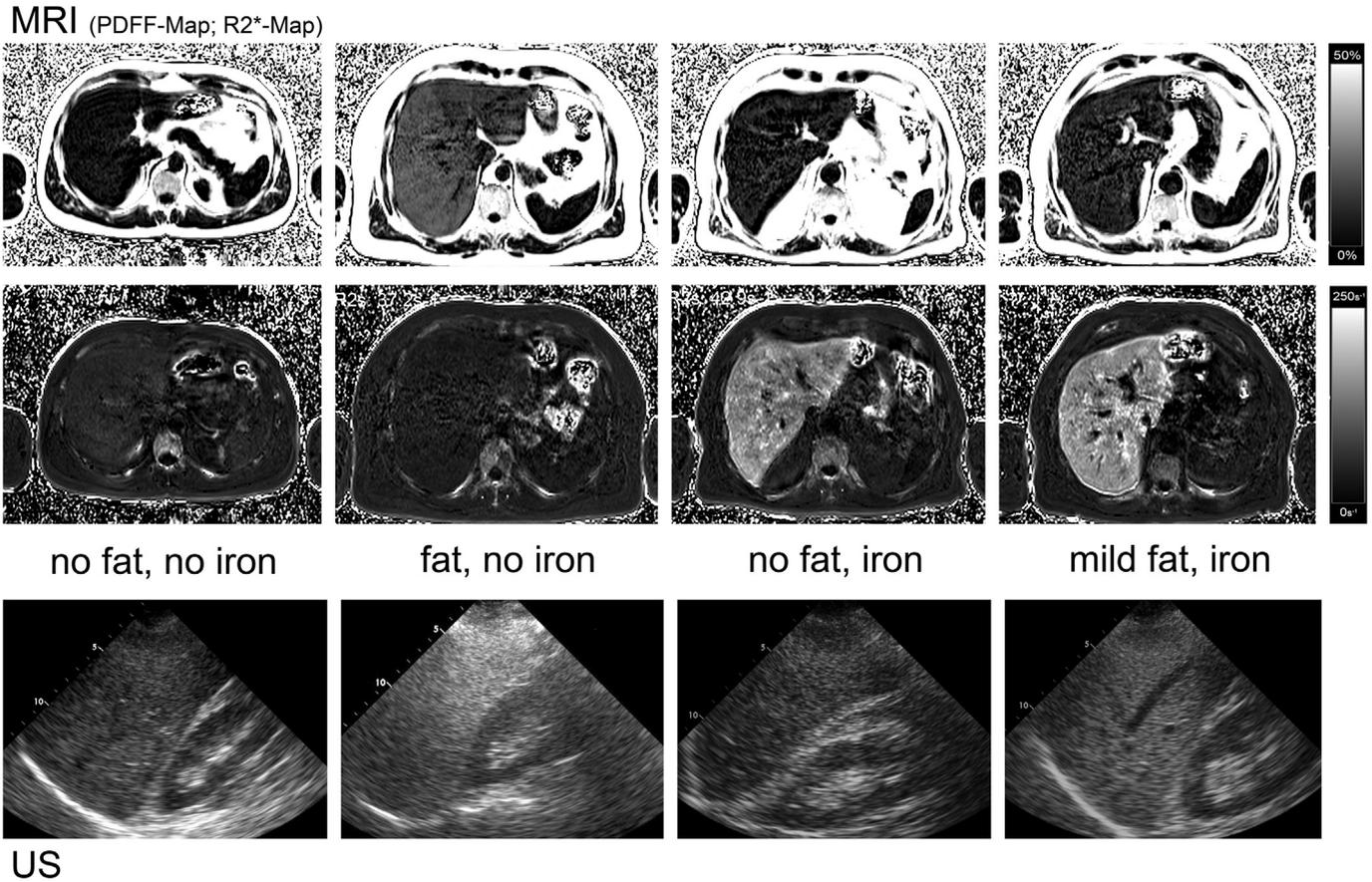


**Figure 2** Calibration plot for liver fat determined by MRI as predictor of hepatic steatosis on ultrasound.

ultrasonography was investigated. The AUCs for the prediction of hepatic steatosis using liver enzyme levels were 0.7456 (95% CI=0.7271–0.7642) for alanine transaminase (ALAT), 0.6589 (95% CI=0.6383–0.6796) for aspartate transaminase (ASAT), 0.7435 (95% CI=0.7252–0.7618) for gamma-glutamyl transferase (GGT), and 0.7648 (95% CI=0.7469–0.7827) for the combination of all three liver enzymes. All of these models showed good calibration (Fig 5). The best cut-offs to discriminate between individuals with and without hepatic steatosis were 22.8 IU/L for ALAT, 18.6 IU/L for ASAT, and 28.8 IU/L for GGT. Applying these cut-offs, the sensitivity for hepatic steatosis at MRI was best for GGT (76.7%), followed by ALAT (72.7%) and



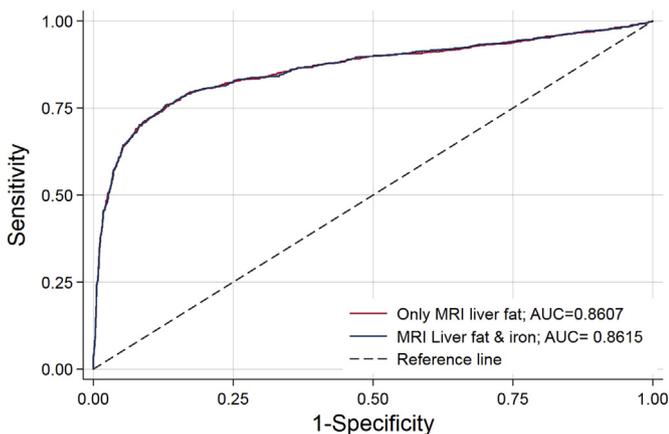
**Figure 1** There was excellent agreement between confounder-corrected MRI (upper row) and ultrasound (lower row) for (a) patients without hepatic steatosis and (b) patients with an advanced stage of hepatic steatosis. Most patients were classified correctly. (c) In small number of patients, however, ultrasound was FP for hepatic steatosis.



**Figure 3** Liver PDFF-maps (upper row), R2\*-maps (middle row) and corresponding ultrasonography of selected volunteers with no fat/no iron (PDFF 3%/R2\* 44/second); fat/no iron (PDFF 17%/R2\* 37/second); no fat/iron (PDFF 5%/R2\* 163/second); and mild fat/iron (PDFF 10%/R2\* 154/second). Liver iron did not significantly influence the accuracy of assessment of hepatic steatosis using ultrasound.

ASAT (57.6; [Table 2](#)). The specificity was highest for ASAT (65.7%), followed by ALAT (64.8%) and GGT (59.5%). Combining all three liver enzymes increased the specificity to 84.9%, while the sensitivity dropped to 45.1%. When combining all three liver enzymes with hepatic steatosis on

ultrasound, the specificity for hepatic steatosis on MRI further increased to 97.4%, but the sensitivity dropped to 37.8%. Applying this definition to predict the three stages of hepatic steatosis revealed a sensitivity of 26.5% for mild, 59.6% for moderate, and 81.6% for severe hepatic steatosis.

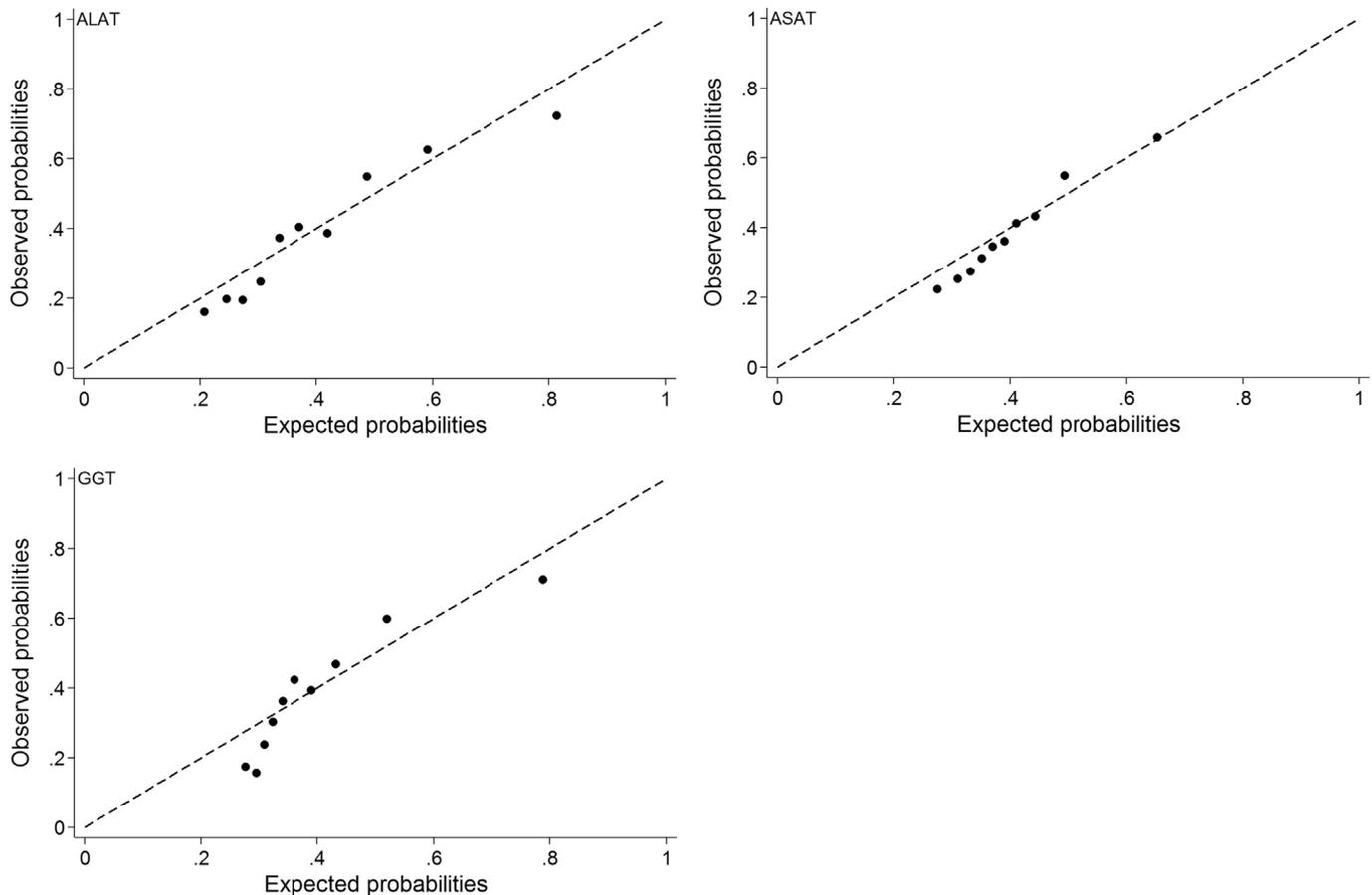


**Figure 4** ROC curves for the prediction models on hepatic steatosis using ultrasonography (MRI liver fat only versus MRI liver fat and MRI liver iron). Adding MRI liver iron does not significantly improve the prediction of the model.

### Discussion

The present study investigated the accuracy of liver ultrasound in the detection of liver fat in comparison to MRI-based PDFF as standard of reference. Moreover, the impact of hepatic iron concentration and liver enzymes on the detection and assessment of hepatic steatosis by ultrasound was also studied. The present results show excellent sensitivity and specificity of ultrasound for the estimation of fatty liver disease in patients with moderate and high liver fat content; however, in patients with a low fat content, the sensitivity of ultrasound is reduced and thus it is recommended that MRI is used for assessing the status of liver fat. Additional quantification of liver enzymes optimises the specificity by reducing the sensitivity. Finally, the present data do not show liver iron to be a significant confounder for the sonographic detection of hepatic steatosis.

The accuracy of ultrasound in the assessment of hepatic steatosis in comparison to established techniques, such as



**Figure 5** Calibration plot for liver enzymes as predictor of hepatic steatosis on MRI.

**Table 2**

Performance of liver enzyme levels in combination with/without ultrasonography for the detection of hepatic steatosis in comparison to MRI as the reference standard.

	ALAT $\geq 0.38$ $\mu\text{katal/l}$	ASAT $\geq 0.31$ $\mu\text{katal/l}$	GGT $\geq 0.48$ $\mu\text{katal/l}$	All liver enzymes increased	All liver enzymes increased & liver ultrasound positive
N	2,783	2,783	2,783	2,783	2,783
Sensitivity (%)	72.7 (71; 74.3)	57.6 (55.8; 59.5)	76.6 (75.1; 78.2)	45.1 (43.3; 47)	37.8 (36; 39.6)
Specificity (%)	64.8 (63; 66.5)	65.7 (63.9; 67.4)	59.5 (57.7; 61.3)	84.9 (83.5; 86.2)	97.4 (96.8; 98)
True positive	808 (29%)	641 (23%)	852 (30.6%)	502 (18%)	420 (15.1%)
True negative	1,082 (38.9%)	1,097 (39.4%)	994 (35.7%)	1,418 (51%)	1,628 (58.5%)
False positive	589 (21.2%)	574 (20.6%)	677 (24.3%)	253 (9.1%)	43 (1.5%)
False negative	304 (10.9%)	471 (16.9%)	260 (9.3%)	610 (21.9%)	692 (24.9%)
PPV	57.8 (56; 59.7)	52.8 (50.9; 54.6)	55.7 (53.9; 57.6)	66.5 (64.7; 68.2)	90.7 (89.6; 91.8)
NPV	78.1 (76.5; 79.6)	70 (68.3; 71.7)	79.3 (77.8; 80.8)	69.9 (68.2; 71.6)	70.2 (68.5; 71.9)

Data in parentheses are 95% confidence intervals.

PPV, positive predictive value; NPV, negative predictive value.

biopsy, MR spectroscopy, and computed tomography (CT), has been controversially discussed in recent publications.<sup>10,13,21</sup> For example, Bohte *et al.* compared ultrasound and MR spectroscopy for the assessment of hepatic steatosis and found a sensitivity of 85.4% and specificity of 55.4% in 104 obese adolescents (MRI-based detection of steatosis in 46.2% of study participants).<sup>21</sup> They concluded that ultrasound alone does not accurately predict the presence and severity of hepatic steatosis in obese adolescents and that the additional use of MRI is required. Clinical studies in adults reported sensitivities and specificities of

ultrasonography for assessing liver fat ranging from 60–94%.<sup>13,22–26</sup> Unlike other studies, the present study used a population-based approach and, therefore, included a much higher number of participants. In this study, a sensitivity of 74.5% and a specificity of 86.6% were found. Ultrasonography is an acceptable technique for the detection of hepatic steatosis, if the grade of hepatic steatosis is ignored. In accordance with Fishbein *et al.* and Dasarathy *et al.*, the performance of ultrasound was poor in patients with a low liver fat content.<sup>27,28</sup> For those patients, either an additional image method could be used to assess liver fat,

for example MRI, which allows liver fat quantification in less than 20 seconds, or alternatively, further investigation may be waived regarding the minor clinical impact of mild steatosis. Furthermore, the present population-based study clearly demonstrates the feasibility of examining a large number of volunteers using MRI.

Additionally, the present results show that, when liver enzymes are considered, specificity can be increased to 97.4% across all grades of hepatic steatosis, albeit at the expense of sensitivity. In order to preselect patients with possible hepatic steatosis, a combination of ultrasound and liver enzyme quantification would, therefore, be a suitable diagnostic procedure, which can be followed by an additional MRI examination in those cases suggesting a mild steatosis in order to rule out FPs.

MRI is able to quantify hepatic fat content, which is also relevant for scientific studies. Current studies focus on the detection of steatohepatitis and cirrhosis using MRI.<sup>10,11,16</sup> Currently available data suggest that MRI biomarkers for the assessment of early stages of inflammation and chronic liver disease could replace biopsy in the future.

A secondary aim of the present study was to investigate if liver iron is a confounder for the detection of hepatic steatosis using ultrasound. Approximately 15–20% of patients with hepatic steatosis have concomitant iron overload.<sup>29–32</sup> Although liver fat quantification by other imaging methods such as CT and MRI is influenced by iron, detection of hepatic steatosis by ultrasonography was not affected by the presence of liver iron in the present study.

The study has several limitations. First, the results demonstrate that ultrasound is an excellent tool for the detection of fatty liver diseases in patients with moderate and high fat content, but limited in patients with a low fat content. Other imaging methods such as quantitative MRI might be used for robust detection of fatty liver disease; however, the clinical relevance of a low liver fat content is critically discussed. Recent studies suggest that, technically, it is feasible to quantify liver fat content using ultrasonography.<sup>33–35</sup> This technique was not used in the present study because quantitative ultrasound is still an investigational technique.

In conclusion, liver ultrasound is an excellent tool to assess liver fat in the clinical setting in individuals with higher amounts of liver fat. The weakness of ultrasound in assessing small amounts of liver fat should be considered and compensated by additional liver enzyme quantification or MRI. The assessment of hepatic steatosis using ultrasound is not affected by liver iron.

## Conflict of interest

The authors declare no conflict of interest.

## Acknowledgements

The work is part of the Community Medicine Research net (CMR) of the University of Greifswald, Germany. The CMR encompasses several research projects that share data

from the population-based SHIP project (<http://ship.community-medicine.de>). SHIP is funded by following institutions: Federal Ministry of Education and Research (grants 01ZZ9603, 01ZZ0103, 01ZZ0403, 01ZZ0701, 03ZIK012), Ministry of Cultural Affairs as well as the Social Ministry of the Federal State of Mecklenburg-West Pomerania, Federal Ministry of Nutrition, Agriculture and Consumer's Safety (07HS003), German Research Foundation (projects Gr 1912/5-1, Ko 799/5-1, Vo 955/5-1, Vo 955/6-1, Vo 955/10-1), Competence Network Heart Failure (01GI0205), Competence Network Diabetes (01GI0855), German Asthma and COPD Network (COSYCONET; BMBF 01GI0883), Genopathomik (BMBF FZK 03138010), Alfried Krupp von Bohlen und Halbach Foundation, Alexander v. Humboldt Foundation, Leibniz Society, Siemens AG, Health Care Sector (Erlangen, Germany), Pfizer Pharma GmbH (SBU Endocrinology and Ophthalmology; Berlin Germany), Novo Nordisk (Mainz, Germany), Data Input GmbH (Darmstadt, Germany), GABA International AG (Therwil, Switzerland), Imedos Systems (Jena, Germany) and Heinen and Löwenstein (Bad Ems, Germany).

## References

- Rampal S, Mahadeva S, Guallar E, et al. Ethnic differences in the prevalence of metabolic syndrome: results from a multi-ethnic population-based survey in Malaysia. *PLoS One* 2012;**7**(9):e46365.
- Browning JD, Szczepaniak LS, Dobbins R, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology* 2004;**40**(6):1387–95.
- Schwimmer JB, Deutsch R, Kahen T, et al. Prevalence of fatty liver in children and adolescents. *Pediatrics* 2006;**118**(4):1388–93.
- Targher G, Bertolini L, Rodella S, et al. Non-alcoholic fatty liver disease is independently associated with an increased prevalence of chronic kidney disease and proliferative/laser-treated retinopathy in type 2 diabetic patients. *Diabetologia* 2008;**51**(3):444–50.
- Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *N Engl J Med* 2010;**363**(14):1341–50.
- Clark JM, Diehl AM. Hepatic steatosis and type 2 diabetes mellitus. *Curr Diab Rep* 2002;**2**(3):210–5.
- Roden M. Mechanisms of Disease: hepatic steatosis in type 2 diabetes—pathogenesis and clinical relevance. *Nat Clin Pract Endocrinol Metab* 2006;**2**(6):335–48.
- Muhidin SO, Magan AA, Osman KA, et al. The relationship between nonalcoholic fatty liver disease and colorectal cancer: the future challenges and outcomes of the metabolic syndrome. *J Obes* 2012;**2012**:637538.
- Bernard S, Touzet S, Personne I, et al. Association between microsomal triglyceride transfer protein gene polymorphism and the biological features of liver steatosis in patients with type II diabetes. *Diabetologia* 2000;**43**(8):995–9.
- Reeder SB, Cruite I, Hamilton G, et al. Quantitative assessment of liver fat with magnetic resonance imaging and spectroscopy. *J Magn Reson Imaging* 2011;**34**(4):729–49.
- Permutt Z, Le TA, Peterson MR, et al. Correlation between liver histology and novel magnetic resonance imaging in adult patients with non-alcoholic fatty liver disease — MRI accurately quantifies hepatic steatosis in NAFLD. *Aliment Pharmacol Ther* 2012;**36**(1):22–9.
- Roldan-Valadez E, Favila R, Martinez-Lopez M, et al. Imaging techniques for assessing hepatic fat content in nonalcoholic fatty liver disease. *Ann Hepatol* 2008;**7**(3):212–20.
- Celle G, Savarino V, Picciotto A, et al. Is hepatic ultrasonography a valid alternative tool to liver biopsy? Report on 507 cases studied with both techniques. *Dig Dis Sci* 1988;**33**(4):467–71.

14. Kuhn JP, Meffert P, Heske C, et al. Prevalence of fatty liver disease and hepatic iron overload in a northeastern German population by using quantitative MR imaging. *Radiology* 2017;**284**(3):706–16.
15. Volzke H, Alte D, Schmidt CO, et al. Cohort profile: the study of health in Pomerania. *Int J Epidemiol* 2011;**40**(2):294–307.
16. Kuhn JP, Hernando D, Munoz del Rio A, et al. Effect of multipeak spectral modeling of fat for liver iron and fat quantification: correlation of biopsy with MR imaging results. *Radiology* 2012;**265**(1):133–42.
17. Hernando D, Levin YS, Sirlin CB, et al. Quantification of liver iron with MRI: state of the art and remaining challenges. *J Magn Reson Imaging* 2014;**40**(5):1003–21.
18. Meisamy S, Hines CD, Hamilton G, et al. Quantification of hepatic steatosis with T1-independent, T2-corrected MR imaging with spectral modeling of fat: blinded comparison with MR spectroscopy. *Radiology* 2011;**258**(3):767–75.
19. Yu H, Buch K, Li B, et al. Utility of texture analysis for quantifying hepatic fibrosis on proton density MRI. *J Magn Reson Imaging* 2015;**42**(5):1259–65.
20. Bannas P, Kramer H, Hernando D, et al. Quantitative magnetic resonance imaging of hepatic steatosis: validation in *ex vivo* human livers. *Hepatology* 2015;**62**(5):1444–55.
21. Bohte AE, Koot BG, van der Baan-Slootweg OH, et al. US cannot be used to predict the presence or severity of hepatic steatosis in severely obese adolescents. *Radiology* 2012;**262**(1):327–34.
22. Joseph AE, Saverymuttu SH, al-Sam S, et al. Comparison of liver histology with ultrasonography in assessing diffuse parenchymal liver disease. *Clin Radiol* 1991;**43**(1):26–31.
23. Saverymuttu SH, Joseph AE, Maxwell JD. Ultrasound scanning in the detection of hepatic fibrosis and steatosis. *Br Med J (Clin Res Ed)* 1986;**292**(6512):13–5.
24. Needleman L, Kurtz AB, Rifkin MD, et al. Sonography of diffuse benign liver disease: accuracy of pattern recognition and grading. *AJR Am J Roentgenol* 1986;**146**(5):1011–5.
25. Mathiesen UL, Franzen LE, Aselius H, et al. Increased liver echogenicity at ultrasound examination reflects degree of steatosis but not of fibrosis in asymptomatic patients with mild/moderate abnormalities of liver transaminases. *Dig Liver Dis* 2002;**34**(7):516–22.
26. Hepburn MJ, Vos JA, Fillman EP, et al. The accuracy of the report of hepatic steatosis on ultrasonography in patients infected with hepatitis C in a clinical setting: a retrospective observational study. *BMC Gastroenterol* 2005;**5**:14.
27. Fishbein M, Castro F, Cheruku S, et al. Hepatic MRI for fat quantitation: its relationship to fat morphology, diagnosis, and ultrasound. *J Clin Gastroenterol* 2005;**39**(7):619–25.
28. Dasarathy S, Dasarathy J, Khiyami A, et al. Validity of real time ultrasound in the diagnosis of hepatic steatosis: a prospective study. *J Hepatol* 2009;**51**(6):1061–7.
29. Dongiovanni P, Fracanzani AL, Fargion S, et al. Iron in fatty liver and in the metabolic syndrome: a promising therapeutic target. *J Hepatol* 2011;**55**(4):920–32.
30. Bonkovsky HL, Jawaid Q, Tortorelli K, et al. Non-alcoholic steatohepatitis and iron: increased prevalence of mutations of the HFE gene in non-alcoholic steatohepatitis. *J Hepatol* 1999;**31**(3):421–9.
31. George DK, Goldwurm S, MacDonald GA, et al. Increased hepatic iron concentration in nonalcoholic steatohepatitis is associated with increased fibrosis. *Gastroenterology* 1998;**114**(2):311–8.
32. Moirand R, Mortaji AM, Loreal O, et al. A new syndrome of liver iron overload with normal transferrin saturation. *Lancet* 1997;**349**(9045):95–7.
33. Lin SC, Heba E, Wolfson T, et al. Noninvasive diagnosis of nonalcoholic fatty liver disease and quantification of liver fat using a new quantitative ultrasound technique. *Clin Gastroenterol Hepatol* 2015;**13**(7):1337–1334 e6.
34. Edens MA, van Ooijen PM, Post WJ, et al. Ultrasonography to quantify hepatic fat content: validation by <sup>1</sup>H magnetic resonance spectroscopy. *Obesity (Silver Spring)* 2009;**17**(12):2239–44.
35. Xia MF, Yan HM, He WY, et al. Standardized ultrasound hepatic/renal ratio and hepatic attenuation rate to quantify liver fat content: an improvement method. *Obesity (Silver Spring)* 2012;**20**(2):444–52.