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Do regions of interest location and type influence liver stiffness measurement using magnetic resonance elastography?

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KEYWORDS
Liver fibrosis;
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ROI;
Reproducibility

Abstract
Purpose: To assess the variability of liver stiffness measurements using magnetic resonance elastography (MRE) at 1.5 T, depending on different approaches of regions of interest (ROIs) drawing.
Material and methods: Fifty consecutive patients with successful liver MRE were included. There were 32 men and 18 women with a mean age of 52 ± 14 (SD) years (range: 20—85 years). MRE was acquired using a gradient recalled-echo MRE sequence. At the level of the portal bifurcation, one observer drawn in the right liver first 3 elliptical ROI and then one free-hand ROI, as large as possible based on the confidence map and the anatomy. Three additional elliptical ROIs were further drawn on the slice above and 3 other on the slice below, for a total of 9 elliptical ROIs. The average value of liver stiffness in the 3 elliptical ROIs of the central slice and the one from the 9 elliptical ROIs were computed. Three liver stiffness values were obtained for each patient from the 3 measurement methods (one free-hand ROI, 3 elliptical ROIs and 9 elliptical ROIs). Inter-method variability was assessed using the intra-class correlation coefficient (ICC) and Bland-Altman analysis.
Results: The variability between the 3 methods was excellent with ICC > 0.978 ($P < 0.0001$). The Bland-Altman analysis revealed high agreement between the 3 methods with bias < 0.45 kPa and limits of agreement < ±1.13 kPa. The variability was lower when comparing a large free-hand ROI and the 3-elliptical ROIs, than when comparing the 9-elliptical ROIs to one of the other methods.

Abbreviations: BALA, Bland-Altman limits of agreement; CR, coefficient of reproducibility; GRE, gradient recalled echo; HASTE, half Fourier single shot turbo spin echo; HCV, hepatitis viral C; ICC, intra-class correlation coefficient; MMDI, multimodel direct inversion; MR, magnetic resonance; MRE, magnetic resonance elastography; NAFLD, non-alcoholic fatty liver disease; PACS, picture archiving communication system workstation; ROI, region of interest; SNR, signal-to-noise ratio.

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Conclusion: Our results show that the variability between the 3 methods of ROI drawing and placement is very low.

Introduction

Chronic liver disease is an increasing worldwide health issue, due to increased frequency of non-alcoholic fatty liver diseases (NAFLD). The main complications of chronic liver disease are linked to the development of liver fibrosis, whose diagnosis and staging are necessary for optimal and adequate management. Until recently, liver fibrosis was assessed mostly using a liver biopsy, which is still the gold standard [1]. However, liver biopsy has some drawbacks, like its invasiveness, its sampling errors and the inter and intraobserver variability of its analysis [2—4]. Multiple non-invasive methods have been developed to replace liver biopsies for liver fibrosis assessment, at baseline or for follow-up.

Among those non-invasive methods, elastography, either using ultrasound or magnetic resonance imaging (MRI), is an imaging method, based on shear waves displacement analysis that provides an estimation of the tissue stiffness. It has been shown that magnetic resonance elastography (MRE) is accurate to diagnose and stage liver fibrosis and that it outperforms ultrasound elastography techniques and serum markers [5—9]. Therefore, the place and the role of magnetic resonance elastography MRE are increasing in clinical routine.

Measurement reproducibility and repeatability are needed to allow daily practice uses of any quantitative imaging modalities, including MRE measurement of liver stiffness. Some studies have shown a high test-retest repeatability, and a high intra and interobserver reproducibility, a high inter-platform reproducibility from different vendor or with different field strength [10—15].

To obtain liver stiffness values, regions of interest (ROIs) are drawn on the stiffness map, and based on the confidence map in order to have reliable results. The number of ROIs can vary among studies and local habits, and the ROI can have a geographic shape, an elliptical shape or be free-hand drawn.

To assess the variability of liver stiffness measurements using MRE at 1.5 T, depending on different approaches of regions of interest (ROIs) drawing.

Materials and methods

Patients

This retrospective study was performed in a single center. Informed consent was waived. All consecutive patients who underwent liver MRI, including MRE during a 2-month period between March and April 2017, were initially selected. The first 50 patients without failed MRE acquisition (a failure was defined as the absence of visualized wave propagation on the wave images and/or no pixel with a confidence index higher than 95% on the confidence map), and with a large analyzable right liver area without liver lesions and on the confidence map were selected by observer 1, a radiology resident (H. C.) [16]. The number of patients was chosen in order to have a sufficient sample size. The final study population included 50 patients (32 men and 18 women) with a mean age of 58 ± 14 (SD) years (range: 20—85 years). A flow chart of the study is presented in Fig. 1.

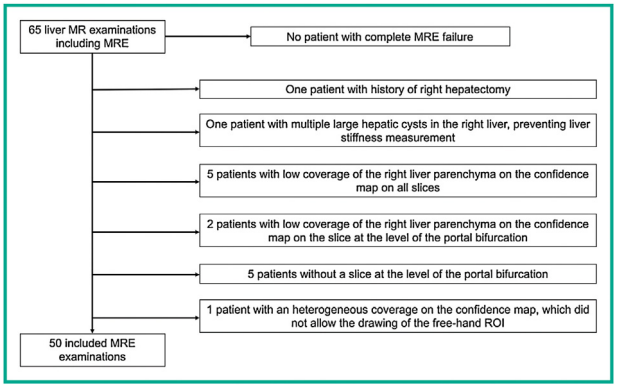

Figure 1. Flow chart of the study.

MRI data acquisition

For all MRI examinations, a 1.5-T clinical system (Magnetom AERA®, Siemens Healthineers) was used with an 18-channel body phased-array coil. MRE acquisition was performed after intravenous administration of a gadolinium-based contrast agent per clinical protocol (gadoterate meglumine, Dotarem®, Guerbet or gadobenate dimeglumine, Multihance®, Bracco) [17]. Patients were asked to fast for 4 h prior to liver MRI to eliminate postprandial effects on portal venous blood flow [18].

For MRE acquisition, 60-Hz shear waves were generated by using a 19-cm-diameter, 1.5-cm-thick, passive acoustic driver, which was placed against the right anterior chest wall at the level of the xiphoid process overlying the liver. Wave imaging was performed by using a modified two-dimensional phase-contrast GRE pulse sequence with motion-encoding gradients along the z-axis. Six transverse sections were placed through the largest transverse dimension of the liver.

The pulse sequence parameters were as follows: repetition time, 50 msec; echo time 23 msec; field of view, adapted to body size (350 × 280); matrix, 204 × 256; number of signal acquired, one; phase offsets, four, bandwith, 260 Hz/pixel; section thickness, 5 mm; array coil spatial sensitivity encoding factor, two; acquisition time, 114 s split into 6 breath-holds. The stiffness maps were generated automatically using the multimodel direct inversion (MMDI) algorithm [19,20]. A confidence index (ranging from 0—100%) for stiffness measurement was estimated and automatically provided by the software for each stiffness map.

Additionally, the liver MRI protocol included the following sequences: coronal and axial T2-weighted half Fourier single shot turbo spin echo (HASTE) images without fat saturation, axial T2-weighted images with fat saturation, diffusion-weighted imaging (*b* value = 0, 150 and 600 s/mm^2), T1-weighted images using the Dixon technique pre and post-contrast, at the arterial, portal venous, interstitial and delayed phases.

Image analysis

Image analysis was performed by two independent observers, using a picture archiving communication system workstation (PACS Carestream®, version 11.4.0, Carestream Health) further referred to as observer 1 and observer 2 (A. C.). Both observers were trained using 10 MRI examinations, which were not included in the study analysis. For the analysis, the images were displayed on a screen using 4 boxes: top-left, axial T2-weigthed images without fat saturation to allow morphology and anatomy analysis; top-right, MRE magnitude images; bottom-left, MRE stiffness map and bottom-right, MRE confidence map.

Observer 1 was initially asked to select the slice at the level of the portal bifurcation and to save the slice number. Then, he was asked to draw two types of regions of interest (ROI). First, a free-hand ROI was drawn on the selected slice. The ROI had to be as large as possible, excluding large vessels, parenchyma edge and fissures, excluding liver lesions, based on magnitude images analysis, and excluding all the pixels with a confidence index lower than 95%, based on confidence map analysis. As the magnitude images have a low spatial resolution, in case of doubt, the observers were able to use the T2-weighted images. Second, 3 elliptical ROIs with a size between 200 and 250 mm^2 were drawn on the same slice, 3 elliptical ROIs on the slice above and 3 on the slice below, for a total of 9 elliptical ROIs. The elliptical ROIs also had to exclude large vessels, parenchyma edge and fissures, and pixels with a confidence index lower than 95% (Fig. 2).

Drawing elliptical ROIs may lead to liver stiffness value variations between observers, because the liver stiffness values depend on the location of the ROIs. Therefore, observer 2 was asked to draw the 9 elliptical ROIs, using the method described above for observer 1, in order to assess the interobserver reproducibility of the ''elliptical ROI'' methods. Observer 2 was aware of the selected slices, chosen by observer 1. The high interobserver reproducibility of the free-hand ROI has already been published, so observer 2 was not asked to draw the free-hand ROI [14]. Liver stiffness value was extracted for both observers from each ROI in kilopascals (kPa). The average values of liver stiffness of the 3 elliptical ROIs of the center slice and of the 9 elliptical ROIs were computed.

Statistical analysis

Quantitative data were expressed as mean ± standard deviation (SD) and range. Qualitative data were expressed as raw numbers, proportions and percentages. First, the heterogeneity of the measurements between the 3 and the 9-elliptical ROIs was assessed for observer 1. Second, the interobserver reproducibility for the elliptical ROI methods, using only the values from the 3 ROIs of the center slice (called ''3-elliptical ROIs method'') or using the values from the 9 ROIs (called ''9-elliptical ROIs method''), was assessed. In a third part, the reproducibility between the 3 approaches was analyzed, using the measurement of observer 1 (based on the results of the first part of the analysis).

The heterogeneity between the 3 and the 9-elliptical ROIs was assessed using the coefficient of variation of the values in the ROIs. Both interobserver and intermethod reproducibility were assessed using intra-class coefficient correlation (ICC) and Bland-Altman analysis. The analyses were performed by comparing the methods 2-by-2 and globally. For ICC, the 95% confident intervals (CI) were computed. ICC values of 0—0.2, 0.2—0.4, 0.4—0.6, 0.6—0.8 and 0.8—1 are representative of slight, fair, moderate, substantial and almost perfect reliability. The Bland-Altman analysis included the computation of the bias, the 95% limits of agreement (BALA) as well as the coefficient of reproducibility (CR = 1.96 × standard deviation of bias). All analyses were performed using MATLAB (version R2015a, MathWorks).

Results

Indications for liver MRI examinations were chronic liver disease follow-up and hepatocellular carcinoma screening/surveillance (37/50; 74%), focal liver lesions (10/50; 20%), steatosis screening (2/50; 4%) and liver transplant follow-up (1/50; 2%). A total of 37/50 patients (74%) had an underlying chronic liver disease that included chronic viral hepatitis C (8/50; 16%), chronic viral hepatitis B (8/50; 16%), non-alcoholic steatohepatitis (3/50; 6%), alcohol abuse (5/50; 10%), other etiologies (3/50; 6%) or a combination of various etiologies (10/50; 20%).

Liver stiffness values depending on the ROI method are presented in Table 1. The mean size of the free-hand ROI was 46.49 ± 14.06 (SD) cm2.

Heterogeneity of the measurement between the 3 or 9 elliptical ROIs

There was some heterogeneity between the elliptical ROIs, which trended to be higher among the 9-elliptical ROIs than among the 3-elliptical ROIs. Among the 3-elliptical ROIs, the coefficient of variation was 17.1% ± 8.3 (SD) % [range: 2.6%-36.9%]. Among the 9-elliptical ROIs, the coefficient of variation was 21.0% ± 7.8 (SD) % [range: 9%—44%].

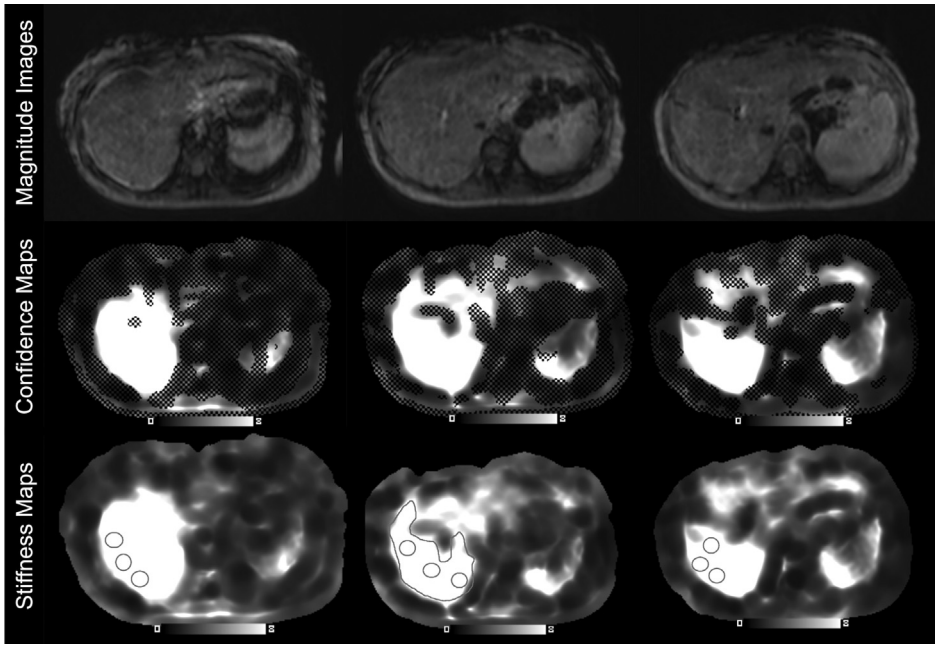

Figure 2. Example of ROIs placement on the 3 used slices: top row: magnitude images, middle row: confidence maps, lower row: stiffness maps. The free-hand ROI was drawn as large as possible, excluding large vessels, parenchyma edge, fissures, and liver lesions and including only the pixels with a confidence index higher than 95%, based on confidence map analysis. Three elliptical ROIs were drawn on the same slice in the right liver, 3 elliptical ROIs on the slice above and 3 on the slice below, for a total of 9 elliptical ROIs.

Table 1 Liver stiffness values obtained with different regions of interest by the 2 observers (observer 1, O1 and observer 2, O2).

	Liver stiffness (kPa)
Free-hand ROI	3.780 ± 1.811 [1.61—11.95]
3-elliptical ROIs O1	3.913 ± 2.080 [1.48—13.83]
9-elliptical ROIs O1	4.225 ± 2.150 [1.62—12.91]
3-elliptical ROIs O2	4.062 ± 2.143 [1.47—13.56]
9-elliptical ROIs O2	4.289 ± 2.249 [1.64—13.69]

ROI: region of interest. Data are presented as mean ± standard deviation. Numbers in brackets are ranges.

Interobserver reproducibility of the 3- and the 9-elliptical ROIs methods

The agreement between the 2 readers was almost perfect with ICC equal to 0.989 for the 3-elliptical ROIs and 0.991 for the 9-elliptical ROIs. The Bland-Altman analysis confirmed the low variability with low bias (|bias| < 0.15 kPa) (Table 2, Figs. 3 and 4).

Inter-method reproducibility

The global agreement between the 3 methods, as well as the agreement between the methods when compared 2-by-2, were almost perfect with ICC > 0.9 (global analysis, ICC 0.988; 3 vs. 9-elliptical ROIs methods, ICC 0.983; large free-hand ROI vs. 3-elliptical ROIs ICC 0.987; large free-hand ROI vs. 9-elliptical ROIs, ICC 0.978) (Table 3, Figs. 5 and 6).

The Bland-Altman analysis confirmed the excellent inter-method agreement with |bias| < 0.45 kPa. The variability was lower when comparing a large free-hand ROI and the 3-elliptical ROIs, than when comparing the 9-elliptical ROIs to one of the other methods.

Discussion

In this study, we compared 3 methods of ROIs drawing and placement for liver stiffness measurement on MRE images. We found that the 3 methods are highly reproducible. Our study confirms the high reproducibility for interobserver analysis, as described by Yasar et al., despite the fact that the method for ROIs selection was different [14]. Indeed, in Yasar et al. study free-hand ROIs on all of the available slices were drawn, including the largest possible area of liver, based on the anatomy and the confidence map [14]. With easier methods, using only elliptical ROIs, which are faster to draw, the interobserver reproducibility is still high. The variability in the current study is lower than that reported by Lee et al. who also used elliptical ROIs [12]. However, in the study by Lee et al., ROIs were not based on confidence maps, which may have misjudged the results [12].

The second part of our study reveals a high reproducibility and a low variability between 3 methods of ROIs drawing and placement for liver stiffness measurement using MRE images. To our knowledge, no previous studies have compared free-hand and elliptical ROIs methods. Several factors can potentially influence MRE measurement, and link to a variability of the measurement. Those factors include image quality, the setup used, the system used and its magnetic field, and the analysis of the observer. In the current study, we focused on the last parameter. It includes factors linked

Table 2 Interobserver reproducibility with 2 methods using elliptical regions of interest.

	ICC			Bland-Altman analysis		
	ICC	95%CI	*P*	Bias	BALA	CR
3-elliptical ROIs	0.989	[0.981—0.994]	< 0.0001	−0.1491	±0.8582	0.8985
9-elliptical ROIs	0.991	[0.985—0.995]	< 0.0001	−0.0686	±0.555	0.8041

ICC: intra-class correlation coefficient; 95%CI: 95% confident interval; BALA: Bland-Altman limits of agreement; CR: coefficient of reproducibility; ROI: region of interest.

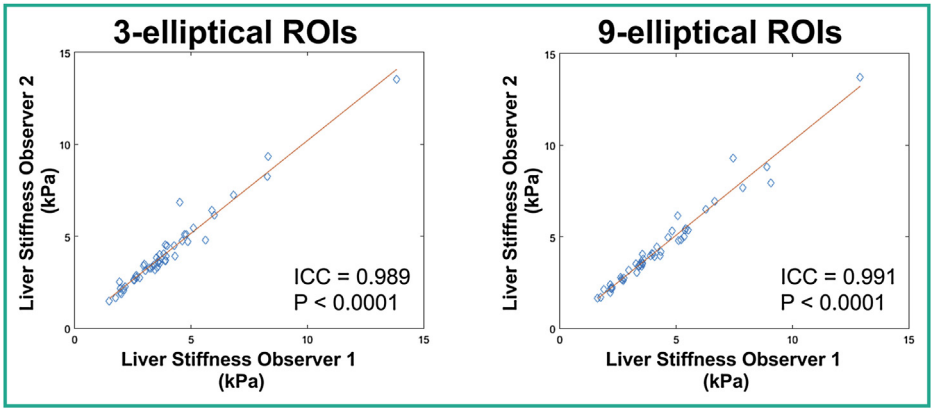

Figure 3. Graphs show correlation of liver stiffness measurement by the 2 observers.

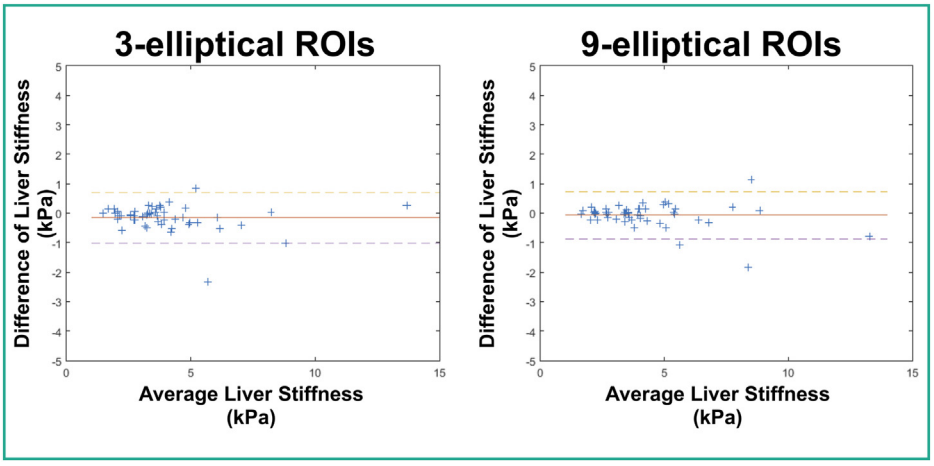

Figure 4. Bland-Altman graphs show interobserver reproducibility of liver stiffness measurement using elliptical ROIs. Dashed lines represent Bland-Altman limits of agreement (1.96 SD). Red line represents bias (see also Table 2). The interobserver reproducibility was excellent with low bias (< −0.15 kPa) and low CR (< 0.90 kPa).

to the observer by itself, assessed by the interobserver reproducibility analysis, and the method of analysis chosen in the study. To obtain liver stiffness values, ROI(s) must be drawn on the stiffness map. It is commonly admitted that the ROI(s) is(are) usually placed in the right liver and should exclude artifacts like the one secondary to the edges and fissures, large vessels (> 3 mm), artifactual hotspot and areas of low confidence index, usually lower than 95% [6,21]. The confidence index is automatically computed and includes multiple parameters, such as SNR, wave amplitude, wave interference and inversion algorithm performance, in order to calculate a statistical confidence [20]. Location and size of ROI(s) greatly vary in the literature. Free-hand ROIs as large as possible are attractive because they allow the analysis of a larger sample of the liver parenchyma, which is one of the advantages of MRE over ultrasound elastography techniques [5,21]. However, they are time consuming to ensure exclusion of artifacts areas and the inclusion

Table 3 Inter-method reproducibility (for observer 1).

	ICC			Bland-Altman analysis		
	ICC	95%CI	*P*	Bias	BALA	CR
Global analysis	0.988	[0.982—0.993]	< 0.0001	//	//	//
3 vs. 9-elliptical ROIs methods	0.983	[0.969—0.990]	< 0.0001	−0.3084	±1.0864	1.2336
Large free-hand ROI vs. 3-elliptical ROIs	0.987	[0.978—0.993]	< 0.0001	0.1331	±1.1331	0.8854
Large free-hand ROI vs. 9-elliptical ROIs	0.978	[0.962—0.988]	< 0.0001	0.4415	±0.8547	1.4167

ICC: intra-class correlation coefficient; CI95%: 95% confident interval; BALA: Bland-Altman limits of agreement; CR: coefficient of reproducibility; ROI: region of interest.

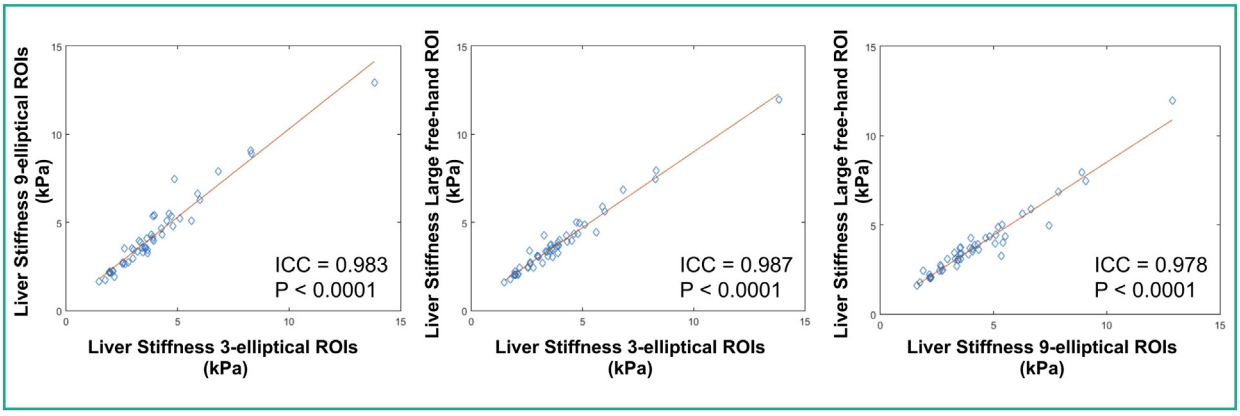

Figure 5. Graphs show correlation of liver stiffness measurements by the 3 different ROI methods (observer 1).

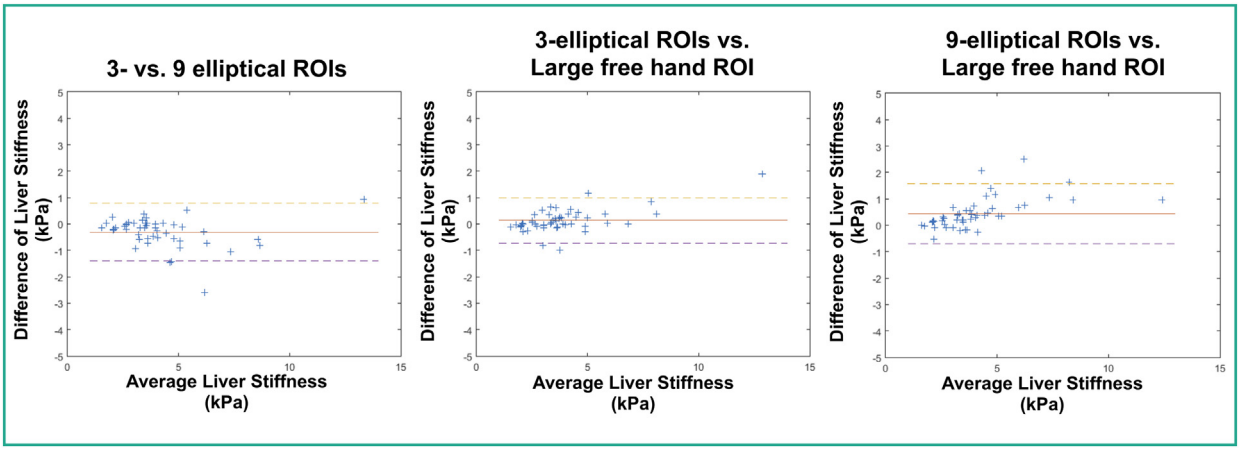

Figure 6. Bland-Altman graphs show inter-method reproducibility of liver stiffness measurements (observer 1). Dashed lines represent Bland-Altman limits of agreement (1.96 SD). Red line represents bias (see also Table 3). The inter-method reproducibility was excellent with low bias (< 0.45 kPa) and low CR (< 1.42 kPa).

of the maximum area of liver parenchyma. On the other hand, elliptical ROIs are fast and easy to draw. A correct and accurate placement is also easy to do, with adequate image display, including magnitude, confidence map and stiffness map. Our results showed that the liver stiffness values obtained with elliptical ROIs are closer when compared to the ones obtained with the free-hand ROI. Moreover, there is no added value to increase the number of the elliptical ROIs, particularly on adjacent slices.

Our study has several limitations to be acknowledged. First, our sample size was quite small, as we included only 50 patients. However, in most of the reproducibility studies, the scale of the sample size was similar. Second, we did not perform the interobserver analysis for the free-hand

ROI method. However, the good/high reproducibility of this method has already been shown [14]. Moreover, the idea of this study was to show that a simpler and faster method, such as the 3-elliptical ROIs method, could give the same results and could replace the free-hand ROI method which is more time consuming. Third, we did not have pathological results for the studied patients, did not compare our results to a pathological fibrosis score, like the METAVIR score, and therefore did not assess the performance of each method for fibrosis staging. However, there are many published studies showing the accurate performance of MRE for fibrosis staging whatever the type of used ROIs [5,22—25]. Moreover, it was not the aim of the current study, which focused on the variability between the ROI methods.

In conclusion, the variability between the 3 methods of ROIs drawing and placement is very low. In this context, the fastest and easiest method, which is the placement of 3 elliptical ROIs on the slice closest to the level of the portal vein bifurcation, could be used routinely in clinical practice.

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Authors contribution

Adrien Cogneau: acquisition of the data, data analysis, interpretation of the data, statistical analysis, drafting of the article, final approval.

Hyoun Cho: acquisition of the data, data analysis, interpretation of the data, final approval.

Olivier Lucidarme: conception and design of the study, revising of the paper, final approval.

Mathilde Wagner: conception and design of the study, data analysis, interpretation of the data, statistical analysis, writing and revising of the paper, final approval.

Disclosure of interest

The authors declare that they have no competing interest.

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