Diagnostic value of optimised real-time sonoelastography in the assessment of liver fibrosis in chronic hepatitis B and C

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Abstract

Aim: To optimise the method of real-time elastography (RTE) in the assessment of liver fibrosis using an in-house prepared method for elastogram analysis, as well as a semiquantitative analysis based on newly introduced parameters.

Material and methods: Sonoelastography was performed in 94 patients with various degrees of liver fibrosis and also in 25 healthy volunteers. As a reference method for diagnostic efficacy of sonoelastography-based parameters used for the assessment of fibrosis degree in patients with chronic B and C hepatitis, a liver biopsy was used. Patient's elastograms were analysed using in-house prepared software, Pixel Count, calculating two semiquantitative parameters: mean stiffness fraction (MSF%) and intrinsic stiffness ratio (ISR).

Results: Statistically significant differences between distributions of the above presented parameters for different degrees of liver fibrosis were revealed. Indices of diagnostic efficacy for detection of significant liver fibrosis ($F \geq 2$) using MSF% amounted to: sensitivity – 76%, specificity – 87% and ISR: 81% and 87%, respectively. Sensitivity of both parameters in detection of cirrhosis ($F = 4$) was equal to 88% and specificity amounted to: for MSF% – 84% and ISR – 86%. Interobserver reproducibility determined for both of the above parameters was high, intraclass correlation coefficients (ICC) were 0.91 for MSF% and 0.93 for ISR.

Conclusions: Real-time elastography applied in this study, using in-house prepared Pixel Count software, provided good reproducibility and diagnostic efficacy, especially specificity, in the assessment of liver fibrosis degree.

Introduction

Progressive liver fibrosis is a consequence of chronic diseases of this organ. It is particularly important from a clinical point of view to focus a diagnostic process on detection of fibrosis and monitoring of its progress in chronic hepatitis B and C. Moreover, detection of fibrosis degree, which provides an indication for antiviral therapy, is also especially significant. A reliable method applied for diagnosis of cirrhosis is also crucial. Liver biopsy still remains a gold standard in the assessment of the liver fibrosis grade and plays a leading role in diagnosis of chronic liver diseases (CLD). It is, however, an invasive method, posing a risk of complications. Contraindications for its use are also frequent. The diagnostic efficacy of this method is also compromised by many other factors. For those reasons, efforts aiming at introduction of alternative, non-invasive methods for diagnosis of liver fibrosis are being made at present. Methods used for the assessment of liver fibrosis degree, based on analysis of several blood markers (Fibrotest, Forns score, aspartate transaminase-to-platelet ratio index) have not been validated in all conditions. A promising technique of magnetic resonance elastography is also limited by high cost and low availability [1, 2].

In the last decade dynamic development of ultrasound elastographic methods has been observed. Transient elastography (TE) has been introduced as the first one. This technique is integrated into a FibroScan device (Echosens, Paris, France), which incorporates a 3.5 MHz ultrasound transducer mounted on the axis at a vibrator [3–5]. Next, techniques integrated into standard ultrasonographic devices, such as real time elastography (RTE), acoustic radiance force impulse (ARFI), and shear wave elastography (SWE), became available. In these methods region of interest (ROI) can be chosen in conventional B-mode imaging of the liver, excluding interfering structures, such as large intrahepatic blood vessels. The TE, ARFI, and SWE modalities, based on measurement of velocity of shear wave propagation in tissues of varying stiffness, enable quantitative assessment of liver fibrosis. Studies applying these modalities aim mostly at selection of optimal threshold values of measured parameters for different degrees of liver fibrosis in chronic diseases of this organ [2, 5].

Real time elastography differs from other ultrasound-based elastography in that it does not provide a quantitative estimate of liver stiffness. Real time elastography measures probe-induced deformation (strain), generating colour-coded maps of strain distribution, which are only a qualitative presentation of the relative elasticity of anatomic structures included in the B-mode image (fibrotic tissues are more stiff than normal ones) [6, 7]. A secondary analysis of real-time elastograms is required to obtain semiquantative information. Different methods of elastogram analysis have been developed to provide a semiquantitative estimate of liver fibrosis.

Aim

The aim of this work was to optimise diagnostic criteria and assess the diagnostic usefulness of RTE with application of an in-house prepared methodology based on software used for the assessment of elastograms.

Material and methods

Sonoelastography of the liver was performed in 94 patients (42 males and 52 females) aged between 20 and 68 (mean value 54) years, with chronic hepatitis B (38 patients) and C (56 patients), and also 25 healthy volunteers (6 males and 19 females) aged between 20 and 59 (mean value 50) years. In 94 patients with CLD the degree of liver fibrosis was assessed prior to the study in a Batts-Ludwig scale (as F1–F4) based on histopathological examination of a bioptate obtained from a biopsy as:

– F1 – portal fibrosis of low intensity – in 20 patients,
– F2 – periportal fibrosis with rare septa – in 27 patients,
– F3 – periportal fibrosis with considerable number of septa connecting adjacent periportal spaces – in 15 patients,
– F4 – severe fibrosis of cirrhosis type – in 32 patients.

The time interval between liver biopsy, used as a reference method, and sonoelastography was between 1 and 10 (mean value 3) months. Clinical conditions of patients did not change during this period of time, and no clinical factors possibly affecting the results of comparative analysis between the results of both methods were noted.

None of the 25 healthy volunteers had in their medical history liver diseases or other illnesses possibly affecting this organ. Biochemical studies performed the day before elastography did not reveal liver damage. Results of serological tests for hepatotropic viruses were also negative. Liver fibrosis in these patients was assessed as $F = 0$.

Real-time elastography was performed using a Hitachi EUB 7500 ultrasonographic device equipped with a Real-time Tissue Elastography-Hi-RTE system, making use of a linear probe L735 (6–13 MHz). A probe was applied to provide 15–20 elastograms: 10–12 views presented a right lobe acquired through the intercostal spaces, 2–4 – subcostal views of a right lobe, and 3–4 – subcostal views of the left lobe.

The analysed elastograms met the following criteria:
– controlled probe compression during the study was maintained at the appropriate reference level: 3–4 according to the scale of the device,
– ROI was positioned at least 2 cm below Glisson's liver capsule,
– vessel artefacts took no more than 30% of ROI (Figure 1).

The results of the elastography were stored as images, in which individual pixels were coded in colours reflecting local elasticity of the liver. Those colours were further processed as three components: red, green, and blue (RGB). Based on RGB components in every pixel, the following parameters were determined: brightness in the range 0–1, saturation (0–1), and colour (1–360). Pixels with brightness or saturation below 0.25 were excluded from further analysis as artefacts. Analysis of every elastogram was based on the determination of the percentage of blue pixels – presenting a stiff (fibrotic) tissue, for which values of a colour parameter were in the range 170–300 in all colour pixels contained inside ROI. In the next step, software calculated the percentage of a stiff tissue (stiffness fraction – SF%) in the delineated ROI.

Based on values of SF%, calculated in the way described above, two parameters were determined for every patient assessed toward their degree of liver stiffness: mean stiffness fraction (MSF%) – mean per-

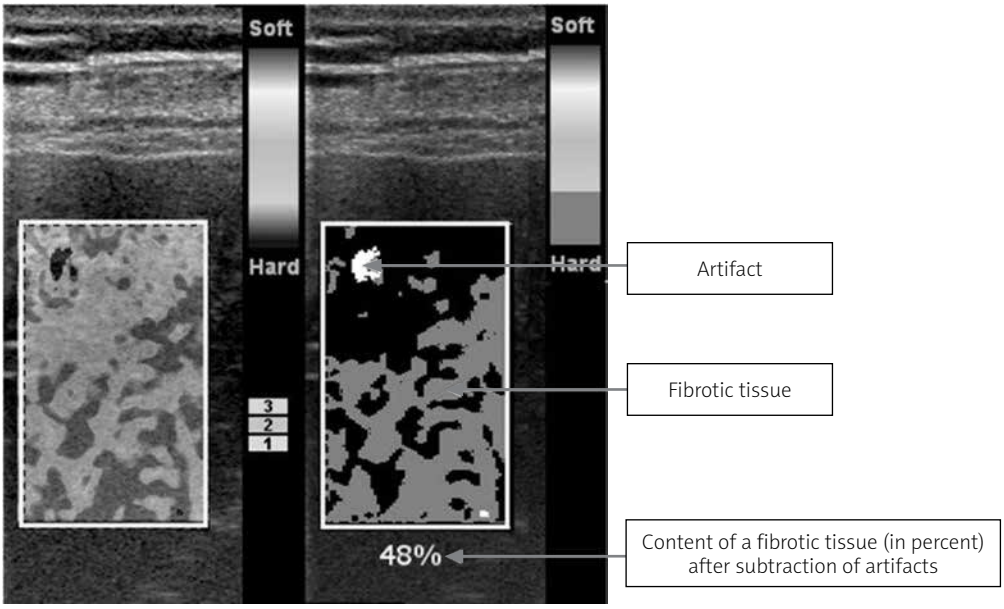

Figure 1. An example of an elastogram

centage of stiff tissue calculated as the mean value of SF% parameters for all 15–20 elastograms and intrinsic stiffness ratio (ISR) – intrinsic index of stiffness, reflecting asymmetry of stiffness distribution between elastograms (a trend toward more frequent occurrence of elastograms with higher SF% values) and calculated as the ratio of the number of elastograms (N) with SF% higher and lower than a threshold (TH) value: $ISR = (N_{SF\% > TH} + 1)/(N_{SF\% \leq TH} + 1)$.

Values of "1" were added in the denominator (and also in the numerator) to prevent the occurrence of zero values in the denominator. A threshold value providing maximal values of area under ROC curve for patient classification to groups with biopsy results [F1–F2] vs. [F3–F4] turned out to be 34%.

In 33 randomly selected patients (9 from the control group and 6 from each of the four subgroups with different degrees of fibrosis classified according to liver biopsy) sonoelastography was performed twice on the same day by two physicians (experienced and less experienced) in order to study a reproducibility (interobserver variability) of both parameters – MSF% and ISR.

The study was approved by the Medical University Bioethics Committee.

Statistical analysis

Data described by means of basic descriptive statistics of location and dispersion (mean and standard deviation) were analysed with use of nonparametric tests of significance for independent data (the Manna-Whitney *U* test or Kruskal-Wallis test in the case of more than two groups). Associations between biopsy results and elastographic parameters (MSF% and ISR) were qualified by means of rang Spearman correlations. Optimal diagnostic threshold values of stiffness indices (MSF% and ISR) in the classification of degree of liver fibrosis, particularly for the detection of early and advanced stages of liver stiffness, were achieved with use of receiver operating characteristic (ROC) curve method.

The diagnostic efficacy of the proposed classification methods was assessed by parameters of sensitivity, specificity, and area under the ROC curve (AUC). Interobserver reproducibility of stiffness indices (MSF% and ISR) in two independent measurements was assessed with use of intraclass correlation coefficients (ICC). Statistical significance was considered achieved for a p-value ≤ 0.05. All the calculations were derived by means of Statistica 10.0 software.

Results

Distributions of stiffness parameters MSF% and ISR differed significantly ($p < 0.0001$) in the subgroups of patients with different grades of liver fibrosis ($F = 0, 1, 2, 3, 4$). Associations between stiffness indices (MSF% and IRS) and histopathological grade of liver fibrosis were highly significant, too ($r = 0.75$; $p < 0.0001$ for both parameters).

Optimal threshold values for stiffness indices MSF% and ISR and values of sensitivity, specificity, and AUC (with 95% confidence interval) achieved in the classification of liver fibrosis are presented in Tables I and II.

Interobserver reproducibility of both parameters was very high: ICC = 0.91 (0.83–0.95) for MSF% and ICC = 0.93 (0.86–0.96) for ISR.

Table I. Accepted threshold values for stiffness parameter MSF% and values of sensitivity, specificity, and AUC (with 95% confidence interval) for classification between different grades of liver fibrosis

Fibrosis grade (*F*)	Classification	Threshold value	Sensitivity (%)	Specificity (%)	AUC	95% CI AUC
$F \geq 1$	{F0} vs. {F1, F2, F3, F4}	29	82	88	0.88	(0.82; 0.95)
$F \geq 2$	{F0, F1} vs. {F2, F3, F4}	33	76	87	0.87	(0.80; 0.91)
$F \geq 3$	{F0, F1, F2} vs. {F3, F4}	35	83	78	0.88	(0.82; 0.94)
$F = 4$	{F0, F1, F2, F3} vs. {F4}	38	88	84	0.89	(0.84; 0.95)

Table II. Accepted threshold values for stiffness parameter IRS and values of sensitivity, specificity, and AUC (with 95% confidence interval) for classification between different grades of liver fibrosis

Fibrosis grade (*F*)	Classification	Threshold value	Sensitivity (%)	Specificity (%)	AUC	95% CI AUC
$F \geq 1$	{F0} vs. {F1, F2, F3, F4}	0.46	79	84	0.88	(0.81; 0.94)
$F \geq 2$	{F0, F1} vs. {F2, F3, F4}	0.75	81	87	0.87	(0.80; 0.93)
$F \geq 3$	{F0, F1, F2} vs. {F3, F4}	0.89	87	78	0.89	(0.84; 0.95)
$F = 4$	{F0, F1, F2, F3} vs. {F4}	1.75	88	86	0.91	(0.86; 0.96)

Discussion

Needle biopsy of the liver, in spite of its substantial limitations, e.g. invasiveness, possible serious complications, and limitations of the histopathological examination to a small, local bioptate, still remains a gold standard in the grading of liver fibrosis. In the present study, as in other publications, it provides a reference method for evaluation of the diagnostic efficacy of sonoelastographic parameters used for the assessment of liver fibrosis degree.

In the vast majority of publications a histopathological Metavir score was used, which is in practice equal to Batts-Ludwig grading. In both scorings the first grade of fibrosis ($F = 1$) is defined as the absence of connective tissue septa, a phenomenon widely acknowledged as very significant in the process of cirrhosis development ($F = 4$) during CLD [8–10]. Connective tissue septa are specific for a significant fibrosis ($F \geq 2$) in both histopathological classifications.

The time interval between RTE and needle biopsy was between 1 and 10 (mean value 3) months. We regarded this time interval as acceptable taking into account the fact that according to Poynard *et al.* [11] the progression rate of fibrosis is equal to 0.12–0.16 Metavir score per year, so this time interval could not influence comparative results of both studies.

The method applied in our work for RTE performance consisted of 15–20 views of both liver lobes (acquired through intercostal as well as subcostal spaces). Other authors usually apply only a few views taken from the right lobe through intercostal spaces [2, 12–15]. Koizumi *et al.* [16] even determined six recommended sites of probe position in intercostal spaces. Only Orlacchio *et al.* [17] obtained views of both liver lobes and proved that results obtained from the right and left lobe do not differ significantly ($p = 0.21$). We believe that, due to the documented heterogeneity of liver fibrosis process [18], a larger number of views taken from both lobes allows the determination of the grade of fibrosis in the whole liver more accurately.

The proposed earlier qualitative (visual) method used for RTE assessment [15] is currently being replaced with semiquantitative methods. Some authors determine the elastic ratio in two ROIs: including liver and other soft tissues, i.e. perihepatic [2, 19, 20], intercostal muscles [2, 13], diaphragm [2], or small interhepatic veins [16]. This kind of normalisation of liver elasticity using an internal point of reference aims to limit subjective factors present in the assessment of elastograms. The fibrosis index is another semiquantitative method used for analysis of elastograms. It evaluates liver fibrosis grade using several parameters obtained from a histogram of relative strain in pixels of a colour-coded sonoelastogram [21–27]. Tatsumi *et al.* [21] studied the usefulness of nine parameters in an analysis of sonoelastograms: mean of relative strain value, standard deviation of relative strain value deviation (SD), ratio of blue area in analysed region (%AREA), complexity of blue area (COMP), kurtosis of strain histogram (KURT), skewness of strain histogram (SKEW), entropy (ENT), inverse difference moment (IDM), and angular second moment (ASM).

It is very important from a clinical point of view to diagnose correctly a significant grade of liver fibrosis

$F \geq 2$ because it forms one of the basic criteria for the introduction of antiviral therapy in patients with chronic hepatitis B and C. Qualification for this expensive therapy and its performance should be always considered on an individual basis, taking into account its advantages as well as adverse reactions. Under these circumstances it is particularly important to provide a high specificity of sonoelastographic study in the detection of liver fibrosis of $F \geq 2$ grade in order to minimise the probability of introducing antiviral therapy too early. It is also very important in clinical practice to diagnose cirrhosis, which is characterised by fibrosis grade $F = 4$, early enough. For the reasons specified above, most examinations studying the diagnostic potential of sonoelastography focus on optimisation of its diagnostic efficacy in the detection of fibrosis grades $F \geq 2$ and $F = 4$. Sensitivity and specificity of quantitative sonoelastographic methods, especially TE and ARFI, in the detection of liver fibrosis of grade $F \geq 2$ in patients with hepatitis B and C have been studied quite thoroughly and amount to: for TE – 78% and 84% and also 78% and 89%, respectively (according to two meta-analyses of multicentre studies [22, 28]), and for ARFI – 74% and 84% and also 83% and 91%, respectively (meta-analyses) [28, 29], and for the newest SWE method: 90% and 100% and also 88% and 95%, respectively [23, 24].

In the detection of high grade of fibrosis – cirrhosis ($F = 4$), sensitivity and specificity are assessed to be in the following ranges: for TE: 88–89% and 87–89% [22, 24, 25, 28], for ARFI: 84–87% and 86–90% [24, 25, 28, 29], and for SWE: 88% and 100% and 87% and 97% [23, 24], respectively. The diagnostic efficacy of RTE using semiquantitative parameters, like elastic ratio or fibrosis index, is reported in the literature to be in a wide range. Sensitivity of those parameters in detection of fibrosis of $F \geq 2$ grade is assessed to be in the range between 73% and 86%, and specificity 61% to 85% [21, 23–27]. Only Ferraioli *et al.* [23] obtained a sensitivity of fibrosis index in the detection of this grade of fibrosis ($F \geq 2$) as high as 94%, but the specificity was low, amounting to only 56%. In the detection of fibrosis grade $F = 4$ sensitivity and specificity of RTE was determined to be 71–93% and 73–85%, respectively [21, 23–27]. Although Friedrich-Rust *et al.* [12] obtained a specificity of fibrosis index amounting to 91% in the detection of cirrhosis, the sensitivity was unacceptably low, at 29%. Ferraioli *et al.* [24] compared the diagnostic efficacy of RTE using fibrosis index with quantitative methods TE and SWE, stressing a lower specificity of the former method in the detection of $F \geq 2$ and $F = 4$.

The semiquantitative index MSF% introduced in the present study is defined in a similar way to one of the components of the fibrosis index and evaluates a mean percentage of fibrotic tissue, but it is obtained from 15 to 20 sonoelastograms of both liver lobes. The other one (ISR) determining the ratio of the number of elastograms with a higher than a threshold value (34%) percentage of stiff (fibrotic) tissue to the number of elastograms with a percentage less than the threshold value of such a tissue, is a parameter applied for the first time to detect fibrosis with RTE. It reflects additionally the differentiation of fibrosis measurements obtained from those 15–20 views. Sensitivities of MSF% and ISR in the detection of fibrosis degree $F \geq 2$, amounting to 76% and 81%, respectively, are similar to other sensitivities of parameters of RTE mentioned in the literature. However, high sensitivity of 88%, comparable to quantitative sonoelastographic methods (TE, ARFI, SWE) in the detection of $F = 4$ fibrosis degree as well as high specificities for $F \geq 2$ and $F = 4$, equal to 87% and 84%, respectively, for MSF% and 87% and 86%, respectively, for ISR, are worth noticing.

A potentially lower reproducibility of results due to impulse generation by the operator's freehand compression of the ultrasonographic probe, although its strength is approximately standardised by a scale that can be read on the monitor, is considered a basic limitation of RTE. In some modalities an internal compression and relaxation obtained with the heartbeat are used for this purpose, which is intended to limit study subjectivity [2]. However, the reproducibility of parameters determined in our study was high: for MSF% it was equal to 0.91 and for ISR – 093, and it was comparable with the reproducibility of quantitative methods, e.g. TE, ARFI, and SWE, which is determined to be 0.84–0.98 [21, 29–31].

Conclusions

Both RTE parameters of liver fibrosis obtained from in-house prepared software are characterised by similar, good reproducibility and diagnostic efficacy in the assessment of liver fibrosis degree in patients with chronic hepatitis B and C. Moreover, their specificities in detection of $F \geq 2$ and $F = 4$ fibrosis degrees are higher than the specificities of most semiquantitative RTE parameters used by other authors, and comparable with newly introduced quantitative sonoelastographic modalities.

Conflict of interest

The authors declare no conflict of interest.

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