Strain Elastography for Noninvasive Assessment of Liver Fibrosis: A Prospective Study with Histological Comparison

Abstract

Aim: To prospectively evaluate the diagnostic performance of strain elastography (SE) for the assessment of liver fibrosis in patients with chronic liver disease using Ishak [0-6] histology stage as a reference standard.

Materials and Methods: Ninety-eight consecutive patients with suspected chronic liver disease scheduled for liver biopsy (n=78) or histologically confirmed cirrhosis (n=20) were enrolled. Liver Fibrosis (LF) Index calculated by SE, liver stiffness by transient elastography (TE), and serum fibrosis markers (aspartate aminotransferase-to-platelet ratio index [APRI], King's Score) were measured. Spearman's correlation coefficient between the LF Index, liver stiffness, serum fibrosis markers and fibrosis stage were calculated and compared using areas under the receiver-operating characteristics (AUROCs) curves.

Results: Among 73 patients who underwent SE, there was weak correlation between fibrosis stage and the LF Index (Spearman's: ρ=0.385 for Ishak score; *P*=0.001). Among 52 patients who underwent SE and TE, the AUROC values using LF Index, TE, APRI, and King's Score for diagnosing significant fibrosis (Ishak score ≥3) were 0.79, 0.87, 0.86, and 0.85, respectively (*P<0.0001*); and 0.83, 0.94, 0.92, and 0.92 (*P<0.0001*), respectively for diagnosing severe fibrosis/cirrhosis (Ishak score ≥5). When comparing the diagnostic performance using LF index, TE, APRI and King's score, TE shows a significantly higher AUROC value than LF index in detecting severe fibrosis (P=0.0149).

Conclusion: The diagnostic performance of LF Index calculated by SE was not statistically significantly different to the other non-invasive tests for the assessment of significant liver fibrosis but inferior to TE for the assessment of severe fibrosis/cirrhosis.

Introduction

Assessment of the degree of liver fibrosis is important in patients with chronic liver disease to estimate prognosis, to determine surveillance intervals and guide treatment decisions. At present, liver biopsy is used as the reference standard for the assessment of liver fibrosis. However, it is an invasive method associated with patient discomfort and, on occasion, with serious complications (1). In addition, the accuracy of liver biopsy is limited due to significant intra- and inter-observer variability and sampling errors (2–4).

Non-invasive ultrasound-based methods for the assessment of liver fibrosis in patients with chronic liver disease have been widely adopted in recent years using a measure of liver 'stiffness', termed elastography. A variety of elastography methods are available for the assessment of liver fibrosis. Transient elastography (TE) and shear wave elastography (SWE) methods, including point SWE (pSWE) and multidimensional SWE (2D-SWE and 3D-SWE), all measure the propagation speed of a shear wave transmitted from a transducer through the liver (5). As hepatic fibrosis progresses, the propagation speed increases. The shear waves can be generated by an external push (TE), by ultrasound radiation force enabling a single measurement (pSWE) or by an image (2D-SWE and 3D-SWE).

In contrast to the above elastography methods, strain elastography (SE) diagnoses hepatic fibrosis using the tissue deformation (strain) within the liver induced by an external compression (6,7). From transducer-induced deformation of tissues measured between consecutive echo signal frames, a colour-coded map of the strain distribution (elastogram) is overlaid on the B-mode image. The extent of the tissue deformability of the tissue (strain) is related to its stiffness. SE provides a qualitative measurement of higher or lower stiffness, which is displayed with color-coded mapping (6). Quantitative stiffness values can be obtained by converting the colour mapping scale to a numerical scale using various measurements generated by the elastography

module (8). The first commercial application of SE was developed by Hitachi Medical Systems (Tokyo, Japan) and given the real time modality of this technique it is frequently called real-time tissue elastography (RTE). Several studies have demonstrated the usefulness of RTE in the assessment of liver fibrosis (9–17). Despite promising results for the prediction of liver fibrosis in Asian patients, several studies have shown its performance in European patients to be inferior to TE (11,18). In view of this, guidelines recommend that further research regarding the use of SE in the assessment of liver fibrosis is required (19).

The aim of this study was to evaluate the diagnostic performance of SE, using RTE, for the assessment of liver fibrosis in multi-ethnic, urban patients in a European setting, with chronic liver disease using histology fibrosis staging (Ishak) as a reference standard.

Methods

Study population

We prospectively enrolled 98 adult patients with suspected chronic liver disease scheduled for liver biopsy or with confirmed (histological or clinical) cirrhosis in our institution over a one-year period (between October 2011 and October 2012). Inclusion criteria were age >18 years; suspected chronic liver disease based on clinical history, serum biochemistry, prior imaging or prior liver biopsy; referral for ultrasound and liver biopsy for staging and grading of fibrosis and/or cirrhosis. The cohort of patients with confirmed cirrhosis on imaging were not required to undergo further liver biopsy. Exclusion criteria included liver transplantation within the last six months, suspected or known acute liver disease, and pregnancy. The study was performed following ethical approval (study and registration number: 11/LO/0552, KCH11-143) and informed consent was obtained from all participants.

Strain elastography

B-mode standard ultrasonography and SE measurements were performed prior to liver biopsy using a Hitachi HI VISION Preirus machine (Hitachi Medical Systems, Tokyo, Japan), with a EUP-L52 linear (3–8 MHz) transducer. Subjects were examined in a supine position with the right arm extended over the head by three trained observers (SV, JJ, and OB). The transducer was placed in a right intercostal space and angled manually towards the heart (external compression source) without exerting any manual pressure with the transducer. The rectangular region of interest (ROI) of the hepatic parenchyma was 25 x 25 mm with the top of the ROI positioned approximately 10 mm inside the capsule of the liver to avoid multiple reflections and any large vessels (20)[Figure 1].

The elastography module is based on real-time analysis of tissue displacement (strain) induced by dynamic cardiac movement of the ROI. A colour map is generated showing hard (blue), intermediate (green) and soft (red) tissue areas. The measurement area was chosen when the

colour-coded elastogram was stable with any vessel or rib shadows minimised and recorded for 5 seconds. Patients were instructed to hold their breath (in a neutral phase) during imaging acquisition (at least 5 heart beats). The best image at negative peak strain on the strain graph was recorded when the image was subjectively most green and then most blue. The strain histogram was visualized, and analysis performed in the ROI. Image acquisition and strain histogram measurements were repeated a further two times. Digital images were stored at maximum quality and reviewed off-site by the ultrasound manufacturer. Image features were extracted from each elastography image (21). Multiple regression analyses were then performed with the following 9 image features: 1. mean of relative strain value, 2. standard deviation of relative strain value deviation; 3. ratio of blue area in the analysed region; 4. complexity of blue area; 5. Kurtosis of strain histogram; 6. Skewness of strain histogram; 7. entropy; 8. inverse difference moment; 9. angular second moment to calculate the Liver Fibrosis Index (LF Index) using a previously described formula (22). The LF Index equation using these 9 features was based on an equation adapted from Japanese patients with hepatitis C (12,23). The mean value of the three LF Index measurements was used as the result. A higher LF index indicates harder hepatic elasticity, and by inference more advanced liver fibrosis or cirrhosis.

Transient elastography

For logistical reasons, TE examinations (FibroScan®, Echosens, France) could not be performed on the same day as the liver biopsy, however they were performed in all patients within three months of the liver biopsy using methods described previously (24), by experienced observers as part of routine clinical practice. Measurements were performed on the right lobe of the liver through the right intercostal spaces. The medians of 10 measurements were recorded and the results expressed in kilopascals.

Serum fibrosis markers

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), total bilirubin, platelet count, international normalised ratio (INR), alkaline phosphatase (ALP) were measured on the same day as the SE and the AST-to-platelet ratio index (APRI) (25) and King's Score (26) then calculated. The APRI index was calculated as: AST (/upper limit of normal range) x 100/platelet count (10^9/L) (25). The King's Score was calculated as: age x AST x INR/platelet count (10^9/L) (26).

Liver histology

The histology specimens were taken on the same day following SE in the right lobe or from archived biopsy specimens in patients with documented cirrhosis. SE was performed before biopsy to avoid tissue disturbance due to the biopsy. All biopsies were performed percutaneously under ultrasound guidance using an 18-G Tru-Cut needle (Argon Medical Devices Inc., Athens, Texas). The biopsy specimens were fixed in formalin and embedded in paraffin according to standard procedures. All biopsy specimens were evaluated by a single experienced liver histopathologist (AQ) who was blinded to the patients' clinical data and ultrasound measurements. Liver fibrosis stage was scored using the biopsy criteria described for the Ishak stage scoring systems (27).

Statistical analyses

Statistical analysis was performed using Statistical Packages for the Social Sciences (SPSS) for Windows (v22, IBM, Chicago) and MedCalc for windows, v17.6, All predictors for the stage of fibrosis (SE [using LF index], TE, King's Score and APRI) are continuous variables and were therefore summarized as mean ± standard deviation or as medians and range. The diagnostic performances of these non-invasive tests for the prediction of fibrosis in each of the patients were then assessed by plotting the receiver-operator characteristic (ROC) curves. Optimal cut-off values were chosen to maximize the sum of the sensitivity and specificity using the Youden Index for different fibrosis thresholds: Ishak 0-2 vs 3-6 (Ishak ≥3), Ishak 0-4 vs 5-6 (Ishak ≥5). For this

study, significant fibrosis was defined as Ishak stages 3 and above and severe fibrosis/cirrhosis, now termed advanced stage liver disease (28) as Ishak stage 5 or above. Diagnostic accuracy was also evaluated by comparing the sensitivity, specificity, positive and negative predictive values based on these cut-off values. The 95% confidence intervals were determined for the non-invasive markers and utilized when comparing the area under the ROC (AUROCs) curves. Differences between the AUROCs were compared by using a Delong test (29). Spearman's Correlation coefficient was calculated to test for the relationship between Ishak liver fibrosis stage and the non-invasive tests (SE, TE, King's Score and APRI). Weak, moderate, strong correlation were defined if Spearman's correlation coefficient $\rho<0.4$; $0.4\leq\rho<0.59$, $\rho\geq0.60$ respectively. All tests were two-sided and P <.05 signified a significant difference.

Results

Patient characteristics

Ninety-eight patients met the inclusion criteria and were enrolled in the study. Of these, 78 patients underwent liver biopsy; a further 20 patients with a confirmed clinical diagnosis of cirrhosis underwent B-mode standard ultrasonography and SE without further liver biopsy.

Relationship between LF Index, serum markers and liver biopsy histologic findings

Of the 98 enrolled patients, SE measurements were successful in 97 patients (success rate 98.98%). 24 patients were excluded from this analysis because of unreliable clinical assessment of cirrhosis on repeat ultrasound (n=6), no histology report due to inadequate samples (n=2), SE measurement that could not be analyzed (n=16). This left 73 patients suitable for analysis. Their characteristics are summarized in **Table 1**. The patient ethnicity of the study cohort are: 37.0% Caucasian (n=27), 31.5% African-Caribbean (n=23), 20.5% Asian (n=15), 8.2% other (n=6) and 2.7% mixed (n=2). Most patients with chronic liver disease had hepatitis B (n=52/73, 71.2%). The proportion of patients with significant (Ishak stage ≥3) and severe fibrosis/cirrhosis (Ishak stage ≥5) was 27.4% (n= 20/73) and 9.6% (n=7/73), respectively. The median (minimum, maximum value) LF index, APRI and King's score for each Ishak fibrosis stage are listed in **Table 2** and displayed as box and whisker plot in **Figure 2**. There was weak significant correlation between fibrosis stage and the LF Index (Spearman's ρ=0.385; *P=0.001*). There were moderate significant correlations between fibrosis stage and serum markers (APRI: Spearman's ρ=0.524, P<0.001; King's score: Spearman's ρ=0.582, P<0.001)

Relationship between TE and liver fibrosis scores

A further 21 patients were excluded from this analysis due to lack of TE measurements, leaving 52 patients suitable for analysis. Their characteristics are summarized in **Table 1**. The TE measured in the study patients ranged from 3.3 KPa to 36.9.1KPa. The median (minimum,

maximum value) TE value for each Ishak fibrosis stage are listed in **Table 2, Figure 2**. There was strong significant correlation between fibrosis stage and the TE measurement (Spearman's ρ=0.675; *P=0.001*).

Diagnostic accuracy of LF index, TE and serum markers using Ishak histological scores.

The accuracy of SE (using LF index), TE, APRI and King's Score in predicting significant (Ishak ≥3) and severe (Ishak ≥5) liver fibrosis are shown in **Tables 3, Figure 3.**

The AUROCs of LF index, SE, TE, APRI and King's Score for diagnosis of significant fibrosis did not differ significantly (*P* >0.05) (**Figure 3a**). Comparison of the AUROCs of SE (using LF index), TE, APRI and King's Score for the diagnosis of severe fibrosis/cirrhosis showed that TE had significantly higher accuracy compared to SE (using LF index) P = 0.0149. No significant differences were detected when comparing AUROC between the other parameters (**Figure 3b**).

Discussion

Recent interest in non-invasive evaluation of liver disease is related to the risk of complications associated with liver biopsy and technical limitations of the procedure (30). In view of this, various noninvasive methods have been developed to predict the presence of clinically significant fibrosis. In this study, we evaluated the use of LF Index calculated by SE in predicting the presence of significant liver fibrosis, using liver biopsy as a reference standard. The principle finding of this study was that LF index by SE was not a useful predicator of histologic fibrosis stages as determined by the Ishak scores. Secondary analyses showed that the diagnostic performance of SE in this heterogeneous population including predominant Caucasian and African-Caribbean patients was similar to other non-invasive tests for the assessment of significant liver fibrosis but inferior to TE for the assessment of severe fibrosis/cirrhosis in patients with suspected chronic liver disease.

A number of studies have evaluated the diagnostic performance of SE using RTE for the assessment of liver fibrosis in patients with chronic liver disease. Since RTE is essentially a qualitative technique, various semi-quantitative methods have been developed to analyse the elastograms produced by SE (8). These include the elasticity index (14,31), the elasticity ratio (15,16,32) and the LF Index (12,21–23,33,34). The elastic ratio refers to the ratio of these values in the hepatic parenchyma to the values in a reference tissue such as intercostal muscles and intrahepatic venous vessels. The elastic index, elasticity score, and LF Index are all calculated by formulas including several descriptive statistics (e.g. mean, median, maximum) derived from quantified pixel data. In this study, the LF index was used as the analytic method of SE. It was the first quantitative method developed involving use of 9 parameters (21). A meta-analysis of 5 studies (722 subjects) in 2014 showed significant heterogeneity when using the LF index for the assessment of significant fibrosis, thereby limiting an assessment of the overall accuracy of RTE. The authors reported that RTE showed limited potential as a substitute for TE in the assessment of liver fibrosis (35). A further meta-analysis in 2015 of 15 studies (1,626 subjects) reported that the overall accuracy of RTE was nearly identical to TE for the evaluation of significant fibrosis, but

less accurate for the evaluation of cirrhosis (36). The variable results reported with the different quantitative methods have therefore limited the clinical use of RTE (35). There are however conflicting results to the 2015 meta-analysis whereby RTE was shown to have a strong positive correlation with histologic liver fibrosis and high diagnostic accuracy in predicting significant and severe fibrosis (17,22,37). We postulate that the observed difference in diagnostic accuracy may be because prior studies were exclusively performed in East Asian populations where the body mass index is lower than in our study population, although this could not be analysed formally as body mass index from our study cohort was not collected at the time of the study.

The two endpoints used in this study were significant fibrosis (Ishak stage 3 or greater), which is an indication for anti-viral treatment in patients with chronic hepatitis B and C; and severe fibrosis/cirrhosis (Ishak stage 5 or greater) which leads to closer monitoring of complications: portal hypertension, hepatic insufficiency and hepatocellular carcinoma (38). We used these liver fibrosis categories as they enable reliable identification of liver cirrhosis, as well as the ability to distinguish low risk of fibrosis (Ishak 0–2) from more advanced stages of liver fibrosis (Ishak 3–6). We evaluated the use of SE with liver histology using the 7-point Ishak staging systems which allows a more detailed description of advanced stage liver disease (stage 5 and 6) compared with the Metavir score. It has been argued that the gap between 3 (numerous septa without cirrhosis) and 4 (cirrhosis) in the Metavir score is too large and an additional level is required to differentiate between severe fibrosis and cirrhosis (39).

The strength of this study is that it not only compares the diagnostic accuracy of SE with the reference standard, liver biopsy, but also with TE and serum markers.TE was used as a comparative method of measuring liver stiffness in this study and it demonstrated AUROC values consistent with findings reported in meta-analyses for predicting significant fibrosis (F≥2, AUROC = 0.88) and severe fibrosis (F≥3, AUROC = 0.91) (40). A limited number of studies have compared the diagnostic accuracy of LF index and serum fibrosis markers.

Limitations exist with our study. Firstly, this was an unblinded study performed in a wide group of unselected patients with varying aetiologies of chronic liver disease, introducing possible bias due to histologic differences of the varying etiologies of liver disease. However, most patients (>90%) had chronic viral hepatitis B or C. Further multicenter studies of larger patient cohorts, using a similar study design are needed to establish optimal cut-off values for each fibrosis stage and etiology. Secondly, the distribution of patients in our study was not equal through Ishak scores. We enrolled consecutive patients undergoing liver biopsy and the underlying distribution of patients reflects that normally observed in clinical practice. Finally, the same operators were used in the study and there was no patient control group. However, whilst each operator was aware that the patient had fibrosis, they were blinded to the pathological stage of the patient.

In conclusion, the diagnostic performance of SE using RTE in this population was similar to other non-invasive tests for the assessment of significant liver fibrosis but inferior to TE in the assessment of severe fibrosis/cirrhosis in patients with suspected chronic liver disease.

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Figures Legends

Figure 1a. Real-time tissue elastogram from a 27 year-old male with hepatitis B viral hepatitis which demonstrates relative “soft” liver texture. The histological fibrosis stage is Ishak 1.

Figure 1b. Real-time tissue elastogram from a 63 year-old female with hepatitis C viral hepatitis which demonstrates relative “hard” liver texture. The histological fibrosis stage is Ishak 6.

Figure 2 Box and whisker plots of (**a**) liver fibrosis (LF) index, (**b**) TE, (**c**) APRI and (**d**) King’s Score according to different Ishak fibrosis stage. The length of the box represents the interquartile ranges (second and third quartiles) in which 50% of the values are located. Circles or stars represent outliers. The thick line through each box represents the median value. The error bars show the minimum and maximum values (range). Open circles and stars represent outliers.

Figure 3 Comparison of the receiver operating characteristic curves of non-invasive methods for diagnosis of (**a**) significant fibrosis (Ishak ≥ stage 3) and (**b**) severe fibrosis/cirrhosis (Ishak ≥ stage 5) in patients with chronic liver disease in the study population