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● *Original Contribution*

PERFORMANCE OF 2-D SHEAR WAVE ELASTOGRAPHY IN LIVER FIBROSIS ASSESSMENT COMPARED WITH SEROLOGIC TESTS AND TRANSIENT ELASTOGRAPHY IN CLINICAL ROUTINE

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Abstract—Liver stiffness values assessed with 2-D shear wave elastography (SWE), transient elastography (TE) and simple serologic tests were compared with respect to non-invasive assessment in a cohort of 127 consecutive patients with chronic liver diseases. The rate of reliable liver stiffness measurements was significantly higher with 2-D SWE than with TE: 99.2% versus 74.8%, $p < 0.0001$ (different reliability criteria used, according to current recommendations). In univariate analysis, liver stiffness measured with 2-D SWE correlated best with fibrosis stage estimated with TE ($r = 0.699$, $p < 0.0001$), followed by Forns score ($r = 0.534$, $p < 0.0001$) and King's score ($r = 0.512$, $p < 0.0001$). However, in multivariate analysis, only 2-D SWE-measured values remained correlated with fibrosis stage ($p < 0.0001$). The optimal 2-D SWE cutoff values for predicting significant fibrosis were 8.03 kPa for fibrosis stage ≥2 (area under the receiver operating characteristic curve = 0.832) and 13.1 kPa for fibrosis stage 4 (area under the receiver operating characteristic curve = 0.915), respectively. In conclusion, 2-D SWE can be used to obtain reliable liver stiffness measurements in almost all patients and performs very well in predicting the presence of liver cirrhosis. (E-mail: arnulf.ferlitsch@meduniwien.ac.at) © **2015 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Liver stiffness, Liver fibrosis, Serologic tests, Transient elastography, Aixplorer, Shear wave elastography.**

INTRODUCTION

Non-invasive evaluation of liver fibrosis by means of ultrasound-based elastographic techniques is increasingly being used in clinical practice. Transient elastography (TE), acoustic radiation force impulse and 2-D shear wave elastography (2-D SWE) are all shear wave-based elastographic techniques, in which tissue excitation is mechanically induced using an external transducer in the case of transient elastography or ultrasound waves produced by the probe in the other methods (Bamber et al. 2013; Bercoff et al. 2004; Sandrin et al. 2003). The first and the most widely used method is TE. Various studies have documented the usefulness of this method in liver fibrosis assessment, especially for predicting severe fibrosis and liver cirrhosis (Cardoso et al. 2012; Castera et al. 2005; Reiberger et al. 2012b; Tsochatzis et al. 2011; Wong et al. 2010). However, up to 20%–30% of patients cannot be properly evaluated by TE using the standard M-probe (Castera et al. 2010; Ferlitsch et al. 2012; Salzl et al. 2014; Sirli et al. 2013), especially in the presence of obesity or perihepatic ascites. 2-D SWE is a new ultrasound-based technique for non-invasive evaluation of liver fibrosis. The published data on 2-D SWE are promising (Bavu et al. 2011; Cassinotto et al. 2014; Ferraioli et al. 2012; Leung et al. 2013; Poynard et al. 2013; Sporea et al. (2013a, 2013b)), but comparative data on other non-invasive methods are still lacking.

Among the various ultrasound-based elastographic techniques, today, only TE is well validated and already being recommended in some guidelines for diagnosis and management of patients with chronic liver disease (European Association for the Study of the Liver [EASL] 2011, 2012).

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Another non-invasive method for evaluation of liver fibrosis is the use of simple serologic tests. These may be based on routine laboratory parameters, such as the aspartate transaminase/platelet ratio index (APRI) (Wai et al. 2003), Lok score (Lok et al. 2005), Forns score (Forns et al. 2002), Fibrosis 4 (FIB-4) score (Sterling et al. 2006), fibrosis index (FI) (Ohta et al. 2006), King's score (Cross et al. 2009), or on the use of more advanced/more sophisticated serum markers, as in commercially available composite scores (Guha et al. 2008; Poynard et al. 2002).

The aim of this study was to assess the diagnostic performance of 2-D SWE in non-invasive assessment of liver fibrosis in comparison to simple serologic tests (APRI, Forns score, King's score, FIB-4 score, Lok score, FI) and TE.

METHODS

Patients

Our prospective study included 127 consecutive patients with chronic liver disease of various etiologies undergoing both TE and 2-D SWE. In addition, biochemical parameters were obtained and various non-invasive fibrosis scores were calculated.

The patients signed an informed consent. This study was performed in accordance with the latest version of the Helsinki Declaration and approved by the local ethics committee (EK 2075/2013).

Transient elastography

Transient elastography was performed in all patients under fasting conditions, using a FibroScan device (EchoSens, Paris, France). Patients were positioned supine, with the right arm in maximum abduction. Measurements were made through an intercostal approach, using a standard M-probe. In each patient, we aimed for 10 valid TE measurements and then used the median value, expressed in kilopascals (kPa). A reliable liver stiffness (LS) measurement was defined as the median value of 10 valid LS measurements with a success rate (number of successful acquisitions/total number of acquisitions rate) ≥60% and an interquartile range (IQR)/median LS value ratio <30% (IQR = range of the middle 50% of the data) (Castera et al. 2010). The operators who performed TE measurements were blinded to all clinical, biochemical and SWE data. The severity of liver fibrosis was classified using TE cutoffs according to the latest meta-analysis (Tsochatzis et al. 2011): 6 kPa for presence of fibrosis (F ≥1), 7.2 kPa for significant fibrosis (F ≥2), 9.6 kPa for severe fibrosis (F ≥ 3) and 14.5 kPa for liver cirrhosis (F = 4).

2-D SWE

Two-dimensional shear wave elastography measurements were performed with an Aixplorer ultrasound system (SuperSonic Imagine, Aix-en-Provence, France), using a SC6-1 convex probe. Similar to TE, all SWE procedures were performed under fasting conditions, in the supine position, with the right arm in maximum abduction, through an intercostal approach, in the right liver lobe, 1.5–3 cm under the liver capsule, avoiding areas with large vessels. We used a 3.5 × 2.5-cm box in which a 1.2- to 1.5-cm-diameter circular region of interest was selected (Fig. 1). If the box was not filled completely with color or if there were artifacts, the measurement was considered a failure measurement, as recommended by the manufacturer.

The results of LS measurements by 2-D SWE can be expressed in kPa or m/s. Three valid 2-D SWE measurements were performed in each patient, and then the mean value was calculated and expressed in kPa. Inability to obtain a valid LS measurement by 2-D SWE was defined as the inability to obtain three valid measurements after 12 attempts. As for TE, the operators performing 2-D SWE measurements were blinded to all clinical, biochemical and TE data.

To date, no quality criteria parameters are recommended for LS measurements by 2-D SWE. We investigated the influence of the standard deviation (SD) as a quality parameter on the strength of the correlation of 2-D SWE values with liver fibrosis estimated by TE and LS values obtained by TE. For this analysis, we considered the mean of three valid 2-D SWE measurements with an SD <30% of the mean as reliable.

Non-invasive fibrosis scores

Fibrosis scores were calculated using biochemical parameters obtained by venous blood sampling on the same day the elastographic measurement were performed. All biochemical parameters were evaluated in the Department of Laboratory Medicine of the Medical University of Vienna: alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (AP), γ-glutamyl transpeptidase (GGT), total bilirubin, serum albumin, serum creatinine, cholesterol, triglycerides, prothrombin time and platelet count.

On the basis of these biological parameters, the following non-invasive fibrosis scores were calculated:

- APRI = [(AST/upper limit of normal AST) × 100]/platelet count (10^9/L) (Wai et al. 2003)
- Lok score = log odds = −5.56 − 0.0089 × platelet count (10^3/mm^3) + 1.26 × (AST/ALT) + 5.27 × INR
- Lok = [exp(log odds)]/[1 + exp(log odds)] (Lok et al. 2005)
- Forns score = 7.811 − 3.131 × ln[platelet count (10^9/L)] + 0.781 × ln[GGT (U/L)] + 3.467 × ln[age (y)] − 0.014[cholesterol (mg/dL)] (Forns et al. 2002)
- FIB-4 = [age (y)] × [AST (U/L)]/[platelet count (10^9/L)] × ALT $(U/L)^{1/2}$] (Sterling et al. 2006)