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● *Original Contribution*

DIAGNOSTIC ACCURACY OF 2-D SHEAR WAVE ELASTOGRAPHY FOR THE NON-INVASIVE STAGING OF LIVER FIBROSIS IN PATIENTS WITH ELEVATED ALANINE AMINOTRANSFERASE LEVELS

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Abstract—This study assessed the diagnostic accuracy of 2-D shear wave elastography (2-D-SWE) for the non-invasive staging of liver fibrosis and compared the findings with those for biochemical markers (the aspartate aminotransferase-to-platelet index and fibrosis-4 index) of liver fibrosis in patients with elevated alanine aminotransferase (ALT) levels (>5 × the upper limit of normal). Patients with chronic liver diseases and elevated ALT levels who underwent liver biopsy were consecutively included. Receiver operating characteristic (ROC) curves were constructed to assess overall accuracy and to identify optimal cutoff values. After exclusions, data from 105 patients were analyzed. The areas under the ROC curves (AUROCs) for significant fibrosis, severe fibrosis and cirrhosis were 0.83, 0.86 and 0.91, respectively. The optimal cutoff values for predicting significant fibrosis, severe fibrosis and cirrhosis were 10.6, 13.2 and 17.6 kPa, respectively. The AUROCs of 2-D-SWE were significantly higher than those of biochemical markers for predicting significant fibrosis, severe fibrosis and cirrhosis (all p values < 0.05). Therefore, the diagnostic performance of 2-D-SWE in assessing liver fibrosis stages in patients with elevated ALT levels was promising. The optimal cutoff values were increased but appropriate for this cohort because the baseline levels of liver stiffness measurements were increased in these patients, even in the absence of fibrosis. (E-mail: zhengrq@mail.sysu.edu.cn)

Key Words: **Biochemical marker, Liver fibrosis, Liver stiffness, 2-D shear wave elastography, Ultrasound.**

INTRODUCTION

Accurate staging of the degree of fibrosis is essential for determining the prognosis, surveillance and treatment (including antiviral therapy) of patients with chronic liver diseases. Although liver biopsy (LB) has long been the gold standard, it is an invasive procedure with potential complications such as bleeding and severe pain (Bravo et al. 2001; Cadranel et al. 2000). Therefore, substantial interest has been focused on the development of non-invasive techniques for the diagnosis of liver fibrosis. Liver stiffness measurement (LSM) using ultrasound elastography has been reported to be a reliable and accurate surrogate for LB in assessing the severity of liver fibrosis (Cosgrove et al. 2013; Ferraioli et al. 2015). Ultrasound elastography (*i.e.,* transient elastography) has been recommended for the non-invasive staging of liver fibrosis by the clinical practice guidelines of the European Association for the Study of the Liver and the Asian-Pacific Association for the Study of the Liver (European Association for the Study of the Liver 2012; Sarin et al. 2016).

Two-dimensional shear wave elastography (2-D-SWE) is an ultrasound elastography technique that is available on a clinical diagnostic ultrasound scanner and can create a real-time, 2-D quantitative map of liver tissue stiffness superimposed on a B-mode image (Shiina et al. 2015). It can measure liver stiffness based on the shear wave velocity estimation. The overall diagnostic accuracy of 2-D-SWE is high, and it is clinically useful for the staging of liver fibrosis (Jiang et al. 2016; Li et al. 2016). However, confounding factors, such as edema, inflammation, extra-hepatic cholestasis and congestion, can increase liver stiffness and elevate the measurements, independently of fibrosis (Ferraioli et al. 2015). These confounding factors might affect the diagnostic accuracy of 2-D-SWE for staging liver fibrosis in patients with chronic liver

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diseases. Inflammation is an important process to document in the evolution of liver diseases (Barr et al. 2015). The World Federation for Ultrasound in Medicine & Biology (WFUMB) guidelines and recommendations for clinical use of ultrasound elastography indicate that findings of LSM using 2-D-SWE may be higher in patients with elevated alanine aminotransferase (ALT) levels (more than five times the upper limit of normal); thus, the effects of inflammation should be taken into account, and the results should always be evaluated in the clinical setting (Ferraioli et al. 2015). Therefore, it is important to investigate the accuracy and specificity of 2-D-SWE in measuring liver stiffness in patients with elevated ALT levels. Although increased liver stiffness caused by inflammation has been reported by the Society of Radiologists in an ultrasound consensus conference statement and in the WFUMB guidelines (Barr et al. 2015; Ferraioli et al. 2015), no published studies have examined the diagnostic accuracy of 2-D-SWE for the staging of liver fibrosis in patients with ALT levels greater than five times the upper limit of normal.

In addition to ultrasound elastography, multiple non-invasive methods based on inexpensive laboratory tests can be used to predict liver fibrosis, including the aspartate aminotransferase-to-platelet index (APRI) and the Fibrosis-4 index (FIB-4), which is based on four factors. These two models have been widely investigated with respect to their diagnostic accuracy in detecting liver fibrosis resulting from different causes (Xiao et al. 2015).

Therefore, the goal of this study was to assess the diagnostic accuracy of 2-D-SWE for the non-invasive staging of liver fibrosis and to compare the findings with those for biochemical markers of liver fibrosis (APRI and FIB-4) in patients with ALT levels greater than five times the upper limit of normal. LB samples that were scored with the histology-based METAVIR staging system were used as the diagnostic reference standard.

METHODS

Patients

Informed consent was obtained from all patients, and the study was approved by the clinical medical research ethics committee of our hospital. Between June 2011 and June 2016, consecutive patients with chronic liver diseases who underwent a 2-D-SWE examination were enrolled. The inclusion criteria consisted of the following: chronic liver diseases; patients undergoing 2-D-SWE examination and LB; ALT levels greater than five times the upper limit of normal. Excluded were patients younger than 18 y; patients for whom consent for the 2-D-SWE examination was lacking; biopsy samples less than 15 mm long or with fewer than six portal tracts on microscopic examination; and transplanted liver. The interval between LB and 2-D-SWE was shorter than 3 d. The following data were collected from all patients: age; gender; weight; height; ALT, aspartate aminotransferase (AST), serum alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), total bilirubin and serum albumin concentrations; platelet count; and prothrombin time (PT). The body mass index (BMI) was calculated as weight (kg)/[height (m)]^2.

2-D shear wave elastography

Three radiologists (J. Zeng, J. Y. Jin and J. Zheng) performed the procedures. All radiologists had at least 6 m of experience in performing 2-D-SWE examinations. The radiologists were blinded to the patients' clinical information and pathology results. The 2-D-SWE procedure was performed using the Aixplorer US system (SuperSonic Imagine, France) with a convex broadband probe (SC6-1, 1–6 MHz). All patients had fasted for at least 6 h before the examination. The 2-D-SWE measurements were performed on the right lobe of the liver through the intercostal spaces with the patient lying in the supine position and with the right arm in maximal abduction. The operator located the target area of the liver under the guidance of conventional, real-time B-mode imaging. When the target area was located, the SWE mode was employed, and during quiet breathing, the patient was asked to hold his or her breath for approximately 5 s. The elasticity image box, which was approximately 4 × 3 cm, was set 1–2 cm deeper than Glisson's capsule of the liver and in an area of the liver parenchyma free of large vessels.

A circular region of interest (ROI) with a 2-cm diameter was drawn inside the elasticity image box, and the liver stiffness mean, minimum, maximum and standard deviation (SD) were calculated (Fig. 1). The mean value represented the LSM for each 2-D-SWE image. Five consecutive 2-D-SWE images were obtained for each patient, and the mean value of the LSMs was used for the statistical analysis. The entire 2-D-SWE examination lasted 3–5 min for each patient.

As noted above, five consecutive 2-D-SWE images were acquired for each patient. Measurements were classified as failed when no or little signal was obtained in the SWE box for all acquisitions (Ferraioli et al. 2012a).

Biochemical markers of liver fibrosis

All laboratory data, including specific parameters for calculating the APRI and FIB-4, consisting of age, AST level, ALT level and platelet count, were obtained on the day of LB. Based on 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) and FIB-4 = [age (y)] × [AST (U/L)]/[platelet count (10^9/L)] × [ALT (U/L) $^{1/2}$] (Sterling et al. 2006).