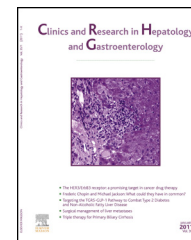




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ORIGINAL ARTICLE

# Longitudinal monitoring of liver stiffness by acoustic radiation force impulse imaging in patients with chronic hepatitis B receiving entecavir

Sheng-Di Wu<sup>a,1</sup>, Hong Ding<sup>b,1</sup>, Li-Li Liu<sup>a</sup>, Yuan Zhuang<sup>b</sup>,  
Yun Liu<sup>a</sup>, Li-Sha Cheng<sup>a</sup>, Si-Qi Wang<sup>a</sup>, Yu-Jen Tseng<sup>a</sup>,  
Ji-Yao Wang<sup>a</sup>, Wei Jiang<sup>a,\*</sup>

<sup>a</sup> Department of gastroenterology and hepatology, Zhongshan hospital, Shanghai institute of liver diseases, Fudan university, 200032 Shanghai, China

<sup>b</sup> Department of ultrasound, Zhongshan hospital, Fudan university, 200032 Shanghai, China

## KEYWORDS

Acoustic radiation force impulse;  
Liver stiffness;  
Liver fibrosis;  
Chronic hepatitis B;  
Antiviral therapy

## Summary

**Background:** Acoustic radiation force impulse (ARFI) imaging measures liver stiffness (LS), which significantly correlates with the stage of liver fibrosis in treatment-naive patients with chronic hepatitis B (CHB).

**Aim:** We aimed to prospectively assess the clinical usefulness of ARFI during long-term antiviral therapy in CHB.

**Method:** Seventy-one CHB patients were consecutively recruited and paired liver biopsies were performed in 27 patients. LS was assessed by ARFI semiannually during entecavir therapy.

**Results:** LS gradually decreased with treatment and continued to decrease after normalization of alanine aminotransaminase. Overall, 97.2% patients achieved improvement of LS, whereas 19.7% patients had more than 30% reduction in LS values between baseline and week 104. Multivariate linear regression analysis showed that the degree of LS reduction significantly correlated with the baseline levels of LS value, platelet and cholinesterase. In the 27 patients who underwent paired liver biopsies, LS significantly correlated with stage of fibrosis and inflammatory grade at baseline. LS values decreased more significantly in patients with fibrosis regression than those with static histological fibrosis.

\* Corresponding author.

E-mail address: [jiang.wei@zs-hospital.sh.cn](mailto:jiang.wei@zs-hospital.sh.cn) (W. Jiang).

<sup>1</sup> These two authors contributed equally to the paper.

**Conclusion:** In CHB patients, LS assessed by ARFI was gradually reduced during antiviral therapy. Longitudinal monitoring of LS may be a promising noninvasive assessment of fibrosis regression during long-term antiviral therapy in CHB. Further large sample studies are needed.  
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## Introduction

Chronic hepatitis B (CHB) often leads to serious health conditions including decompensated liver cirrhosis and hepatocellular carcinoma [1]. There is compelling evidence that liver fibrosis and even cirrhosis can be reversed after suppression of hepatitis B virus (HBV) [2,3]. Thus, longitudinal assessment of regression/progression of fibrosis is essential for CHB patients receiving oral antiviral treatment [4].

The gold standard to evaluate liver fibrosis improvement remains as liver biopsy. However, it is difficult to perform repeatedly due to its invasive nature. In the past few years, elastography techniques have evolved and became a relevant tool, assisting clinicians in the management of chronic liver disease including CHB [5]. Acoustic radiation force impulse (ARFI) imaging is a relatively newer ultrasound-based elastography method that has integrated a conventional ultrasound machine. It enables the exact localization of ARFI-measurement site during B-mode ultrasound. Several meta-analysis revealed that ARFI elastography show higher rate of yielding reliable measurements and similar predictive value compared to transient elastography (TE) for significant fibrosis and cirrhosis [6,7]. ARFI also provides comparable diagnostic accuracy for fibrosis assessment compared to TE in CHB [8,9].

Several studies revealed that liver stiffness (LS) measurement by ARFI decreased significantly after active antiviral treatment in chronic hepatitis C [10–12]. However, most of them were retrospective and lacked paired liver biopsy results. It remains unclear that whether a decrease in LS in treated patients reflects a regression of liver fibrosis or a decrease in hepatic necroinflammation secondary to viral suppression [13]. So far, the use of ARFI elastography to monitor change in liver fibrosis has not been properly evaluated during antiviral therapy in CHB patients. The aim of this prospective study was to investigate the long-term changes of LS examined by ARFI in CHB patients treated with entecavir, and to identify whether subsequent improvement of LS values indicate a regression of liver fibrosis.

## Patients and method

### Patients

Between July 2013 and December 2014, 71 consecutive CHB patients at our hospital (Zhongshan Hospital, Fudan University, China) were prospectively recruited for two multicenter randomized controlled trials (NCT01938781, NCT01938820) sponsored by National Science and Technology Major Project of China. Key inclusion criteria were as follows: 18 to 65 years of age; positive HBsAg for at least 6 months before screening; nucleos(t)ide analog-naïve; HBV DNA lev-

els higher than 20,000 IU/mL for HBeAg-positive patients or 2000 IU/mL for HBeAg-negative patients. Exclusion criteria included coinfection with hepatitis C or human immunodeficiency virus; the presence of other forms of chronic liver disease; decompensated liver diseases; concurrent malignant tumor; any complications of other important systematic diseases; previous treatment of antiviral drugs. Patients with alanine aminotransaminase (ALT) > 5 × ULN at baseline or cases with high necroinflammatory activity in liver biopsy at 78 weeks were also excluded, since LS at such high ALT levels and high necro-inflammatory activity in liver would likely overestimate the severity of liver fibrosis.

All the patients received oral antiviral therapy with entecavir (0.5 mg, Chia Tai Tianqing Pharmaceutical Group Co., Ltd., China) after enrollment, according to the Chinese guideline of prevention and treatment for CHB. Paired liver biopsies were performed in 27 patients at baseline and week 78 of entecavir therapy. The duration of follow-up was 104 weeks for every patient.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's human research committee. The study was approved by the Ethics Committee of our hospital before study initiation. Written, informed consent was obtained from each patient included in the study.

### Liver stiffness measurement by ARFI elastography

LS was measured by ARFI elastography using the Siemens Acuson S2000 ultrasound system (Siemens, AG, Germany) with 4C1 transducer (1.5–4.0 MHz). ARFI elastography was performed at baseline and every 26 weeks in the follow-up by two masked physicians (H. D. and Y. Z.), each with more than 3 years of experience with ultrasonography and performed over 300 examinations with ARFI elastography. Details of the examination procedure have been previously described [8,9]. In brief, all measurements were performed on the right hepatic lobe, using an intercostal view with the breath-holding technique. ARFI elastography measurements were performed in an area free of any blood vessels and bile ducts, approximately 2 cm below the surface of the liver (4–6 cm to the transducer), which was chosen as the measuring depth (Supplemental Figure 1). Valid ARFI measurements were obtained when success rate is more than 60%. A total of 10 valid measurements were performed in every patient and the median value was calculated.

### Liver histology and quantification of fibrosis

All patients underwent liver biopsies at baseline, and 27 (38%) patients underwent second liver biopsies at week 78. The liver tissue was obtained via ultrasonography-guided

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