Digestive and Liver Disease 45 (2013) 762–768

Contents lists available at SciVerse ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

# The influence of aminotransferase levels on liver stiffness assessed by Acoustic Radiation Force Impulse Elastography: A retrospective multicentre study

Simona Bota[a,*], Ioan Sporea[a], Markus Peck-Radosavljevic[b], Roxana Sirli[a], Hironori Tanaka[c], Hiroko Iijima[c], Hidetsugu Saito[d], Hirotoshi Ebinuma[d], Monica Lupsor[e], Radu Badea[e], Carmen Fierbinteanu-Braticevici[f], Ana Petrisor[f], Mireen Friedrich-Rust[g], Christoph Sarrazin[g], Hirokazu Takahashi[h], Naofumi Ono[i], Fabio Piscaglia[j], Sara Marinelli[j], Mirko D'Onofrio[k], Anna Gallotti[k], Petra Salzl[b], Alina Popescu[a], Mirela Danila[a]

[a] Department of Gastroenterology and Hepatology, "Victor Babeş" University of Medicine and Pharmacy, Timisoara, Romania
[b] Internal Medicine III, Division of Gastroenterology and Hepatology, Medical University of Vienna, Austria
[c] Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan
[d] Department of Internal Medicine, School of Medicine, Keio University, Tokyo, Japan
[e] III[rd] Medical Clinic, University of Medicine, Cluj Napoca, Romania
[f] II[nd] Medical Clinic and Gastroenterology, University Hospital, Bucharest, Romania
[g] Department of Internal Medicine 1, J.W. Goethe University Hospital, Frankfurt/Main, Germany
[h] Department of Internal Medicine, Saga Medical School, Japan
[i] Department of Gastroenterology, Eguchi Hospital, Mikaduki, Saga, Japan
[j] Division of Internal Medicine, Department of Clinical Medicine, University and General Hospital S. Orsola-Malpighi, Bologna, Italy
[k] Department of Radiology, University Hospital G.B. Rossi, University of Verona, Verona, Italy

ARTICLE INFO

*Article history:*
Received 12 October 2012
Accepted 12 February 2013
Available online 16 March 2013

*Keywords:*
Acoustic Radiation Force Impulse (ARFI) Elastography
Aminotransferase levels
Liver fibrosis
Liver stiffness
Transient Elastography

ABSTRACT

*Background:* Acoustic Radiation Force Impulse Elastography is a new method for non-invasive evaluation of liver fibrosis.
*Aim:* To evaluate the impact of elevated alanine aminotransferase levels on liver stiffness assessment by Acoustic Radiation Force Impulse Elastography.
*Methods:* A multicentre retrospective study including 1242 patients with chronic liver disease, who underwent liver biopsy and Acoustic Radiation Force Impulse. Transient Elastography was also performed in 512 patients.
*Results:* The best Acoustic Radiation Force Impulse cut-off for predicting significant fibrosis was 1.29 m/s in cases with normal alanine aminotransferase levels and 1.44 m/s in patients with alanine aminotransferase levels > 5× the upper limit of normal. The best cut-off for predicting liver cirrhosis were 1.59 and 1.75 m/s, respectively.

Acoustic Radiation Force Impulse cut-off for predicting significant fibrosis and cirrhosis were relatively similar in patients with normal alanine aminotransferase and in those with alanine aminotransferase levels between 1.1 and 5× the upper limit of normal: 1.29 m/s vs. 1.36 m/s and 1.59 m/s vs. 1.57 m/s, respectively.

For predicting cirrhosis, the Transient Elastography cut-offs were significantly higher in patients with alanine aminotransferase levels between 1.1 and 5× the upper limit of normal compared to those with normal alanine aminotransferase: 12.3 kPa vs. 9.1 kPa.
*Conclusion:* Liver stiffness values assessed by Acoustic Radiation Force Impulse and Transient Elastography are influenced by high aminotransferase levels. Transient Elastography was also influenced by moderately elevated aminotransferase levels.


## 1. Introduction

Noninvasive elastographic methods for liver fibrosis assessment are increasingly being used, in an attempt to replace liver biopsy (LB), which is still considered the "gold standard" for liver fibrosis assessment [1,2]. Liver biopsy is an invasive method and, in 1–5%

* Corresponding author at: Department of Gastroenterology, University of Medicine and Pharmacy, Timisoara, 2, Intrarea Martir Angela Sava Str., 300742 Timisoara, Romania. Tel.: +40 721 656147; fax: +40 256 488003.
*E-mail addresses:* bota_simona1982@yahoo.com, simona_doctor@yahoo.com (S. Bota).

1590-8658/$36.00 
http://dx.doi.org/10.1016/j.dld.2013.02.008

of cases, serious complications following diagnostic LB may occur [3], including death (up to 1–3/10,000 cases) [4]. In addition, inter- and/or intra-observer diagnostic discrepancies can occur in up to 10–20% of LBs [5].

Transient Elastography (TE) (FibroScan®) was the first ultrasound-based elastographic method developed. It uses a 5-MHz ultrasound transducer mounted on the axis of a vibrator. The vibrator generates a painless vibration similar to a "flick" (with a frequency of 50 Hz and an amplitude of 2 mm), which penetrates the subcutaneous tissue and generates shear waves into the liver. Displacements induced by the shear wave into the liver are evaluated by cross-correlating the successive ultrasound lines acquired with the ultrasound probe. The shear wave velocity is directly related to tissue stiffness [6], evaluated by using the Young modulus and expressed in kiloPascals (kPa).

Transient Elastography was first validated for liver fibrosis evaluation in patients with chronic hepatitis C and subsequently in other etiologies of chronic liver disease [7–9]; some studies have also demonstrated that TE is a good screening tool for liver fibrosis and portal hypertension [10]. The latest published meta-analysis, which included 40 studies, showed a 79% pooled sensitivity (Se) and a 78% pooled specificity (Sp) of TE for the diagnosis of significant fibrosis ($F \geq 2$, according to METAVIR score system classification) and 83% pooled Se with 89% pooled Sp for the diagnosis of liver cirrhosis [11].

Several studies have demonstrated that liver stiffness (LS) values assessed by TE are influenced by elevated aminotransferase levels [12–14], by extrahepatic cholestasis [15], by differences in central venous pressure [16] or the use of beta-blockers [17].

In recent years, other ultrasound-based elastographic methods for the noninvasive evaluation of liver fibrosis have been developed and, for three of them, studies were carried out and published by the end of 2011: Acoustic Radiation Force Impulse (ARFI) Elastography [18–20], Real-Time Elastography (Hi-RTE) [21,22] and SuperSonic Shear Imaging [23]. Unlike TE, ARFI, Hi-RTE and SuperSonic Shear Imaging are real-time ultrasound-based elastographic methods integrated into a conventional ultrasound system.

Acoustic Radiation Force Impulse (ARFI) Elastography uses short acoustic high-intensity impulses with a fixed transmit frequency of 2.67 MHz which are sent into the tissue inducing local tissue displacements. These displacements lead to a propagation of shear waves away from the region of excitation. The propagation velocity of these transversal shear waves can be measured by ultrasonographic waves (in metres/second (m/s)). The propagation speed increases with the severity of the fibrosis. Shear wave speed may be quantified, in a precise anatomical region, focused on a region of interest, with a predefined size, provided by the system [24].

The aim of this international multicentre study was to establish whether LS values assessed by means of ARFI elastography are influenced by elevated aminotransferase levels.

## 2. Patients and methods

### 2.1. Patients

Our retrospective international multicentre study included 1242 patients (10 centres in 5 countries) with various etiologies of chronic liver disease: mono-infection with hepatitis B or C, hepatitis B and C co-infection, hepatitis B and D co-infection, hepatitis C and human immunodeficiency virus (HIV) co-infection, or a non-viral aetiology (such as alcoholic liver disease, nonalcoholic fatty liver, nonalcoholic steatohepatitis, autoimmune hepatitis or an unknown aetiology of liver disease).

Liver fibrosis was evaluated by means of LB, ARFI and, in a subgroup of patients, also by TE.

The majority of LBs were performed percutaneously (99.3% of cases) while a transjugular LB was performed in 0.7% of patients.

Some patient data have been published in previous studies which investigated ARFI elastography for evaluation of liver fibrosis [18,19,25–29], irrespective of aminotransferase levels. The majority of patients with chronic hepatitis C were also included in a retrospective study [30] which evaluated the accuracy of ARFI elastography, using LB as the "gold-standard" for liver fibrosis evaluation, irrespective of aminotransferase levels.

None of the patients included in our study had either focal liver lesions or ascites on abdominal ultrasound examination.

The study was approved by the local Ethical Committee of each centre and was in accordance with the Helsinki Declaration of 1975.

### 2.2. ARFI elastography

Acoustic Radiation Force Impulse Elastography was performed in all patients using Siemens Acuson S2000™ ultrasound systems (Siemens AG, Erlangen, Germany) with 4CI transducers. Scanning was performed with a right intercostal approach, in the right liver lobe, segments V–VIII, 1–2 cm (Hyogo, Timisoara) or 2–3 cm (other centres) under the liver capsule, with minimal scanning pressure applied by the operator while the patients were asked to stop normal breathing for a moment in order to minimise breathing motion. A total of 5 (Saga), 6 (Bologna and Verona) or 10 valid measurements (in the other centres included in the study) were carried out on each patient; median values were calculated for each patient, the result being measured in m/s. If the measurement was not reliable "X-X-X" was displayed on the screen.

The operators carrying out the ARFI measurements were blinded to all patient clinical, serologic and histological data.

### 2.3. Transient Elastography

Liver stiffness was measured by means of TE using a FibroScan® device (Echosens, Paris, France) in 512 patients in the same session as the ARFI measurements. Patient distribution in the centres participating in this study was as follows: Timisoara (Romania), 152 (29.7%); Tokyo (Japan), 136 (26.6%); Cluj-Napoca (Romania), 96 (18.7%); Frankfurt (Germany), 85 (16.6%); Bologna (Italy), 38 (7.5%) and Vienna (Austria), 5 (0.9%).

In each patient, 10 valid TE measurements were carried out, the median value was calculated and the results were expressed in kPa. We considered only LS measurements with a success rate (ratio of the number of successful acquisitions over the total number of acquisitions) of at least 60% and an interquartile range (IQR = the difference between the 75th and 25th percentile, essentially the range of the middle 50% of the data) lower than 30% to be reliable.

### 2.4. Liver biopsy

Liver biopsy was performed using different methods in the participating centres: percutaneous LB using a Menghini needle (Hepafix; B Braun Melsungen AG, Germany) in 5 centres (Timisoara, diameter of the needle 1.4 or 1.6 mm; Bucharest, 1.4 mm; Bologna and Verona, 1.4 or 1.6 mm; Frankfurt, 1.2 mm), percutaneous LB using the TruCut technique (Bard GMBH, Karlsruhe, Germany or Pro-Mag™, Medical Device Technologies, Gainesville, FL, USA), with an automatic needle device in one centre (Hyogo-16-G needle), percutaneous LB using semi-automatic instruments (Super-Core™, Dartmouth, MA, USA) in 2 centres (Saga-16-G needle and Tokyo-18-G needle) and transjugular LB in one centre (Vienna). Only LB fragments at least 1.5 cm long were included in the study. The LBs were assessed according to the METAVIR score by a senior pathologist, blinded to the results of the LS measurements. Fibrosis was staged on a 0–4 scale: F0 – no