Arab Journal of Gastroenterology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Arab Journal of Gastroenterology

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

Original article

Establishing ultrasound based transient elastography cutoffs for different stages of hepatic fibrosis and cirrhosis in Egyptian chronic hepatitis C patients

Aisha Elsharkawy [a,*], Mohamed Alboraie [b], Rabab Fouad [a], Noha Asem [c], Mahmoud Abdo [a], Hesham Elmakhzangy [a], Mai Mehrez [d], Hany Khattab [e], Gamal Esmat [a]

[a] Department of Endemic Medicine and Hepatogastroentrology, Cairo University, Cairo, Egypt
[b] Department of Internal Medicine, Al-Azhar University, Cairo, Egypt
[c] Department of Public Health and Community Medicine, Cairo University, Cairo, Egypt
[d] National Hepatology and Tropical Medicine Research Institute, Cairo, Egypt
[e] Department of Pathology, Cairo University, Cairo, Egypt

ARTICLE INFO

Article history:
Received 18 April 2017
Accepted 12 November 2017
Available online xxxx

Keywords:
Chronic hepatitis C
Transient elastography
Fibrosis
Cirrhosis
METAVIR

ABSTRACT

Background and study aim: Transient elastography is widely used to assess fibrosis stage in chronic hepatitis C (CHC). We aimed to establish and validate different transient elastography cut-off values for significant fibrosis and cirrhosis in CHC genotype 4 patients.

Patients and Methods: The data of 100 treatment-naive CHC patients (training set) and 652 patients (validation set) were analysed. The patients were subjected to routine pretreatment laboratory investigations, liver biopsy and histopathological staging of hepatic fibrosis according to the METAVIR scoring system. Transient elastography was performed before and in the same week as liver biopsy using FibroScan (Echosens, Paris, France). Transient elastography results were correlated to different stages of hepatic fibrosis in both the training and validation sets.

Results: ROC curves were constructed. In the training set, the best transient elastography cut-off values for significant hepatic fibrosis (≥F2 METAVIR), advanced hepatic fibrosis (≥F3 METAVIR) and cirrhosis (F4 METAVIR) were 7.1, 9 and 12.2 kPa, with sensitivities of 87%, 87.5% and 90.9% and specificities of 100%, 99.9% and 99.9%, respectively. The application of these cut-offs in the validation set showed sensitivities of 85.5%, 82.8% and 92% and specificities of 86%, 89.4% and 99.01% for significant hepatic fibrosis, advanced hepatic fibrosis and cirrhosis, respectively.

Conclusion: Transient elastography performs well for significant hepatic fibrosis, advanced hepatic fibrosis and cirrhosis, with validated cut-offs of 7.1, 9 and 12.2 kPa, respectively, in genotype 4 CHC patients.

Introduction

Chronic hepatitis C (CHC) is a global health problem affecting more than 150 million people around the world. Egypt has the highest prevalence of CHC among its population. Genotype 4 is the most frequently diagnosed genotype among Egyptians. The diagnosis of CHC and its consequences is essential in determining the treatment and follow-up of Egyptian patients with CHC. Different methods for assessing hepatic fibrosis and cirrhosis (serum biomarkers, transient elastography and others) that decrease the need for liver biopsies are currently used in clinical practice [1]. Transient elastography is one of the most frequently used methods for non-invasive assessments of hepatic fibrosis and cirrhosis worldwide [2]. The principle of transient elastography depends on the measurement of tissue elasticity using controlled generation of a shear wave via a servo-controlled vibration of known frequency and amplitude [3]. Since the first publication regarding transient elastography in 2003 [4], extensive research has been conducted, mainly in Europe, to verify the concept of its use and to validate its cut-off values in different types of chronic liver diseases [5]. In April 2013, the food and drug administration approved its use in chronic liver diseases, and its use has been subsequently expanded to the United States [6]. The cut-off values vary according to the underlying liver disease [7–9]. Moreover, the cut-off

* Corresponding author at: Faculty of Medicine, Cairo University, Cairo 11562, Egypt.
E-mail address: a_m_sharkawy@kasralainy.edu.eg (A. Elsharkawy).

https://doi.org/10.1016/j.ajg.2017.11.002
1687-1979/

values for the same disease vary among different populations [10]. Both serum fibrosis biomarkers (APRI, FIB-4, FORNS and Egy-Score) [11–13] and transient elastography [14] show good correlations with hepatic fibrosis and cirrhosis stages in Egyptian CHC patients. Using locally validated cut-off values may improve the diagnostic accuracy of transient elastography for the assessment of different stages of hepatic fibrosis and cirrhosis in CHC. In this study, we aimed to establish and validate different cut-off values for significant hepatic fibrosis, advanced hepatic fibrosis and cirrhosis in Egyptian CHC patients and to compare the diagnostic accuracy of transient elastography with that of frequently used serum markers of hepatic fibrosis.

Patients and methods

The retrospective data of 100 treatment-naive CHC patients as a training set and of 652 treatment-naive CHC patients as a validation set were analysed. Patients were collected from different CHC treatment centres in Egypt. Patients were identified as having CHC if they had positive hepatitis C virus antibody and positive hepatitis C virus ribonucleic acid (HCV-RNA) results by polymerase chain reaction (PCR) for more than 6 months. Patients with marked elevation of liver enzymes (more than 5 times the upper limit of normal), marked hyperbilirubinaemia (more than 10 times the upper limit of normal), or obstructive jaundice and patients with other types of chronic liver diseases were excluded. As a part of the pretreatment assessment, the patients were subjected to an interview regarding their full history, a standard clinical examination (including body mass index), laboratory investigations (complete blood count, coagulation profile, and liver and kidney function tests), assessments of hepatitis B surface antigen, antinuclear antibody, and serum biomarkers of hepatic fibrosis (aspartate aminotransferase-to-platelet ratio index [15] and FIB-4 score [16]), abdominal ultrasound examination, liver stiffness measurement (LSM) using ultrasound transient elastography (FibroScan®, Echosens, France), liver biopsy and histopathological examination.

Liver stiffness measurement

Ultrasound transient elastography (FibroScan) with both ultrasound]3.5 MHz for the standard medium sized probe (M probe) and 2.5 MHz for the X-large probe (XL probe)[and low-frequency (50 Hz) elastic shear waves was used to measure liver stiffness in fasting patients (at least 4 h). Transient elastography was performed using FibroScan (Echosens, Paris, France) before and in the same week as liver biopsy. XL probes have been primarily used in obese patients (body mass index >30 kg/m^2). The device consists of a probe with an ultrasound transducer mounted on the axis of a vibrating piston. A piston is used to create a mechanical impulse, thus generating a low-frequency shear wave that propagates through the liver tissue. The ultrasound transducer, which is located at the tip of the probe, performs a series of ultrasound acquisitions to measure the speed of shear wave propagation. The liver stiffness, expressed in kPa, is calculated from this shear wave propagation speed. A higher shear wave velocity corresponds to greater liver stiffness, which represents a higher stage of fibrosis [4]. LSM was performed by an experienced hepatologist with more than 5 years of experience in performing the procedure who had completed more than 1000 examinations. The tip of the probe transducer was covered with coupling gel and placed on the skin between the ribs at the level of the right lobe of the liver. The operator, assisted by an ultrasonic time-motion image, located a portion of the liver that was at least 4-cm thick and free of large vascular structures. Measurements were taken using the conventional standard M probe for patients with a body mass index below 30 kg/m^2 or the XL probe for patients with a body mass index greater than 30 kg/m^2. During the acquisition, the subjects were lying on their backs with their right arm behind the head (maximal abduction) in a similar position to that used for liver biopsy. The operator obtained the measurements with the probe placed in the intercostal space. A minimum of 10 valid measurements were taken from the right lobe of the liver for each subject. The median values of the valid measurements were recorded as the LSM in kPa. LSM is considered unreliable if the interquartile range (IQR)/median LSM is >30% and the success rate is <60% [17].

Biomarkers of liver fibrosis

The aspartate aminotransferase-to-platelet ratio index and FIB-4 score were calculated according to the following equations:

APRI score was calculated using Wai's formula [15]:

(AST/upper limit of normal)/platelet count (expressed as plate lets $\times 10^9$/L) $\times$ 100.

The FIB-4 score was calculated using Sterling's formula [16]:

Age (years) $\times$ AST (IU/L)/platelet count ($\times 10^9$/L) $\times \sqrt{}$ALT (IU/L)).

Liver biopsy and histopathological classification

Ultrasound-guided percutaneous liver biopsy was performed using 16-G semi-automated biopsy needles. Liver biopsy specimens (a minimum of 15 mm in length with at least four portal tracts) were fixed in 10% neutral formalin, processed, and then embedded in paraffin. Sections were stained with haematoxylin–eosin and Masson trichrome for the detection of fibrosis. Histopathological examinations were performed according to the METAVIR scoring system, with different stages for fibrosis (F0–F4) and grades for necroinflammatory activity (A0–A3) [18]. Histopathological examinations of liver biopsy specimens were performed by two independent expert pathologists familiar with liver tissue examination, and only concordant results were included in this study. The patients were further divided into three groups according to the stage of hepatic fibrosis: (i) significant hepatic fibrosis $\geq$ F2; (ii) advanced hepatic fibrosis > F3, and (iii) cirrhosis (F4).

Statistical analysis

The data were analysed using SPSS v21.0 for Windows. Categorical variables are summarized as the frequency counts and percentages. Continuous variables are summarized as the means and standard deviations.

In addition, the relationships between different variables were assessed through univariate analysis as follows. Categorical variables were assessed with the chi-squared test or the Fischer exact test where appropriate, and continuous variables were assessed using the independent samples *T* test or the Mann–Whitney *U* test according to the normality of their distribution. A receiver operating characteristic (ROC) curve was generated to determine the appropriate scores for predicting the stage of liver fibrosis that provide optimal sensitivity and specificity. Hypothesis testing was two-sided, and statistical significance was accepted at the 5% level. Significance was expressed as a P value.

Results

Our study included 752 patients in two groups, group 1 (100 patients; training set) and group 2 (652 patients; validation set). Two hundred thirty-five (31.25%) patients were female, and 517

Please cite this article in press as: Elsharkawy A et al. Establishing ultrasound based transient elastography cutoffs for different stages of hepatic fibrosis and cirrhosis in Egyptian chronic hepatitis C patients. Arab J Gastroenterol (2017), https://doi.org/10.1016/j.ajg.2017.11.002