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Are different cut-off values of liver stiffness assessed by Transient Elastography according to the etiology of liver cirrhosis for predicting significant esophageal varices?

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Abstract

Aim: To determine if liver stiffness (LS) measurements by means of Transient Elastography (TE) vary according to the etiology of the underlying liver cirrhosis and to find if there are different TE cut-off values able to predict the presence of significant EV in alcoholic vs. viral etiology of cirrhosis. **Methods:** This retrospective study included patients diagnosed with liver cirrhosis of viral or alcoholic etiology. All patients were evaluated by means of TE (FibroScan) and upper gastrointestinal endoscopy. We performed 10 LS measurements in each patient and a median value expressed in kiloPascals (kPa) was calculated. Only those with a SR≥60% and an IQR<30% were considered as reliable MS measurements. According to the presence of EV the patients were divided in two categories: without significant EV and patients with significant EV (at least grade 2). **Results:** The study included 697 cirrhotic patients with reliable LS measurements. The median LS values assessed by TE were significantly higher in cirrhotic patients with alcoholic etiology as compared with those with viral etiology of liver disease: 41 kPa vs. 21.1 kPa, p<0.0001. In the entire cohort of cirrhotic patients, LS assessed by means of TE for a cut-off value >29.5 kPa, had 77.5% sensitivity and 86.9% specificity for predicting the presence of significant EV (AUROC=0.871). The best LS cut-off value for predicting the presence of significant EV was higher in alcoholic cirrhosis as compared with those with viral etiology of liver cirrhosis: 32.5 kPa (AUROC=0.836) vs. 24.8 kPa (AUROC=0.867). **Conclusions:** LS cut-off values assessed by TE for predicting significant EV are significantly higher in patients with alcoholic cirrhosis as compared with patients with liver cirrhosis of viral etiology.

Keywords: Transient Elastography, alcoholic liver cirrhosis, viral liver cirrhosis, esophageal varices, portal hypertension

Introduction

Chronic hepatopathies are quite common in daily clinical practice and the main etiologies of this diseases are chronic viral infections (B, C or B+D), alcoholic etiology and in lately non alcoholic fatty liver disease (NAFLD). Liver cirrhosis is the final stage of all chronic hepatopathies and it is a well known fact that cirrhosis has lots of important complications such as portal hypertension, hepatocellular carcinoma, hepatic encephalopathy, spontaneous bacterial peritonitis, hepato-renal syndrome etc.

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Elastographic ultrasound-based methods such as Transient Elastography (TE) (FibroScan®) [1-3], Real-Time Tissue Elastography-Hi-RTE [4,5], Acoustic Radiation Force Impulse Elastography-ARFI [6,7], or SuperSonic Shear Imaging [8] are non-invasive methods used more and more for the evaluation of liver fibrosis. Among these, TE is the most studied method [2,3], with many publications proving its value in the staging of chronic hepatopathies with different etiologies, especially in chronic hepatitis B and C, NAFLD, and in post transplant patients [1-3,9-11].

TE is performed with a FibroScan® device (Echosens, Paris, France) which incorporates a 5-MHz ultrasound transducer probe mounted on the axis of a vibrator. The vibrator generates a completely painless vibration (with a frequency of 50 Hz and amplitude of 2 mm), which generates an elastic shear wave that propagates through the skin and the subcutaneous tissue into the liver. The shear

wave velocity (expressed in kiloPascals - kPa) is directly related to the stiffness of the tissue [12].

If the performances of TE for the differentiation of mild from significant fibrosis are only moderate, its real value is for the diagnosis of cirrhosis. A meta-analysis published in 2011 [3] which included 40 studies, showed a very good value of TE for diagnosing liver cirrhosis, the summary sensitivity and specificity being 0.83 (95% confidence interval-CI: 0.79-0.86) and 0.89 (95% CI: 0.87-0.91), respectively.

On the other hand, because LS values evaluated by TE in patients with cirrhosis have a wide range of distribution (between 14 and 75 kPa), several authors tried to find if LS can be predictive for the presence of cirrhosis complications (such as esophageal varices - EV, variceal bleeding, vascular decompensation or hepatocellular carcinoma) [13-15].

In a study by Foucher et al [13], the cut-off values for the presence of significant EV (grade 2 and 3), cirrhosis Child-Pugh B or C, past history of ascites, HCC, and esophageal bleeding were 27.5, 37.5, 49.1, 53.7, and 62.7 kPa, respectively.

Published studies concerning portal hypertension demonstrated that LS values <19 kPa are highly predictive for the absence of significant EV (≥ grade 2) [16]. Cut-off values for at least grade 2 EV range from 27.5 [13] to 48 kPa [17], while for esophageal bleeding, the reported a cut-off values range between 50.7 [14] and 62.7kPa [13]. One of the published studies which included 138 patients with various etiologies of liver cirrhosis, showed different TE cut-off values for predicting the presence of significant EV, according to the etiology of liver disease, higher cut-off values being associated with alcoholic etiology of cirrhosis [17].

Since in previous published studies the range of LS cut-off values found to predict the presence of significant EV is quite large (27.5 - 48 kPa) the **aim** of this study performed in a large cohort of cirrhotic patients was to determine if LS measurements by means of TE vary according to the etiology of the underlying liver disease and to find if there are different TE cut-off values able to predict the presence of significant EV in alcoholic vs. viral etiology of cirrhosis

Material and methods

Patients

Our retrospective study included successive patients diagnosed with liver cirrhosis of viral or alcoholic etiology, which were evaluated in our Department. The diagnosis of liver cirrhosis was established by histological criteria or by the combination of clinical, ultrasound, endoscopic and elastographic criteria.

All patients were evaluated by means of TE and upper gastrointestinal endoscopy. None of the patients had ascites on abdominal ultrasound examination.

All the patients signed an informed consent before TE and endoscopic evaluation, the study was in accordance with the Helsinki Declaration of 1975 and was approved by the local Ethics Committee.

Transient Elastography

Transient Elastography was performed in all patients, by 4 experienced physicians (at least 500 TE measurements performed by each of them), using a FibroScan® device (Echosens, Paris, France) with a standard M-probe.

In all patients TE measurements were performed in the right liver lobe, by intercostal approach, in supine position with the right arm in maximal abduction. The operator, assisted by an ultrasonic time-motion image, chose a liver area free of large vascular structures. Once the measurement area had been located, the operator pressed the probe button to start an acquisition. Ten successful measurements were performed in each patient and a median value expressed in kiloPascals (kPa) was calculated.

All patients included in the final analysis had reliable LS measurements, meaning a median value of 10 valid LS measurements with a success rate (SR = the ratio of the number of successful measurements over the total number of acquisitions) ≥60% and an interquartile range interval (IQR = the difference between the 75th and the 25th percentile, essentially the range of middle 50% of the data) <30%.

The operators who performed TE measurements were blinded to the clinical data of the patients, to the etiology of liver cirrhosis and to the upper gastrointestinal endoscopy results.

Upper gastrointestinal endoscopy

Upper gastrointestinal endoscopy was performed in all cirrhotic patients. The time interval between LS measurements by means of TE and upper gastrointestinal endoscopy was up to 6 months.

Esophageal varices were classified as: small (grade 1) - small straight varices; medium (grade 2) - enlarged tortuous varices occupying less than one third of the lumen; large (grade 3) - large coil-shaped varices occupying more than one third of the lumen.

In this study, cirrhotic patients were divided in two categories according to the presence and size of EV: without varices or small EV and the other group with significant EV (grade 2 and 3).

The operators who performed upper gastrointestinal endoscopy were blinded to the clinical data of patients, to the etiology of liver cirrhosis and to the TE results.

Statistical analysis

The statistical analysis was carried out using MedCalc Software, version 12.4.0. (MedCalc program, Belgium). The distribution of numerical variables was first tested by the Kolmogrov-Smirnov test. In cases of numerical variables with a normal distribution, the mean value and standard deviation were calculated, while in cases of non-normal distribution, the median values with range intervals were used. Differences between numerical variables were analyzed by parametric (t-test) or non-parametric tests (the Mann–Whitney test) according to the normal or non-normal distribution of variables. Qualitative variables were presented as numbers and percentages.

The diagnostic performance of TE for predicting the presence of significant EV was assessed using the area under receiver operating characteristic (AUROC) curves. Optimal cut-off values were chosen in order to maximize the sum of sensitivity (Se) and specificity (Sp). For each predictive test, 95% confidence intervals were calculated and for each statistic test, a p-value less than 0.05 was regarded as significant.

Results

Initially 873 cirrhotic patients were evaluated by means of TE. From those, 176 patients (20.1%) were excluded because they did not have reliable LS measurements. Thus, the final analysis included 697 cirrhotic patients, whose main characteristics are presented in Table I.

The median LS values assessed by TE were significantly higher in cirrhotic patients with alcoholic etiology as compared with those with viral etiology of liver disease: 41 kPa (12-75 kPa) vs. 21.1 kPa (10.9-75 kPa), p<0.0001.

In the group of cirrhotic patients with significant EV, the median LS values assessed by TE were significantly higher in the group of patients with alcoholic cirrhosis as compared with those with viral etiology: 59.3 kPa (12.8-75 kPa) vs. 36.3 kPa (12.6 -75 kPa), p<0.0001.

In the group of cirrhotic patients without EV or with small EV, the median LS values assessed by TE were also significantly higher in cases with alcoholic cirrhosis as compared with those with viral etiology: 21.1 kPa (12-75 kPa) vs. 18.1 kPa (10.9-75 kPa), p=0.002.

Table I. The main characteristics of patients included in study. Numerical variables with normal distribution are presented as mean value ± standard deviation, while variables with non-normal distribution are presented as median values and range intervals. Qualitative variables are presented as numbers and percentages.

Parameter	
Age (years)	57 (19-84)
Gender: – male	n = 399 (57.2%)
– female	n = 298 (42.8%)
Etiology: – viral	n = 513 (73.6%)
– alcoholic	n = 184 (26.4%)
Esophageal varices: – absent	n = 310 (44.5%)
– grade 1	n = 114 (16.4%)
– grade 2	n = 190 (27.2%)
– grade 3	n = 83 (11.9%)

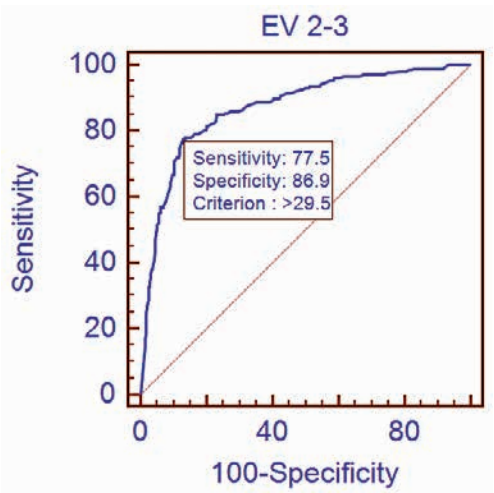

Fig 1. AUROC curve for predicting significant EV in the entire cohort of cirrhotic patients

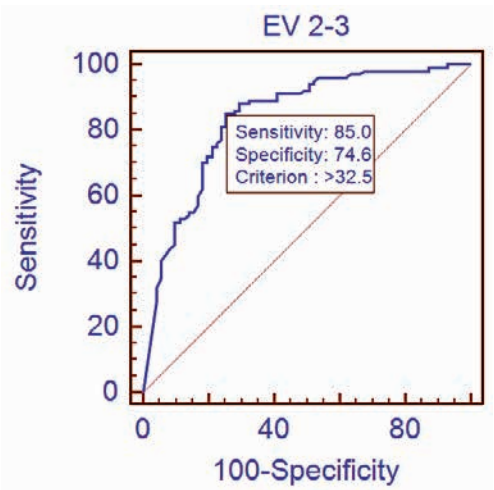

Fig 2. AUROC curve for predicting significant EV in patients with alcoholic cirrhosis

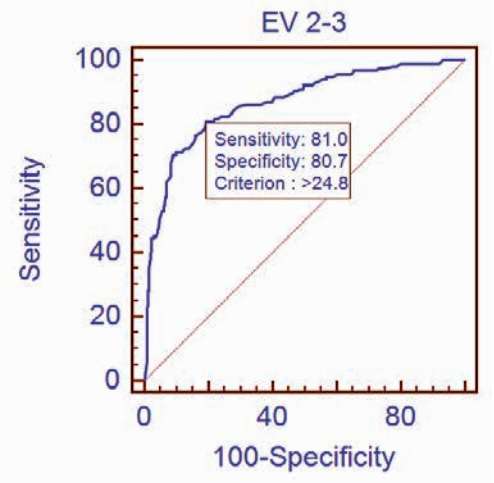

Fig 3. AUROC curve for predicting significant EV in patients with viral cirrhosis

In the entire cohort of cirrhotic patients, for a cut-off value > 29.5 kPa, LS assessed by means of TE had 77.5% Se, 86.9% Sp, 78.9% positive predictive value (PPV), 85.6 % negative predictive value (NPV) and 83.1% accuracy, with an AUROC=0.871 (p=0.0001) for predicting the presence of significant EV (fig 1).

In patients with alcoholic cirrhosis, for a cut-off value > 32.5 kPa, LS assessed by means of TE had 85% Se, 74.6% Sp, 82.3 % PPV, 74.6 % NPV and 80.1 % accuracy, with an AUROC = 0.836 (p=0.0001) for predicting the presence of significant EV (fig 2), while in patients with viral cirrhosis the best TE cut-off value for predicting the presence of significant EV was > 24.8 kPa, with 81% Se, 80.7% Sp, 66.3 % PPV, 90.1 % NPV and 80.8 % accuracy, (AUROC = 0.867, p=0.0001) (fig 3).

Discussions

Esophageal varices and variceal bleeding are feared complications of liver cirrhosis. The hemorrhage risk depends on the varices' size so that primary prevention of variceal bleeding should be applied in all patients with large EV (grade 2 or 3), diagnosis established by periodical upper digestive endoscopy [18]. According to the Baveno V consensus [18] the screening for EV in cirrhotic patients by upper gastrointestinal endoscopy is a strong recommendation. But a screening program of periodical gastroscopy in all cirrhotics is very expensive, and repeated endoscopies are poorly accepted by the patients.

Published studies demonstrated that LS values evaluated by TE <19 kPa are highly predictive for the absence of significant EV [16], but published cut-off values usable to predict their presence range widely, from 27.5 kPa [13] to 48 kPa [17]. In a recently published meta-analysis [19], which included 3644 patients from 18 studies, a 0.87 summary Se (95% CI: 0.80–0.92) with 0.53 summary Sp (95% CI: 0.36–0.69) was obtained for the presence of EV and a 0.86 summary Se (95% CI: 0.71–0.94) with 0.59 summary Sp (95% CI: 0.45–0.72) were obtained for the presence of significant EV. In this meta-analysis [19] the summary ROC curves for predicting the presence of EV and significant EV were 0.84 and 0.78 respectively. According to these results, the authors concluded that TE has a moderate diagnostic utility for the prediction of EV and significant EV.

In our present study performed in large cohort of cirrhotic patients (almost 700) we observed that LS assessed by TE is a valuable method for predicting the presence of significant EV in the entire cohort of patients (AUROC=0.871 with 83.1% accuracy), results similar with those obtained by Kazemi et al [16] and slightly better than those obtained in others studies [13,17,20-22].

Our results showed that LS cut-off values assessed by TE for predicting significant EV are different according to the etiology of liver cirrhosis, being higher in alcoholic cirrhosis (32.5 kPa) as compared with viral etiology of liver diseases (24.8 kPa). These data are in line with those obtained by Nguyen-Khac et al [17], but their cut-off values are different from those obtained in this present study: 47.2 kPa for alcoholic etiology and 19.8 kPa for viral cirrhosis. An explanation for these differences can be the different distribution of significant EV in these two studies: in our study 39.1% of patients had significant EV, while in the Nguyen-Khac et al study [17] only 22.4% of cirrhotics had significant EV. Another explanation can be the fact that since our study is a retrospective one, we did not record at the moment of TE measurements if the patients were or were not under beta-blocker therapy, nor if the patients with alcoholic cirrhosis had stopped drinking, knowing that recently published data showed that beta-blocker therapy influences the LS values assessed by TE [23] and that after alcohol withdrawal, LS values assessed by TE decrease in parallel with the decrease of aminotransferases level [24].

Beside the mentioned limitations of our study, it should be underlined that the accuracy of TE for predicting significant EV was slightly higher than 80%, for both alcoholic and viral etiology of liver cirrhosis, and also, in the case of viral etiology the NPV was very good (90.1%). The results suggest that this method can be used in clinical practice for the non-invasive diagnosis of significant EV, especially in patients with viral cirrhosis.

In order to increase the accuracy of TE for predicting the presence of significant EV, probably it should be useful to also use spleen stiffness measurements by TE [25].

Our study showed that median LS values assessed by TE were significantly higher in alcoholic etiology as compared with viral etiology of liver cirrhosis, these data being in line with other published studies [1, 26].

In **conclusion,** LS cut-off values assessed by TE for predicting significant EV are significantly higher in patients with alcoholic cirrhosis as compared with patients with liver cirrhosis of viral etiology.

Conflict of interest: none

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