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Research Article

Transient Elastography as Non Invasive Assessment of Portal Hypertension in Advanced Chronic Liver Disease

Gómez-Escolar Laura[1*], García-Herola Antonio[1], Palazón José M[2], De España Francisco[3], Perea Sofia[4] and Sánchez-Payá José[5]

[1]Division of Gastroenterology, Hospital Marina Baixa de Villajoyosa, Alicante, Spain

[2]Liver Unit, Hospital General Universitario de Alicante, Spain

[3]Vascular and Interventional Radiology Unit, Hospital General Universitario de Alicante, Spain

[4]Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA

[5]Department of Preventive Medicine, Hospital General Universitario de Alicante, Spain

*Address for Correspondence: Laura Gómez-Escolar, Unidad de Endoscopia Digestiva, Hospital Marina Baixa, Av/ Jaume Botella Mayor, s/n. 03570, Villajoyosa Alicante, Spain, Tel: +34 645468017; Fax: +34 966859800; E-mail: lauragomezescolar@gmail.com

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Abstract

Background: Hepatic cirrhosis (HC) is the most frequent source of clinically significant portal hypertension (CSPH) in Western countries. A reliable, easy-to-use, and noninvasive tool to assess for the presence of CSPH for screening of cirrhotic patients is needed.

Aims: 1) To determine the correlation between liver stiffness (LS), measured by transient elastography (TE) and portal hypertension (PH), by hepatic venous pressure gradient(HVPG), as well as the cut off value of TE for CSPH; 2) To evaluate the correlation between CSPH and LS with the histological findings in liver biopsy; 3) To assess the relationship between the degree of LS and the risk of clinical decompensation in HC.

Methods: Single center, prospective, cohort study. 58 in-and-out-patients with chronic liver diseases were enrolled during a

40-month period.

Results: A statistically significant association between LS (TE), and PH (HVPG) was found (r = 0.71, p < 0.0001). Cut off value of TE for diagnosis of CSPH was 17.15 kPa. Using this cut-off, 81% of the patients presented CSPH while 87% using the HVPG cut-off of ≥10mmHg. Both the nodule size and septal thickening were the two independent predictors of CSPH. The probability of remaining free of developing a hepatic decompensation was significantly superior in the group of patients without CSPH (TE < 17.15 kPa, p < 0.001).

Conclusions:TE is a reliable, non-invasive and affordable tool for assessing CSPH. A statistically significant association between LS measured by TE and HVPG as prognostic tool for development of CSPH in patients with chronic liver disease was established. TE is able to independently identify patients with cirrhosis who are at risk of clinical decompensation.

Key words: Portal hypertension, Hepatic venous pressure gradient, transient elastography, chronic liver disease

Introduction

The ultimate outcome of enduring liver injury is the development of hepatic fibrosis that leads to architectural changes and eventually hepatic cirrhosis (HC) [1]. Progressive hepatic fibrosis is the most important factor leading to parenchymal dysfunction and the development of portal hypertension (PH) that is defined as an increase in porto-systemic pressure gradient in any portion of the portal venous system [2,3].

HC is the most frequent source of PH in Western countries [3]. Although initially asymptomatic, complications may occur in most patients leading to development of gastroesophageal varices, varicose hemorrhage, ascites, spontaneous bacterial peritonitis and hepato-renal syndrome [4]. Measurement of portal venous pressure (PH) is very relevant as its pathological increase predicts several complications associated to HC, such as development of porto-systemic collaterals as well as gastroesophageal varices [5-7].

A reliable and widely available noninvasive tool to assess for the presence of clinically significant PH (CSPH) and liver disease complications should be used to screen patients with HC. Hepatic venous pressure gradient (HVPG) is currently the gold standard method for the measurement of PH as predicts development of complications [8-11]. PH is defined as the increase of HVPG above 5 mm Hg. An HVPG value > 10 mm Hg is used as a cut-off to define CSPH [12]. However, HVPG measurement is an invasive procedure that is expensive and requires special training, limiting its use to tertiary and academic hospitals [13].

Transient elastography (TE) is a noninvasive method that estimates liver stiffness (LS), which has been shown to correlate well with fibrosis stage and the presence of HC in chronic liver disease resulting from multiple etiologies [14-19]. The sensitivity and specificity of LS measurement improve as fibrosis stage worsens [19,20]. Although there is evidence that suggests that TE adequately reflects the results of HVPG for the detection of PH as well as cirrhotic complications, some studies, however, have reported conflicting results [4,21-27].

Liver biopsy is the gold standard, as well as an invasive method, for the assessment of liver inflammation and fibrosis, but only few studies have analyzed the relationship between the histological characteristics of the liver and the presence of portal hypertension and the likelihood to develop clinical complications in patients with HC [28-30].

The overall goal of the present study was to evaluate the diagnostic accuracy of TE compared with that of HVPG measurement, used as a gold standard, for the assessment of CSPH in patients with chronic liver diseases. The following specific objectives were sought: 1) To determine the correlation between LS measured by TE and PH as determined by HVPG, as well as the cut off value of TE for CSPH; 2) To evaluate the correlation between

CSPH (measured by HVPG) and LS (measured by TE), with the histological findings in liver biopsy; 3) To assess the relationship between the degree of LS, measured by TE, and the risk of clinical decompensation in patients with cirrhosis.

Methods

Study design

This was a single center, prospective, cohort study conducted at Hospital General Universitario de Alicante, Spain. During a 6 month-period, in-patients and out-patients from both Liver and Infectious Diseases Units who met eligibility criteria were enrolled and were followed during a 40-month period. Participants were required to give written informed consent before inclusion in the study. The study protocol was approved by the Ethics Committee of the Hospital General Universitario de Alicante, Spain, and was conducted in accordance with the principles of the Declaration of Helsinki.

Inclusion and exclusion criteria

Consecutive adult patients with chronic liver disease, defined as the presence of hepatic inflammation for > 6 months, with significant clinical manifestations and permanent or intermittent alanine transaminase (ALT) increase that fulfilled all or some of the following signs and symptoms were enrolled in the study. The signs and symptoms of chronic liver disease included: Stigmas of chronic liver disease in physical exam (vascular spiders; palmar erythema; nail striations; redness of the distal third of the nails; finger clubbing; Dupuytren's contracture; gynecomastia; testicular atrophy; feminine hair distribution; echymosis/hematomas; hepato/splenomegaly; superficial abdominal collateral circulation; fetor hepaticus, jaundice; asterixis) and/or any of the following alterations: 1) Incidental finding in routine analytics: AST/ALT elevation and/or enzymes of cholestasis, associated with anemia, leukopenia, thrombocytopenia, hypoalbuminemia, and coagulopathy; 2) Incidental finding in ultrasound or upper digestive endoscopy indicative of chronic liver disease with PH (gastroesophageal varices or gastropathy due to PH). A subgroup of patients with HIV infection and manifestations of chronic liver disease was also included. Patients with severe liver inflammation, or ascites and/or morbid obesity [Body Mass Index (BMI) ≥ 35 kg/m^2] (due to the inability to perform TE), as well as those with prior history of hepatocellular carcinoma, hepatic encephalopathy, ingestion of hepatotoxic substances or expected survival ≤ 3 months [Model for End-Stage Liver Disease (MELD) score ≥ 19] were excluded from the study.

Study variables and term definitions

The following demographic and clinical characteristics were recorded: Age, gender and etiology of liver disease [hepatitis C virus (HCV), alcoholic, mixed (alcohol and HVC) and others]. The following analytical variables were collected: serum albumin, platelets, serum gammaglobulin and CD4 lymphocytes count. With these data, patients were stratified using the Child-Pugh and MELD prognostic scales.

To assess clinical outcome, the following terms and definitions were used: *Clinical decompensation* was defined as the emergence of ascites, encephalopathy, hemorrhage due to gastroesophageal varices, diagnosis of hepatocarcinoma or exitus. *Ascites* was defined by the finding of clinical signs of ascites in the physical examination, confirmed by abdominal ultrasound. *Hepatic encephalopathy* was defined by the presence of time/spatial disorientation, asterixis or both, in the absence of other possible causes, different of hepatic origin. *Digestive bleeding* from gastroesophageal was defined following Baveno's criteria V [12]. *Hepatocellular carcinoma* was defined according to EASL-EORTC clinical guidelines [31]. *Septal thickening* was defined as the width of the connective scar tissue that separates the cirrhotic nodules and *Nodular size* was categorized according to the size of the nodule (large, small or mixed).

Radiological and Functional Tests

All patients underwent an abdominal ultrasound to evaluate the presence of splenomegaly and other signs of PH such as collateral circulation or the presence of ascites. An upper digestive endoscopy was performed to evaluate the presence of gastroesophageal varices and gastropathy due to PH. TE (FibroScan®, Echosens) was performed to evaluate the degree of LS, measured in kilopascals (kPa) [15,19,20]. The reported result was the median of 10 different measurements. The TE measurement was valid if the successful rate was above 60%, the interquartile range was less than 30%

of the median and a number of valid shots was at least 10. The measure of HVPG, to evaluate the gradient between the wedged (i.e., balloon-occluded) hepatic venous pressure and the free hepatic venous pressure, representing pressure from the hepatic sinusoids (measured in mm Hg), was also performed in all cases. Two measurements were obtained and the mean value of both was reported. As porto-systemic collaterals develop at HVPG > 10 mmHg, and bleeding from gastroesophageal varices at > 12 mmHg, an HVPG value > 10 mmHg was used as the cut-off value to define CSPH [10-12]. Not all patients consented for a liver biopsy. In a subset of patients that gave consent, a liver biopsy, together with the GPVH measurement was performed in the same procedure (transjugular liver biospy). In a subset of patients, a transjugular liver biopsy was obtained. The histological samples obtained were processed and examined using the Batts-Ludwig classification [32]. Both HVPG and liver biopsy were performed during the same procedure. The histological exam was always performed by the same pathologist to avoid bias.

Statistical analysis

Categorical variables were described using percentages or ratio in each category. Quantitative variables were analyzed using the Kruskal-Wallis test to determine its distribution (parametric or non-parametric). Mean and standard deviation (parametric variables) as well as median and interquartile (non-parametric variables) were used in the analysis. The comparison of the clinical characteristics based on the HVPG and TE was carried out using T-student or Chi-square test. A multivariate logistic regression analysis to determine odds ratios (OR) was also performed. The relationship between the degree of LS and HVPG was established using a linear regression analysis with the Pearson correlation coefficient. The relationship between sensitivity and specificity of LS at different cutoff points, as predictor of CSPH, defined as HVPG > 10 mm Hg, was evaluated by receiver operating characteristic curves (ROC). Optimal LS cutoff values were selected on the basis of sensitivity (Se), specificity (Sp), and positive and negative predictive values (NPV and PPV), respectively. The value with the highest PPV was chosen as cut-off.

The relationship between histological parameters (grouped in two categories: present or absent) and CSPH defined by either HVPG value ≥ 10 mmHg or the value of the TE cut-off obtained, was analyzed using a multivariate logistic regression analysis. In order to avoid report bias, the diagnostic tests (TE, HVPG measurement and histological evaluation) were reviewed by three independent physicians (hepatologist, radiologist and a pathologist). The presence or absence of liver decompensation in the different subgroups was analyzed using Chi-square Test. The variables that had statistical significance in the univariate analysis were included in a multivariate logistic regression analysis. The probability of remaining free of developing a hepatic decompensation after enrollment (time dependent variable) based on the presence or not of CSPH, defined as the cut-off TE value established, was also measured using Kaplan-Meier method and compared using the log-rank test.

For the statistical analysis, the SPSS version 20.0 for Windows statistical package was used. A level of statistical significance of $p < 0.05$ was used for all statistical tests performed.

Results

Patients' characteristics

A total of 58 consecutive patients seen at Hospital General Universitario de Alicante, Spain, between January and June 2008 were enrolled in the study. All patients were Caucasian. Patients were followed up until clinical decompensation or April 2011 (40 months), whatever occurred first. All patients underwent a hepatic hemodynamic study, including HVPG determination as well as measurement of LS by TE. In addition, 38 patients also underwent a transjugular liver biopsy, with its corresponding histological examination. Baseline demographic and clinical characteristics of the whole sample and the subpopulation that underwent liver biopsy are summarized in Tables 1a and 1b. No significant differences were observed among the whole sample and the subpopulation, regarding baseline and clinical characteristics.

Association between degree of LS, measured by TE, PH, measured by HVPG, in patients with chronic live disease

Association between degree of LS and PH

This analysis was performed in the entire study population (n =

Figure 1A: Correlation between TE and HVPG

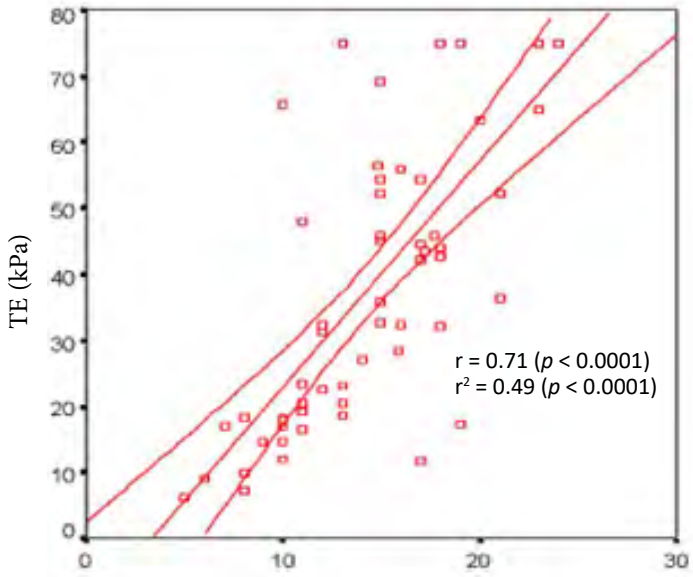

Figure 1B: ROC Curve

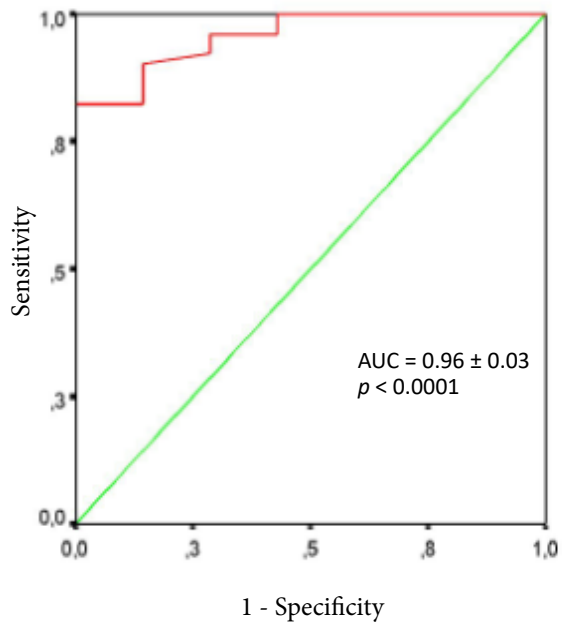

Figure 1: Analysis between TE and HVPG: 1a) Linear regression; 1b) ROC curve.

58). A statistically significant association between LS, measured by TE, and PH, measured by HVPG, was determined. **Figure 1a** summarizes the lineal regression analysis between TE and HVPG (r = 0.71, $p < 0.0001$).

Ability of TE to assess the existence of clinically significant portal hypertension

The cut off value of TE for the diagnosis of CSPH was established at 17.15 kPa, with an area under the curve (AUC) of 96% (0.96 ± 0.003 $p < 0.0001$) and a Se, Sp, PPV and NPV of 90, 86, 86.5, and 89.6% respectively (Figure 1b and Table 2). The likelihood ratios (LR) were LR+=6.43 and LR-=0.15, respectively. Half of the population studied (n = 29, 50%), had advanced chronic liver disease due to HCV. For this subgroup the Se, Sp, PPV and NPV were 96%, 71%, 76.8%, 94.7%, respectively, being the cut off value of 17.9 kPa.

Epidemiological and clinical characteristics of the patients diagnosed of CSPH

Using the mentioned cut off value of TE (≥ 17.15 kPa), 81% of the patients presented CSPH, while 87% were diagnosed using the HVPG cut off value of ≥ 10 mmHg. The epidemiological and clinical characteristics of the patients classified as CSPH using these cut off values of HVPG and TE are summarized in Table 3. Patients were divided in two groups, according to the etiology of the chronic liver disease: HCV (HCV and mixed etiology) and other causes.

The clinical and epidemiological variables related to the presence of CSPH measured by TE that reached statistical significance were male gender, Child-Pugh and MELD score, level of serum albumin, presence of splenomegaly and HVPG. With regards to HVPG, the variables related to the presence of CSPH measured that reached statistical significance were age, etiology of liver disease, Child-Pugh score, level of serum albumin, presence of splenomegaly and the value of TE. The multivariate analysis showed that the value of TE is independently related to HVPG (Table 4).

Association between histological findings and clinically significant portal hypertension measured by HVPG and TE

A total of 38 transjugular liver biopsies were performed. The demographic and clinical characteristics of this subgroup of patients

Table 1: Baseline demographic and clinical characteristics: 1a) total population (n = 58); 1b) population undergoing transjugular liver biopsy (n = 38).

Variables	Total population (N = 58)
Gender (M/F), n (%)	42 (72.4%)/16 (27.6%)
Age, mean ± SD	53.7 ± 13.2
Etiology of chronic liver disease, n (%): Alcohol HCV Alcohol + HCV Others	 16 (27.6%) 29 (50.0%) 6 (10.3%) 7 (12.1%)
HIV	15 (25.9%)
Esophageal varices, n (%): No Yes	 34 (58.6%) 24 (41.4%)
Child-Pugh score, median (interquartile)	6 (5 – 7)
MELD score, mean ± SD	9.5 ± 3.5
Serum albumin (g/dl), mean ± SD	3.4 ± 0.7
Gammaglobulin (g/dl), mean ± SD	1.9 ± 0.6
Platelets (10^9/l)	133.2 ± 62.7
Splenomegaly, n (%)	41 (70.7%)
HVPG, mean ± SD	14.3 ± 4.5
TE, mean ± SD	37.5 ± 21.6

Table 1A

*HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; TE: Transient Elastography; HVPG: Hepatic Venous Pressure Gradient

Variables	Subpopulation (N = 38)
Gender (M/F), n (%)	26 (68.4%)/12(31.6%)
Age, mean ± SD	53.3 ± 12.0
Etiology of chronic liver disease, n (%): Alcohol HCV Alcohol + HCV Others	 9 (23.7%) 19 (50.0%) 5 (13.2%) 5 (13.2%)

Table 1B

*HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; TE: Transient Elastography; HVPG: Hepatic Venous Pressure Gradient

Table 2: Selection of TE cut off value to predict clinically significant portal hypertension.

TE (kPa)	Se	Sp	PPV	NPV
11.8	98	57	69.5	96.6
14.65	96	71	76.8	94.7
17.15	90	86	**86.5**	89.6
17.9	86	86	86	86

*Se: Sensitivity; Sp: Specificity; PPV: Positive Predictive Value; NPV: Negative Predictive Value

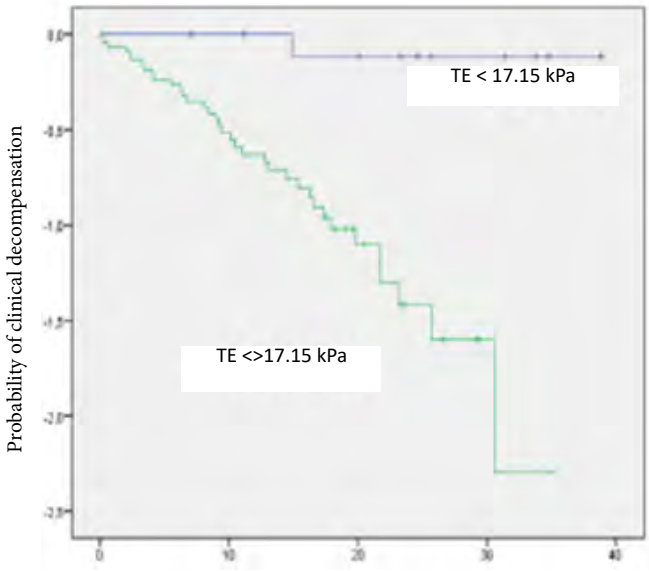

Figure 2: Probability of developing clinical decompensation according to TE values.

are summarized in **Table 1b**. Both the nodule size and septal thickening were the two independent predictors of CSPH, measured either by TE or HVPG (Table 5).

Association between clinical characteristics, clinically significant PH (measured by either HVGP or TE), and risk of decompensation in patients with chronic liver disease

All the patients (n = 58) were followed up until development of an episode of clinical decompensation or until the end of study, whichever occurred first. Mean follow-up time was 26 months. A total of 37 (63.8%) patients developed at least one episode of decompensation during the follow up period (Table 6). The uni-

Table 3: Comparison of the demographic and clinical characteristics of the patients with clinically significant portal hypertension, measured by HVPG (HVPG ≥ 10 mmHg) and TE (TE ≥ 17.15 kPa).

Variables	HVPG < 10 mm Hg n = 7	HVPG ≥ 10 mm Hg n = 51	p-value	TE < 17.15 kPa n = 11	TE ≥ 17.15 kPa n = 47	p - value
Age, mean ± SD	63.4 ± 15.9	52.3 ± 12.4	0.004	57.2 ± 18.1	52.9 ± 12.0	0.5
Gender (M/F), n (%)	4 (57.1%)/3 (42.9%)	38 (74.5%)/13 (25.5%)	0.4	5 (45.5%)/6 (54.5%)	37 (58.7%)/10 (21.3%)	0.05
Etiology of chronic liver disease, n (%): HCV Others	 7 (100%) 0 (0%)	 28 (54.9%) 23 (45.1%)	0.03	 7 (63.6%) 4 (36.4%)	 28 (59.6%) 19 (40.4%)	1
HIV, n (%)	2 (28.6%)	13 (25.5%)	1	3 (27.3%)	12 (25.5%)	1
CD4 (10^9/L), mean ± SD	367 ± 24.0	225.46 ± 141.7	0.2	294.3 ± 127	231.8 ± 146.1	0.5
Esophageal varices, n (%): No Yes	 4 (57.1%) 3 (42.9%)	 30 (58.8%) 21 (41.2%)	1	 9 (81.8%) 2 (18.2%)	 25 (53.3%) 22 (46.8%)	0.1
Child-Pugh score, median (interquartile)	5 (5 -5)	6 (5 – 7)	0.05	5 (5 – 5)	6 (5 – 7)	*0.003*
MELD score, mean ± SD	7.6 ± 2.1	9.8 ± 3.5	0.1	7.6 ± 2.1	9.78 ± 3.5	0.002
Serum albumin (g/dl), mean ± SD	3.9 ± 0.4	3.3 ± 0.7	0.04	3.8 ± 0.4	3.3 ± 0.8	*0.08*
Gammaglobulin (g/dl), mean ± SD	1.8 ± 0.7	1.9 ± 0.6	0.7	2.0 ± 0.6	1.9 ± 0.6	0.8
Platelets (10^9/l)	136.3 ± 100.1	132.8 ± 64.6	0.9	130 ± 65.5	130.0 ± 65.5	0.5
Splenomegaly, n (%)	2 (28.6%)	39 (76.5%)	0.02	3 (27.3%)	38 (80.9%)	0.001
HVPG, mean ± SD	NA	NA	NA	9.1 ± 3.2	15.5 ± 3.8	0.0001
TE, mean ± SD	11.7 ± 4.9	41.0 ± 20.5	0.0001	NA	NA	NA

*M/F: Male/Female; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; SD: Standard Deviation; HVPG: Hepatic venous pressure gradient; TE: Transient Elastography

Table 4: Clinical and epidemiological characteristics significantly related to the presence of clinically significant portal hypertension (HVPG ≥ 10 mm Hg).

	OR	p - value
Child-Plough score: **B/C (7 – 15)** **A (5 - 6)**	 0.71 (0.03 – 16.6) 1	0.8
Splenomegaly: **Yes** **No**	 2.1 (1.2 – 25.7) 1	0.6
TE: **≥ 17.15** **< 17.15**	 44.4 (3.1 – 632.6) 1	0.005

* HVPG: Hepatic venous pressure gradient; TE: Transient Elastography; OR: Odds ratio

variate analysis showed that male gender, presence of esophageal varices, MELD score > 10, serum albumin < 3.5 g/l, presence of splenomegaly, HVPG > 10 mm Hg and TE > 17.15 kPa were predictors of clinical decompensation. However, in the multivariate analysis, only serum albumin < 3.5 mg and LS > 17.15 kPa measured by TE remained as predictors of clinical decompensation.

As shown in Figure 2, the probability of remaining free of developing a hepatic decompensation was significantly superior in the group of patients without CSPH, defined as TE < 17.15 kPa (log rank 12.091, p < 0.001).

Discussion

The aim of the present study was to evaluate whether TE is a useful non-invasive test for the diagnosis of CSPH and prediction of

Table 5: Relationship between histological parameters and the presence of CSPH, measured by either HVPG (≥ 10 mm Hg) or TE.

	HVPG			TE		
	Frequency N (%)	**OR (95% CI)**	**p- value**	**Frequency N (%)**	**OR (95% CI)**	**p- value**
Sinusoidal fibrosis: **Moderate/severe** **Absent/mild**	5/7 (71.4%) 28/31 (90.3%)	0.3 (0.003 – 2.03) 1	0.2	6/7 (85.7%) 26/31 (83.9%)	(0.1 – 11.9) 1	0.7
Nodularity: **Mixed/large** **Absent/small**	28/30 (93.3%) 5/8 (62.5%)	8.4 (1.1 – 63.7) 1	*0.05*	28/30 (93.3%) 4/8 (50%	14 (1.9 – 102.9) 1	*0.01*
Septal thickening: **Medium/thick** **Absent/thin**	24/25 (96%) 9/13 (69.2%)	10.7 (1.04 – 108.7) 1	*0.03*	25/25 (100%) 7/13 (53.8%)	1.8 (1.1 – 3.0) 1	*0.001*
Loss of portal spaces: **26 – 100%** **None/1 -25%**	12/12 (100%) 21/26 (80.8%)	1.2 (1.02 – 1.5) 1	0.13	12/12 (100%) 20/26 (76.9%)	(1.05 – 1.6) 1	0.08
Loss of centrolobulillar veins: **26 – 100%** **None/1 -25%**	14/16 (87.5%) 16/22 (86.4%)	(0.2 – 7.5) 1	0.65	15/16 993.8%) 17/22 (77.3%)	4.4 (0.5 – 42.1) 1	0.9
Lobulillar inflammation: **Moderate/severe** **Absent/mild**	4/4 (100%) 29/34 (85.3%)	(1.02 – 1.3) 1	0.55	4/4 (100%) 28/34 (82.4%)	(1.03 – 1.4) 1	0.5
Interface activity: **Moderate/severe** **Absent/Mild**	10/10 (100%) 23/28 (82.1%)	1.2 (1.02 – 1.4) 1	0.19	10/10 (100%) 22/28 (78.6%)	(1.05 – 1.5) 1	0.1
Steatosis: **26 – 100%** **None/1 -25%**	12/13 (92.3%) 21/25 (84%)	1.2 (1.02 – 1.4) 1	0.2	11/13 (84.6%) 21/25 (84%)	1.04 (0.2 – 6.6) 1	0.7
Iron: **Visible at 250 X- 10 X** **Absent**	4/4 (100%) 29/34 (85.3%)	(1.02 – 1.3) 1	0.5	4/4 (100%) 28/34 (84.2%)	91.04 – 1.4) 1	0.5

*CSPH: Clinically significant portal hypertension; HVPG: Hepatic venous pressure gradient; TE: Transient elastography; OR: Odds Ratio

clinical decompensation in patients with chronic liver diseases. The fact that both in-patients, with more advanced disease stage and with severe complications, and out-patients, in early disease stages (without liver decompensation), were enrolled, allowed us to perform an analysis in a more heterogeneous, therefore representative, group of patients with chronic liver diseases.

As for the etiology of the liver disease, HCV infection was the predominant cause (50%), followed by alcoholic liver disease (27.6%). This distribution is similar to other series previously published [33,34]. Most of the patients were classified as Child class A and MELD score < 10, that correspond to individuals with compensated cirrhosis whose liver function is still preserved. It was found, as was expected, a higher score of both prognostic scales, in those patients who presented CSPH, determined by HVPG and TE.

The present study found a good correlation (r = 0.71) between TE and HVPG, that is in agreement with prior studies, in which the correlation ranged from 0.55 to 0.86 [18-24,35]. The diagnostic accuracy of the TE value of 17.15 kPa to define CSPH was high in the present study (AUC 0.96 ± 0.003 $p < 0.0001$). Furthermore, the sensitivity and specificity were 90% and 86%. When compared to other cut off values previously defined, that ranged from 13.6 to

21, the discrepancy could be explained by the nature of the population included in the present study, that involved patients in early stages of the disease as well as different etiologies of liver disease. The results of the multivariate analysis, regarding the clinical and epidemiological characteristics and the presence of CSPH, show that LS itself, measured by TE, reveals as a good diagnostic test.

Regarding the correlation between CSPH, measured by HVPG and TE, and histological findings in the liver biopsy, the results obtained in our study are consistent with the pathophysiology of PH, as the nodular size and septal thickening correlate with increased intrahepatic resistance. However, our results did not reach statistical significance in the multivariate analysis, probably due to the small sample size (n = 38). These results differ from those reported by Nagula and Kumar, which can be explained probably because the majority of patients included in their study presented alcohol related liver disease, whereas in the present study only 23.7% of the subjects where classified as alcohol etiology hepatopathy [28,29].

With regards to clinical decompensation, it is estimated that the transit from compensated to decompensated cirrhosis occurs at a constant rate of 5% annually, being ascites the most frequent clinical event, followed by the bleeding due to PH, jaundice and hepatic encephalopathy [36]. The development of any of these complications mark the transition from compensated to decompensated phase, which implies a drastic change in the prognosis and a significant decrease in survival. Thus, a patient with compensated HC has a survival and causes of death similar to general population of their age and sex, while a patient with decompensated HC has a mean survival of < 2 years since its first episode of decompensation (median survival 10 -12 years). Hence, classification of cirrhotic patients in two categories (compensated vs. decompensated) is no longer the ideal form of prognostic categorization, since these situations are not static, but rather bidirectional. In this sense, it is possible that other parameters, such as measurement of PH or evaluation of LS through TE, could provide a more accurate information about the progression of the disease, its eventual reversibility as well as the prognosis in each case. The identification of such factors as potential prognostic factors of decompensation and mortality has been studied in recent years, although their role, in most of the cases, has not yet been proven to be relevant [1,37].

The third aim of the study was to find out whether TE was able to identify patients with the worst prognosis that have an increased risk of developing clinical complications. The results of the multivariate analysis showed an independent association between the degree of LS, measured by TE, and the risk of decompensation in patients with chronic liver disease. As noted in the previous sections, CSPH can be estimated by measuring LS with TE. On the other hand, we know that HVPG predicts clinical decompensation. According to these premises, we can infer that the degree of LS measured with TE could predict the development of clinical decompensation. The study of Foucher *et al.*, which included 711 patients with chronic liver diseases established different TE cut-off values for the development of complications in patients with cirrhosis [38]. For the appearance of esophageal varices, the TE threshold value was 27.5 kPa; 49.1 kPa for ascites; 53.7 kPa for hepatocarcinoma and 62.7 kPa for varicose hemorrhage. This study had important limitations, notably, the lack of patient's follow-up, as data were obtained in one-time point and included patients with different disease stages. On the other hand, some events, such as the emergence of ascites or varicose bleeding were evaluated retrospectively. Klibansky *et al.* performed TE in 667 patients that were followed up for 861 days, setting the TE cut off value of 10.5 kPa as a predictor of hepatic decompensation, with a Se of 94.7%, a Sp of 63%, PPV 19.3% and NPP of 99.2% [39]. The patients with a LS value > 12.5 KPa presented a relative risk of clinical event development of 18.99 in comparison with patients with a TE score < 10.5 kPa. The study of Vergniol *et al.* assessed 1,457 patients with chronic HCV hepatitis [40]. The 5-year survival was significantly inferior in those patients who had a TE > 9.5 kPa. It was concluded that the measurement of LS by TE had a clear prognostic value, given that the survival decreased as LS values increased, which would confer a potential role for TE when deciding, even, the indication of liver transplantation. Similarly, Robic *et al.* studied the value of TE to establish the prognosis of chronic liver disease in 41 patients during a 2-year follow-up period. In this interval, 65% of the patients presented decompensation of their disease [41]. While 85.4% of patients with values of TE > 21.1 kPa at diagnosis presented a decompensation, only 29.5% of those with a value of

TE < 21.1 kPa experienced it.

The multivariate analysis of the clinical-epidemiological characteristics of the population showed that only the level of serum albumin was independently associated with the development of clinical decompensation. The analysis of the other aims showed that LS measured by TE correlated with HVPG, and therefore the prognostic value of TE could be the result of a strong association between the HVPG and the LS measured by TE. However, in the multivariate analysis, only TE had significant power to predict the

Table 6: Clinical-epidemiological characteristics and risk of development of clinical decompensation.

Variables	Univariate Analysis			Multivariate Analysis	
	Frequency N (%)	OR (95% CI)	p- value	OR (95% CI)	p- value
Gender: n (%) **M/F**	30 (71.4%)/7(43.8%)	3.2 (0.9 – 10.6) 1	*0.05*	1.9 (1.2 – 8.3) 1	0.86
Etiology: **HCV** **No**	21/35 (60%) 16/23 (69.6%)	0.6 (0.2 – 2.0) 1	0.46	-	-
HIV: **Yes** **No**	10/15 (66.7%) 27/43 (62.8%)	1.18 (0.3 – 4.1) 1	0.79	-	-
Esophageal varices: **No** **Yes**	19/24 (79.2%) 18/34 (52.9%)	3.4 (1.0 – 11.1) 1	*0.04*	0.57 (0.1 – 4.4) 1	0.59
Child-Pugh score: **B/C (7 – 15)** **A (5 – 6)**	18/23 (78.3%) 19/35 (54.3%)	3.0 (0.9 – 9.9) 1	0.06	-	-
MELD score: **≥ 10** **< 10**	25/31 (80.6%) 12/27 (44.4%)	5.2 (1.6 – 16.7) 1	*0.004*	1.9 (0.4 – 9.6) 1	0.46
Serum albumin (g/dl): **≤ 3.5** **> 3.5**	28/33 (82.4%) 9/24 (37.5%)	7.8 (2.3 – 26.0) 1	*0.0001*	8.5 (1.5 – 47.9) 1	*0.01*
Gammaglobulin (g/dl): **≥ 1.85** **< 1.85**	19/29 (65.5%) 18/29 (62.1%)	(0.4 – 3.4) 1	0.78	-	-
Platelets (10^9/L): **≤ 120** **> 120**	22/29 (75.9%) 15/29 (51.7%)	2.9 (0.9 – 8.9) 1	*0.05*	8.5 (1.5 – 47.5) 1	0.75
Splenomegaly: **Yes** **no**	32/41 (78%) 5/17 (29.4%)	8.5 (2.4 – 30.6) 1	*0.0001*	3.3 (0.4 – 26.3) 1	0.25
HVPG (mm Hg): **≥ 10** **< 10**	36/51 (70.6%) 1/7 914.3%)	14.4 (1.6 – 130.0) 1	*0.004*	2.2 (0.03 – 162.5) 1	0.7
TE (kPa): **≥ 17.15** **< 17.15**	36/47 (76.6%) 1/11 (9.1%)	32.7 (3.7 – 284.8) 1	*0.0001*	18.9 (0.9 – 369.5) 1	*0.05*

* M/F: Male/Female; HCV: Hepatitis C virus; HVPG: Hepatic venous pressure gradient; TE: Transient elastography

development of complications. This fact proves that the power of TE to predict the onset of clinical decompensation is independent. The results of the present study support the use of TE to establish the prognosis of chronic liver disease and to predict the development of their complications. In this sense, TE has been proven to be superior to the measurement of HVPG in terms of cost, availability and reduction of the potential risk of complications.

The main limitation of our study is the small size of the sample of the population included. It is clear that, if the size of the sample had been larger, some results, such as the HVPG, could have achieved statistical significance as a predictor of clinical decompensation and death in the multivariate analysis. In addition, the presence of a predominant group in terms of etiology (alcohol and HCV) and the above-mentioned small size of the sample make difficult to reach conclusions regarding the relation between histological findings and the development of CSPH and its complications. It would be necessary to carry out more studies, with a larger number of patients with different etiologies of liver disease, to be able to answer those questions.

Conclusions

It can be concluded that TE is a reliable, non-invasive and affordable tool for assessing the development of CSPH. In addition, a statistically significant association between LS measured by TE and HVPG as a prognostic tool for development of CSPH in patients with chronic liver disease was established. Finally, TE was able to independently identify patients with cirrhosis who were at risk of clinical decompensation.

Conflict of Interest Statement

The authors report no conflict of interest.

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