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Liver stiffness measurement as a predictive tool of clinically significant portal hypertension in patients with compensated hepatitis C virus or alcohol-related cirrhosis

M. LEMOINE*, S. KATSAHIAN†, M. ZIOL‡, P. NAHON*, N. GANNE-CARRIE*, F. KAZEMI*, V. GRANDO-LEMAIRE*, J.-C. TRINCHET* & M. BEAUGRAND*

*Service d'hépatologie, Hôpital Jean-Verdier, AP-HP, Bondy; †Département de biostatistiques et informatiques médicales, Hôpital Saint-Louis, AP-HP, Paris; ‡Département d'anatomopathologie, Hôpital Jean-Verdier, Bondy, France

Correspondence to:
Dr M. Lemoine, Service d'hépatologie, Hopital Jean Verdier, Avenue du 14 JUILLET, 93143 Bondy Cedex, France.
E-mail: maud.lemoine@jvr.ap-hop-paris.fr

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SUMMARY

Background
Hepatic venous pressure gradient (HVPG) is the gold standard for assessing the presence and the severity of portal hypertension (PHT). Liver stiffness measurement (LSM) is a non-invasive method for liver fibrosis assessment.

Aims
To assess the relationship between LSM and HVPG in patients with compensated cirrhosis related to hepatitis C virus (HCV) or alcohol and to define the performance and the best cut-off of LSM for the diagnosis of PHT in these patients.

Methods
Between January 2004 and September 2006, we studied all the consecutive patients with compensated HCV or alcohol-related-cirrhosis referred for transjugular liver biopsy with HVPG measurement and LSM performed the same day.

Results
Ninety-two patients were eligible, 44 had HCV related-cirrhosis and 48 alcoholic cirrhosis. LSM was positively correlated to HVPG in both groups. The area under the receiver operating characteristic curve for the diagnosis of significant PHT was 0.76 $\pm$ 0.07 in HCV patients (best cut-off at 20.5 kPa) and 0.94 $\pm$ 0.03 (best cut-off at 34.9 kPa) in alcoholic patients.

Conclusions
Liver stiffness measurement and HVPG were significantly correlated in patients with compensated cirrhosis because of HCV infection or alcohol. LSM could predict significant PHT in both these groups of patients with a higher cut-off and a better performance in alcoholic patients.

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INTRODUCTION

Portal hypertension (PHT) is a severe complication of cirrhosis, which can lead to fatal complications. The gold standard for assessing the presence and severity of PHT in patients with cirrhosis is the hepatic venous pressure gradient (HVPG) measurement.[1–3] PHT may be moderate and asymptomatic in patients with a HVPG < 10 mmHg or clinically significant (HVPG ≥ 10 mmHg) associated with the risk of cirrhosis-related complications (ascites, encephalopathy and variceal bleeding).[4–8] Unfortunately, this method is invasive, relatively expensive and brings reliable results only when applied by well trained operator in specialized centres – the main limitation for its general use.[9] The diagnosis of PHT is more difficult in patients with compensated cirrhosis, i.e. in the subset of patients who should benefit from screening to avoid complications. Thus, a simple and reliable tool to assess the degree of portal pressure is particularly needed for patients with Child-Pugh class A cirrhosis. To date, serum markers and features in Doppler-ultrasonography have been reported[10–12] to correlate with PHT, although these methods are unable to identify reliable cut-offs to diagnose significant PHT.

Transient elastography (Fibroscan; Echosens, Paris, France) is a recent method that allows the measurement of liver stiffness. Liver stiffness measurement (LSM) has been shown to be correlated to fibrosis stage in various chronic liver diseases with a high sensitivity and specificity for the diagnosis of cirrhosis.[13–16] LSM value above 14.6 kPa allows diagnosing cirrhosis with 0.79 sensitivity and 0.95 specificity in a large cohort of patients with various causes of liver diseases.[17] In cirrhotic patients, LSM values are widely distributed ranging from 5.8 to 75 kPa,[17] probably reflecting the wide range of fibrosis amount.[18] It has been previously shown that LSM could predict the presence of large oesophageal varices,[15, 19] but this issue remains controversial.[20] Two studies have currently addressed the issue of the relationship between HVPG and LSM.[20, 21] The first one was driven in hepatitis C virus (HCV)-infected patients after liver transplantation and the second one included nontransplanted patients with HCV liver disease and advanced fibrosis or cirrhosis scored Child-Pugh class A or B.[20]

The purpose of our study was (i) to confirm the best value of LSM for the diagnosis of clinically significant PHT in HCV-infected patients with Child-Pugh class A cirrhosis; (ii) to assess the relationship between LSM and HVPG in alcoholic Child-Pugh A cirrhotic patients; and (iii) to define the best cut-off of LSM for the diagnosis of clinically significant PHT in those patients.

PATIENTS AND METHODS

Patients

We recorded data from a well-defined population of patients who, the same day, underwent transjugular liver biopsy and LSM (Fibroscan) in our liver unit. Between January 2004 and September 2006, 806 transjugular biopsies have been performed in our department. In this cohort of patients, we selected patients who had LSM and transjugular biopsy with HVPG measurement the same day and who fulfilled the following criteria: (i) histologically proven cirrhosis either because of HCV infection (positive HCV antibodies) or alcohol abuse (≥50 g/day during at least 10 years); (ii) patients scored Child-Pugh class A; and (iii) available hemodynamic data. The exclusion criteria were: (i) other causes of liver disease, in particular, HBV infection and mixed aetiologies (alcohol and HCV, HIV coinfection); (ii) presence of portal vein thrombosis; (iii) ongoing treatment by beta-blockers; (iv) ongoing or recent treatment <6 months by anti-viral therapy; (v) recent gastro-intestinal bleeding or endotherapy; (vi) liver cancer; and (vii) cardiac failure. No patients were liver transplanted or had previous portosystemic shunt.

Transient elastography

Liver stiffness measurement was performed using Fibroscan (Echosens) by two experienced operators who were not aware of the hemodynamic results. Briefly, Fibroscan was performed as previously described on the right lobe of the liver, in the intercostal space with the patient lying in dorsal decubitus with the right arm in maximal abduction.[22, 23] Only procedures with 10 validated acquisitions, interquartile range ≤30% of the median value and a success rate of at least 70% were considered reliable. The median value of all validated acquisitions was considered as LSM and the results were expressed in kilopascal (kPa).

HVPG measurement and liver biopsies

Wedged hepatic venous pressure (WHVP), free hepatic venous pressure (FHPG) and HVPG measurements were performed in the radiologic hemodynamic unit under local anaesthesia and under radiological guidance during hepatic vein catheterization for transjugular liver biopsy following the previously described methods.[3, 9] Briefly, the catheter (Vygon, FG 08, Ecouen, France) was placed into the right internal jugular vein using the Seldinger technique and was used to introduce a seven French balloon-tipped catheter (Boston scientific Medi-Tech, Natick, MA, USA), which was guided to the main right hepatic vein under fluoroscopic control. WHVP was measured by occluding the hepatic vein. The portal pressure gradient was measured as the HVPG, the difference between wedged and free hepatic venous pressures as previously described.[3] All measurements were performed in duplicate. PHT was defined as a HVPG above 5 mmHg, clinically significant PHT as an HVPG ≥10 mmHg according to the consensus definition.[24] A 16G needle (Cook, Bjaverskov, Denmark) connected to a 20-mL syringe was used for transjugular biopsy. In our liver unit, biopsies are performed to confirm the diagnosis of cirrhosis and the transjugular route is mostly chosen for convenience and for hemodynamic investigation.

Liver samples were fixed, paraffin-embedded and stained with hematoxylin-eosin-safran and Masson's trichrome. Liver biopsies were analysed by a single expert pathologist (M.Z) who was unaware of the results of either LSM or HVPG. Four-micrometer-thick sections were stained with hematoxylin-eosin-safran and picrosirius red. All biopsy specimens were analysed by an experienced liver pathologist (MZ) without knowledge of the results of LSM and clinical data. The amount of liver fibrosis was evaluated according to the semi-quantitative Chevallier *et al.* scoring system[25] designed to reflect morphometric measurements of fibrosis and taking separately into account fibrosis deposits in centrilobular veins (CLV), perisinusoidal space (PS), portal tract (PT) and septa along with number (NS) and width of septa (WS). Total score is calculated as follows: Score = CLV + PS + PT + 2(WS × NS).

All patients gave their informed written consent for all the procedures performed.

Clinical and biological investigation

The day of liver biopsy, the following clinical and biological parameters were recorded: age, gender, body mass index, medical treatment and history of alcohol consumption as well as the following parameters: red cells and platelet count (10^3/L), haemoglobin level (g/dL), prothrombin index (%), serum albumin (g/L), bilirubin (μmol/L) and activity of liver enzymes: transaminases (UI/L), gamma-glutamyl transpeptidase (γGT; UI/L), alkaline phosphatase (UI/L).

Statistical analysis

Quantitative variables were described as mean ± standard deviation (s.d.). Categorical variables were presented as counts and per cent of the cohort. Marginal associations between single variables and high HVPG were assessed by Wilcoxon rank-sum tests for quantitative variables and chi-square or Fisher's exact test when more appropriate for qualitative variables. Considered variables were age (years), aetiology (HCV/alcohol), platelet count (10^3/L), prothrombin index (%), serum bilirubin (μmol/L), γGT (UI/L), AST (UI/L), serum albumin (g/L), HVPG (mmHg) and LSM (kPa).

Multiple logistic regression was used to determine independent predictors of diagnosis of clinically significant PHT. All variables achieving statistical significance at a 0.20 level in the univariate analysis were considered in the multiple analysis model. A backward variable selection procedure with *P*-value cut-off at 0.05 was used to identify the set of independent predictors of clinically significant PHT. The validity of the logistic regression models was checked using Hosmer and Lemeshow lack-of-fit test.[26]

Correlation was assessed using Spearman correlation coefficients. Predictive factors of HVPG ≥10 mmHg were studied in univariate and multivariate analysis. The diagnostic value of LSM for the diagnosis of significant PHT was assessed using sensitivity (Se), specificity (Sp), negative and positive predictive values (NPV and PPV) and the area under the receiver operating characteristic curve (AUROC) that was calculated using nonparametric method. All analyses were performed using S-Plus 2000 (MathSoft Inc., Seattle, WA, USA) software packages. All tests were two-sided, with a significance level of 0.05.

RESULTS

Global population

Characteristics of the whole population. Between January 2004 and September 2006, 92 patients were

Table 1. Characteristics of the whole population and both subgroups of patients

	Global population (n = 92)	HCV-related-cirrhosis (n = 44)	Alcohol-related cirrhosis (n = 48)	P*
Age (years)	56 ± 13	57 ± 16	54 ± 11	N.S.
Gender ratio (M/F)	64/28	24/20	40/8	0.003
Platelet count (10^3/L)	125 ± 79	118 ± 52	141 ± 99	N.S.
AST (IU/L)	93 ± 60	110 ± 69	85 ± 45	N.S.
Serum albumin (g/L)	39.8 ± 6	42 ± 6	38 ± 6	0.005
Serum bilirubin (μM, IQ)	9–41.5	16–78	7–20	10^{-5}
Prothrombin index (%)	67 ± 18	76 ± 17	58 ± 15	10^{-6}
HVPG (mmHg)	15 ± 5	12 ± 5	17 ± 7	0.0002
HVPG ≥10 mmHg (n)	74	34	40	N.S.
Liver stiffness measurement (kPa)	38.2 ± 18.5	25.7 ± 14	49.9 ± 21.7	$<10^{-6}$
Size of the liver biopsy (mm)	14	14.5	15	N.S.
Amount of fibrosis according to Chevallier *et al.* scoring system	14.8	11	17.5	0.0005

HVPG, hepatic venous pressure gradient.
* Hepatitis C virus (HCV) vs. alcohol-related cirrhosis.

eligible. All patients had compensated cirrhosis and were scored Child-Pugh class A. The main characteristics of these patients are summarized in Table 1. The characteristics of patients according to the presence of significant PHT are listed in Table 2. Univariate analysis identified six parameters significantly associated with clinically significant PHT: age (P = 0.019), platelet count (P = 0.03), prothrombin index (P < 0.0001), serum albumin (P = 0.0017), bilirubin (P = 0.02) and LSM (P < 0.0001). In multivariate analysis, two parameters were statistically associated with the diagnosis of clinically significant PHT: Age (P = 0.005, OR = 1.05) and LSM (P = 0.0002, OR = 1.09).

Relationship between LSM and HVPG in the whole population. Considering the whole population, there was a statistically significant relationship between LSM and HVPG (R^2 = 0.53, P < 0.0001). Figure 1 illustrates the linear regression analysis

Table 2. Characteristics of the whole population according to the HVPG

	HVPG <10 mmHg (n = 18)	HVPG ≥10 mmHg (n = 74)	P
Age (years)	49 ± 14	57 ± 13	0.03
Aetiology (hepatitis C virus/alcohol)	10/8	34/40	<0.001
Platelet count (10^3/L)	167 ± 125	119 ± 58	0.14
Prothrombin index (%)	85 ± 14	63 ± 18	0.0001
Serum bilirubin (μM, IQ)	6–41	8–78	0.0003
Gamma-glutamyl transpeptidase (IU/L)	340 ± 150	270 ± 275	N.S.
AST (IU/L)	89 ± 46	99 ± 62	N.S.
Serum albumin (g/L)	44 ± 6.5	38.8 ± 5.5	0.001
HVPG (mmHg)	6 ± 2	17 ± 5	10^{-12}
Liver stiffness measurement (kPa)	18.4 ± 8.8	43.1 ± 21.8	10^{-6}

HVPG, hepatic venous pressure gradient.

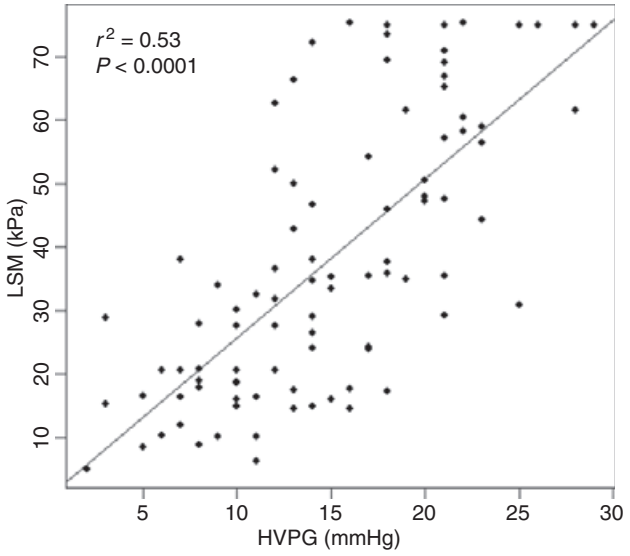

Figure 1. Linear regression analysis between hepatic venous pressure gradient and liver stiffness measurement in the whole population.

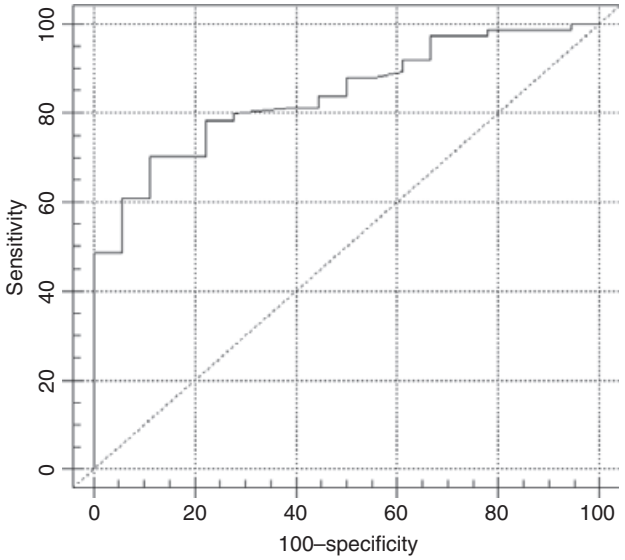

Figure 2. Receiver operating characteristic (ROC) curve showing the prediction of clinically significant portal hypertension (HVPG ≥ 10 mmHg) with liver stiffness measurement in the global population. The area under the ROC curve was 0.84 ± 0.04.

between LSM and HVPG performed in the whole population.

Diagnostic value of LSM for the prediction of clinically significant PHT in the whole population. Figure 2 shows the receiver operating characteristic (ROC) curve of LSM for the prediction of clinically significant PHT defined by an HVPG ≥10 mmHg in the whole population. The area under ROC curve was 0.84 ± 0.04 with a 95% confidence interval (CI) ranged.

HCV-related cirrhotic patients

Characteristics of HCV-infected patients. Forty-four patients had HCV-related cirrhosis. Mean age was 57 ± 16 years, 24 of the patients were men, mean LSM was 25.7 ± 14 kPa and mean HVPG 12 ± 5 mmHg (Table 1). Among these patients, 34 of them had a gradient ≥10 mmHg. Univariate and multivariate analysis identified two significant parameters associated with clinically significant PHT: Age (OR = 1.06, P = 0.01) and LSM (OR = 1.17, P = 0.01).

Relationship between LSM and HVPG in HCV-infected patients. Among the 44 HCV-infected patients, there was a significant correlation between HVPG and LSM (R^2 = 0.46, P < 0.0001) as shown in Figure 3.

Diagnostic value of LSM for the prediction of clinically significant PHT in HCV-infected patients. Figure 4 shows the ROC curve of LSM for the prediction of clinically significant PHT in patients with HCV-related cirrhosis. The area under ROC curve was 0.76 ± 0.07 with a 95% CI ranged. Based on ROC curve and considering the 44 patients, a cut-off at 20.5 kPa had a sensitivity at 0.63, a specificity at 0.70, a PPV at 0.88 and an NPV at 0.35 for the diagnosis of clinically significant PHT.

Discordant case in HCV-infected patients. Considering the cut-off at 20.5 kPa for the diagnosis of clinically significant PHT, among the 44 HCV-infected patients, one case was discordant characterizing with LSM above 20.5 kPa (28 ± 8 kPa) and a gradient below 10 mmHg (8 mmHg). This patient was 39 years old at the time of biopsy, never treated with a viral load at 675 000 IU/L and a type-3 genotype. Prothrombin index was 75%, serum albumin 44 g/L, AST

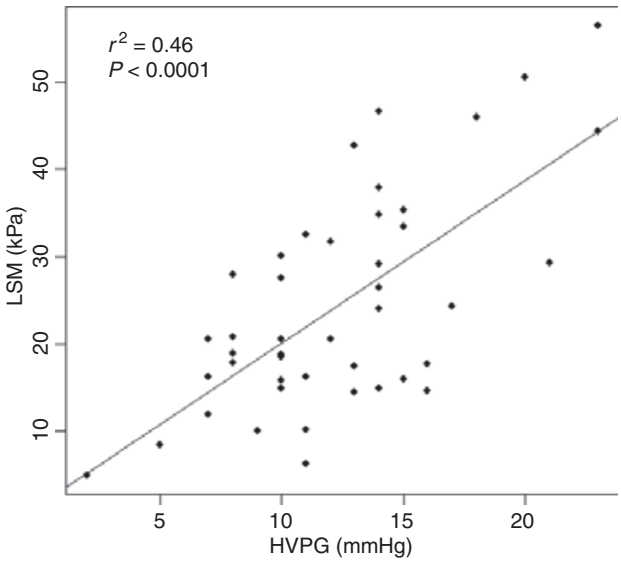

Figure 3. Linear regression analysis between hepatic venous pressure gradient and liver stiffness measurement in the patients with hepatitis C virus-related cirrhosis.

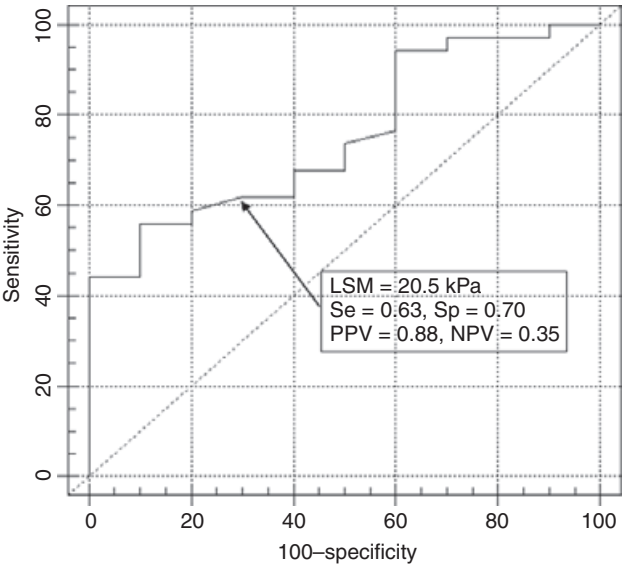

Figure 4. Receiver operating characteristic (ROC) curve showing the prediction of clinically significant portal hypertension (hepatic venous pressure gradient ≥10 mmHg) with liver stiffness measurement in patients with hepatitis C virus-related cirrhosis. The area under the ROC curve was 0.76 ± 0.07.

and ALT were respectively at 168 IU/L (fourfold the upper limit of normal) and 180 IU/L (4.5-fold the upper limit of normal). On liver biopsy, steatosis was

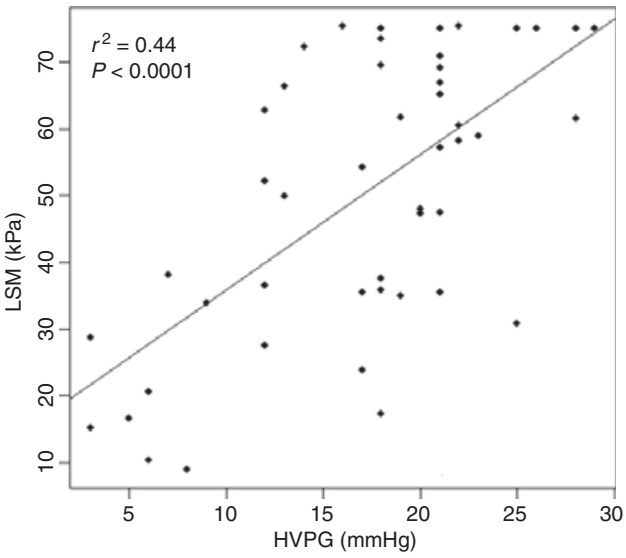

Figure 5. Linear regression analysis between hepatic venous pressure gradient and liver stiffness measurement in the patients with alcohol-related cirrhosis.

estimated at 60% and activity was scored A2 according to METAVIR classification.

Alcoholic cirrhotic patients

Characteristics of alcoholic patients. Forty-eight patients had alcohol-related cirrhosis. Mean age was 54 ± 11 years, 40 of them were men, mean LSM was 49.7 ± 21.7 kPa and mean HVPG 17 ± 7 mmHg (Table 1). Forty patients had an HVPG ≥10 mmHg. Biological markers of liver failure, HVPG and LSM were significantly higher in patients with alcohol-related cirrhosis compared with patients with HCV-related cirrhosis. Univariate and multivariate analysis identified LSM as a significant parameter associated with clinically significant PHT (OR = 1.11, $P = 0.004$).

Relationship between LSM and HVPG in alcoholic patients. Among the 48 patients with alcohol-related cirrhosis, a significant correlation between HVPG and LSM was also observed ($R^2 = 0.44$, $P < 0.0001$) as shown in Figure 5.

Diagnostic value of LSM for the prediction of clinically significant PHT in alcoholic patients. Figure 6 shows the ROC curve of LSM for the

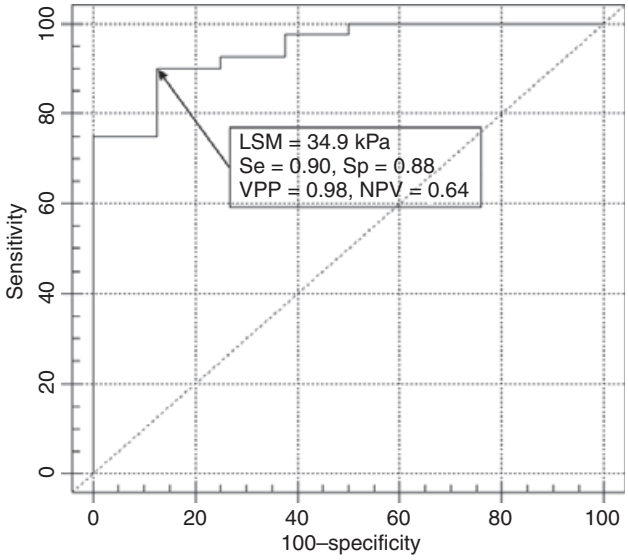

Figure 6. Receiver operating characteristic (ROC) curve showing the prediction of clinically significant portal hypertension (hepatic venous pressure gradient ≥10 mmHg) with liver stiffness measurement in patients with alcohol-related cirrhosis. The area under the ROC curve was 0.94 ± 0.03.

prediction of clinically significant PHT in patients with alcohol-related cirrhosis. The area under ROC curve was 0.94 ± 0.03 with a 95% CI ranged. Based on ROC curve and considering the 48 patients, a cut-off at 34.9 kPa had a sensitivity at 0.90, a specificity at 0.88, a PPV at 0.97 and an NPV at 0.64 for the diagnosis of clinically significant PHT.

Discordant case in alcoholic patients. Considering the cut-off at 34.9 kPa for the diagnosis of clinically significant PHT, one was discordant having LSM at 38.10 ± 10 kPa and an HVPG measured at 8 mmHg. This patient was 70 years old and totally abstinent for 12 months. Prothrombin index was 71%, serum albumin was 39.9 g/L and bilirubin at 12 μmol/L. On liver biopsy, there was no sign of alcoholic hepatitis.

DISCUSSION

In this study, LSM measured by Fibroscan and portal pressure evaluated by the HVPG were significantly correlated in patients with Child-Pugh A compensated cirrhosis either because of alcohol or HCV. So far, direct correlation between HVPG and LSM has only been investigated in HCV-infected patients and we have no data regarding the other causes of cirrhosis.[20] We focused on alcohol abuse and HCV infection for the following reasons: HVPG has been validated in both liver diseases as a reliable method to measure PHT,[3, 27, 28] the relationship between the amount of fibrosis and liver architecture may differ according to the cause of liver disease and alcohol and HCV infection are the main causes of cirrhosis in western countries. We strictly selected a population of Child-Pugh class A cirrhotic, which is the population subjected to screening. However, our study has two major pitfalls: the first one is a bias of selection. Patients in our study were selected for transjugular PBH, but not for HVPG. However, we easily perform transjugular biopsies for comfort-related reasons. The second pitfall is the small size of our studied population. However, it is difficult to have a large population of nondecompensated cirrhotic patients in liver units where patients are mostly referred for complications.

Regarding patients with HCV-related cirrhosis, our study confirms the results of Vizzutti *et al.*,[20] finding a significant correlation between HVPG and LSM.

However, the diagnostic performance of LSM is lower in our study (AUROC at 0.76 vs. 0.99 in Vizzutti's *et al.* study). This discrepancy could be explained by the criteria of selection as we focused on a more homogeneous population excluding patients with severe fibrosis (F3 according to the METAVIR scoring classification). Moreover, we excluded patients scored Child-Pugh B or C who could already be considered at risks of complications.

Our study also shows a similar relationship in patients with alcoholic cirrhosis. These results emphasize the link between liver fibrosis and PHT even in patients with alcohol-related cirrhosis. Interestingly, despite the fact that all patients belong to Child-Pugh class A, the two groups differ according to the mean LSM and HVPG values which are more elevated in the alcoholic group. The optimal cut-off values are, furthermore, different between both cohorts, higher in the alcoholic group (34.9 kPa vs. 20.5 kPa in HCV-infected group) suggesting that LSM values must be closely interpreted according to the cause of the liver disease. These differences suggest that the extent of liver fibrosis and the degree of PHT are more important in the alcoholic patients. According to the Chevallier *et al.* scoring, the amount of liver fibrosis was significantly higher in alcoholic patients than in HCV-infected patients. The type of fibrosis is furthermore different with more perisinusoidal fibrosis in the

alcoholic patients that could contribute to increase the LSM values. Other elementary lesions such as steatosis and inflammation could change the LSM values, but it has not been clearly demonstrated in particular in alcoholic patients, although it has been suggested in viral hepatitis.[29]

For each aetiology, we proposed an optimal cut-off as the best compromise between the sensitivity and the specificity. With these cut-offs, two patients are discordant, which could be explained by the limitation of either HVPG or LSM measurements.

Well-trained operators have performed HVPG and the values recorded were the mean of two measurements but venovenous anastomosis could lead to underestimate portal pressure. LSM is fairly reproducible according to different authors,[30] but the reproducibility in patients with cirrhosis is probably lower because of a more heterogeneous distribution of fibrosis. Nevertheless, this occurs mostly in patients with high values that predict, in any case, the presence of significant PHT. The operators recording LSM had a large experience and one must remind that this parameter is not the result of a single measurement, but the median value of 10 measurements called acquisitions and validated only when the failures rate was <70%.

As elastometry is more and more popular as a non-invasive method to assess fibrosis, it is interesting to know that the same measurement could provide simultaneously a diagnosis of cirrhosis and an estimation of PHT without additional costs. Knowing the predictive value of HVPG for the occurrence of complications in patients with cirrhosis, one can speculate that LSM could help split the Child-Pugh A patients according to their LSM values.

On a practical point of view, our study suggests that LSM could help predict clinically significant PHT in patients with cirrhosis because of alcohol or HCV infection. Studies are warranted to confirm our results.

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