Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Liver stiffness accurately predicts portal hypertension related complications in patients with chronic liver disease: A prospective study

Marie Angèle Robic[1,†], Bogdan Procopet[1,2,†], Sophie Métivier[1], Jean Marie Péron[1,3], Janick Selves[3,4], Jean Pierre Vinel[1,3], Christophe Bureau[1,3,*]

[1]*Service d'Hepato-gastro-entérologie, Pôle Digestif CHU Toulouse, Purpan 31059, Toulouse cedex, France;* [2]*University of Medicine and Pharmacy "Iuliu Hatieganu", Victor Babes Street no. 8, 400012 Cluj-Napoca, Romania;* [3]*INSERM U858 and University of Toulouse, France;* [4]*Service d'anatomie et de cytologie pathologiques. CHU Toulouse Purpan 31059 Toulouse cedex, France*

See Editorial, pages 955–956

Background & Aims: The prognosis of patients with chronic liver disease is to a great extent determined by the presence and degree of portal hypertension (PHT). Hepatic venous pressure gradient (HVPG) has been shown to be an accurate prognostic index in patients with cirrhosis. Transient elastography is a non-invasive procedure that assesses liver fibrosis through the measurement of liver stiffness (LS). In several reports, LS was found to be correlated with HVPG. LS could therefore be useful to identify patients with significant PHT. The aim of the present study was to prospectively assess and to compare the prognostic performances of LS and HVPG in patients with chronic liver disease.

Methods: One hundred patients with chronic liver disease underwent LS and HVPG measurements on the same day. Patients were thereafter followed-up for 2 years or until they experienced a complication related to their liver disease.

Results: Within the two-year follow-up, 41 patients developed, at least, one liver disease related complication. The performances of HVPG and LS for predicting the occurrence of these complications were not significantly different: AUROC 0.815 [0.727–0.903] and 0.837 [0.754–0.920], respectively. When considering only complications related to PHT, both methods were found to be similarly accurate: AUROC 0.830 [0.751–0.910] and 0.845 [0.767–0.823], for HVPG and LS, respectively. When patients were divided in two groups according to a LS value below or above 21.1 kPa, actuarial rates of remaining free of any complication at 2 years were 85.4% *vs.* 29.5%, respectively. When only PHT related complications were considered, these rates were 100% *vs.* 47.5%, respectively. The performances of LS and HVPG were also similar in the subgroup of 65 patients with cirrhosis.

Conclusions: LS proved as effective as HVPG in predicting clinical decompensation and PHT related complications in patients with chronic liver disease. Therefore, LS could be a valuable clinical tool to avoid invasive procedures.

Keywords: Cirrhosis; Portal hypertension; Hepatic venous pressure gradient; Liver stiffness.
Received 15 September 2010; received in revised form 27 January 2011; accepted 30 January 2011; available online 25 February 2011
☆ DOI of original article: 10.1016/j.jhep.2011.03.009.
*Corresponding author. Address: Service d'Hépato-Gastro-Entérologie, Pôle Digestif CHU Toulouse, Purpan 31059, Toulouse cedex, France.
E-mail address: bureau.c@chu-toulouse.fr (C. Bureau).
† These authors contributed equally to this work.

Introduction

In patients with cirrhosis, disease complications are mainly related to portal hypertension (PHT), which in turn correlates with hepatic venous pressure gradient (HVPG) [1]. The complications of cirrhosis are usually observed when HVPG is higher than 10 mmHg [2] and, accordingly, HVPG has been found to be an excellent predictor of clinical decompensation [3]. HVPG measurement is an invasive procedure, which requires hepatic vein catheterization. This procedure is technically difficult and needs specialized settings and training [4]. Until now, non-invasive approaches have proved inaccurate for the early prediction of clinical decompensation in cirrhotic patients [5,6].

Non-invasive methods for measuring liver fibrosis have been recently developed. Transient elastography assesses liver fibrosis by measuring liver stiffness (LS) [7,8]. Several reports showed that, in patients with chronic hepatic diseases, LS increases as fibrosis progresses [7,9,10]. Moreover, LS was found to be correlated with HVPG in several studies and, therefore, was able to detect the presence of significant PHT [11–15]. The aim of the present study was to assess and compare LS and HVPG performances in predicting the occurrence of complications in patients with chronic liver disease.

Patients and methods

Patients

Between November 15, 2005 and October 15, 2006, LS was measured by Fibroscan® (FS) in 150 patients who underwent a transjugular liver biopsy with hemodynamic measurements (HVPG). This was done regardless of the etiology of liver abnormalities or the stage of liver disease. Of the 150 patients, 8 refused to be followed-up, 24 were followed-up in other hospitals, and 18 were excluded due to hematologic diseases or due to the presence of clinical

decompensation at inclusion. Therefore, there remained 100 patients with compensated chronic liver disease, who were prospectively followed-up. All the patients were enrolled after obtaining written informed consent. The study was designed according to the ethical guidelines issued by the 2000 revision (Edinburgh) of the 1975 Declaration of Helsinki. At the time of inclusion, none of the patients had antiviral therapy or portal pressure modifying treatment. Clinical decompensation, liver transplantation or death were considered as primary end points of the study. Patients were followed-up for 2 years or until the first occurrence of a clinical decompensation, liver transplantation, or death. Clinical decompensation was defined as: PHT related bleeding, ascites, hepatorenal syndrome, hepatic encephalopathy, hepatocellular carcinoma, and/or sepsis. Patients were censored at 2 years or at the time of the first clinical decompensation, liver transplantation, or death. PHT related complications (variceal bleeding and/or ascites) were also studied separately. In this analysis, patients were censored at 2 years or at the time of the first PHT related complications, liver transplantation, or death.

Liver stiffness measurement by Fibroscan®

LS and hemodynamic measurements were performed on the same day. By Fibroscan® (Echosens, Paris, France), LS was assessed on the right lobe of the liver, through inter-costal spaces with the patient in the supine position and the right arm in maximal abduction, as described [7,8]. Ten validated measures were performed for each patient. Success rate was calculated as the number of validated measures divided by the total number of measures. Results were expressed in kilopascals (kPa). The median value of 10 successful measures was considered representative of LS. Interquartile range (IQR) was lower than 30% of the median value and success rate was at least 60%, according to the manufacturer's recommendations and previous evidence [7,16]. The operator was not aware of HVPG values when conducting the analyses.

Since we showed in a previous study [12] that the threshold of 21.1 kPa was able to discriminate patients with or without significant PHT, accuracy of this cut-off was assessed and compared with the performance of HVPG for predicting clinical decompensation.

Hemodynamic measurements

The hemodynamic study was performed after a 12-h fasting period, in the supine position and under local anesthesia, as previously described [2]. HVPG was calculated as wedged hepatic venous pressure (WHVP) minus free hepatic venous pressure (FHVP) and expressed in millimeters of mercury (mmHg). HVPG value was calculated as the mean of three measurements. PHT was defined as a HVPG >5 mmHg and clinically significant PHT as a HVPG $\geqslant$10 mmHg [3]. The hemodynamic study was performed by experienced operators not aware of the results of liver biopsy and LS measurement. On liver biopsy, fibrosis was graded according to METAVIR score ranging from F0 (no fibrosis) to F4 (cirrhosis) [17]. The mean liver biopsy length was 17.4 mm.

Statistical analysis

Quantitative variables are expressed as mean ± S.D, and qualitative variables as absolute and relative frequencies. Comparisons between groups of quantitative variables were made by the Student-*t* test or Wilcoxon test. Chi square and Fisher's exact tests were used for qualitative data when appropriate. Correlations between variables were computed with Pearson coefficient. For multivariate analysis, a Cox model was used in order to determine the parameters associated with the judgement criteria. Only variables significantly associated with the judgement criteria in the univariate analysis were considered for the multivariate analysis. Child–Pugh and MELD scores were not included in the multivariate analysis in order to avoid colinearity with bilirubin, prothrombin index, and because not all patients in the cohort were cirrhotic.

To assess the performance of HVPG and LS in predicting clinical decompensation, sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), and receiver operating characteristic (ROC) curves were calculated. The ROC curve is a plot of sensitivity versus 1-specificity for all possible cutoff values. The most commonly used index of accuracy is the area under the ROC curve (AUROC), in which values close to 1 indicate higher diagnostic accuracy. AUROC comparisons were performed using the Hanley test. Actuarial rates of complications were calculated using the Kaplan–Meier plots and compared by the Log rank test. p <0.05 was considered as the level of significance. Statistical analysis was performed using the SPSS software version 18 (SPSS Inc Chicago, IL, USA).

Table 1. Main characteristics of the 100 patients at inclusion. Quantitative variables are presented as mean ± SD and [range].

	Patients
Sex: Males-Females	59-41
Age (years)	56 ± 13 (47-66)
Cause of liver disease	
Alcohol	38
Viral hepatitis B or C	28
Alcohol + virus	6
NASH	8
Auto-immune hepatitis	8
Cholestatic liver disease	3
Miscellaneous	9
BMI (kg/m^2)	25 ± 4 (13-34)
Follow-up (days)	491 ± 282 (8-730)
HVPG (mmHg)	11 ± 8 (0-36)
HVPG ≥10 mmHg (%)	51
Liver Stiffness (kPa)	30.7 ± 26.3 (30.8-75)
Prothrombin Index (%)	78 ± 19 (36-100)
Platelets count (10^3/mm^3)	168 ± 83 (32-468)
Serum albumin (g/L)	35 ± 9 (13-52)
Serum bilirubin (μmol/L)	59 ± 111 (5-589)
Serum sodium (mmol/L)	137 ± 4 (125-145)
γGT (UI/L) (N = 7-38 UI/L)	225 ± 271 (17-2072)
AST (UI/L) (N <30 UI/L)	111 ± 238 (16-2041)
ALT (UI/L) (N <34 UI/L)	105 ± 250 (8-1968)
Serum creatinine (μmol/L)	82 ± 22 (50-211)
Fibrosis grade	
F0	9
F1	5
F2	11
F3	10
F4 = Cirrhosis	65

Results

Patient characteristics

Main clinical and biochemical characteristics of the 100 patients are presented in Table 1. Mean follow-up period was 491 days. HVPG was higher than 10 mmHg in 51 patients. Cirrhosis was diagnosed in 65 patients, whose mean Child–Pugh score and MELD score were 7.6 [5–11] and 12.2 [5–15], respectively. In the subgroup of cirrhotic patients, no varices were found in 18 patients (27.5%). Esophageal varices were grade 1 in 18 patients (27.7%), grade 2 in 25 patients (39%), and grade 3 in 4 patients (6%).

LS could be initially measured in 96 patients. Failure to obtain valid measures was due to obesity in 4 patients. No failure of hemodynamic measurement was encountered during the study period.

Table 2. Details of the 71 events that occurred in 41 patients.

Events	Patients (n)
Variceal bleeding	8
Ascites	13
Encephalopathy	13
Hepatocarcinoma	4
Sepsis	13
Liver transplantation	3
Death	17

Clinical complications

Forty-one patients (41%) experienced at least one clinical complication within a mean period of 245 ± 244 [8–730] days. A total of 71 complications were observed and are detailed in Table 2. In 18 patients, 21 complications were considered to be directly related to portal hypertension: variceal bleeding, and/or ascites. None of the patients developed hepatorenal syndrome, and, therefore hepatorenal syndrome was not considered for further analysis.

Parameters associated with clinical complications

The clinical parameters listed in Table 1 were compared between patients with or without clinical complications. In univariate analysis, the occurrence of a complication was observed significantly more often in the presence of cirrhosis, in patients with higher age, higher HVPG, higher LS value, higher bilirubin, lower prothrombin index, lower platelet count, lower albumin, lower serum sodium, higher Child–Pugh score, and higher MELD score (Table 3). Mean values of HVPG in patients free of or with clinical decompensation were 7 mmHg and 17 mmHg, respectively (p <0.001). Corresponding mean values of LS were 19.3 kPa and 48.1 kPa, respectively (p <0.001). All clinical variables associated with clinical decompensation using univariate analysis were considered for multivariate analysis with a Cox model. Child–Pugh and MELD scores were not included in the analysis, since they are used only for patients with cirrhosis. Platelet count was the only variable associated independently with clinical decompensation (p = 0.05).

Of the 38 patients with alcohol-related liver disease, 23 had alcohol withdrawal. There were no significant differences between the two groups in terms of total complications. Moreover, 7 abstinent patients *vs.* 9 alcohol abusers experienced PHT-related complications.

When considering only the 65 patients with cirrhosis, 57.8% experienced at least one complication during follow-up and 26.5% developed complications related to PHT. Using univariate analysis, the risk of clinical decompensation in this subgroup was significantly associated with higher age, higher LS value, higher HVPG, lower prothrombin index, lower platelet count, lower serum albumin, higher Child–Pugh, and MELD scores. The mean values of HVPG in patients with cirrhosis with or without clinical decompensation were 17.8 mmHg [0–36] *vs.* 11.1 mm Hg [2–29], respectively (p <0.001). Corresponding mean values of LS were 51.7 kPa [4.4–75.0] *vs.* 36.7 kPa [3.8–75], respectively (p = 0.002). Using multivariate analysis, none of the above-mentioned parameters was independently associated with the risk of clinical decompensation.

Table 3. Comparison of demographic, clinical, and laboratory characteristics between patients who experienced or not at least one event during follow-up.

	Patients without event (n = 59) mean ± SD	Patients with event (n = 41) mean ± SD	p value
Sex: Males-Females (%)	34-25	24-17	n.s.
Age (years)	53 ± 13	60 ± 12	0.005
BMI (kg/m^2)	24 ± 4.3	25 ± 4.1	n.s.
Liver Stiffness (kPa)*	19.3 ± 21.2	48.1 ± 23.7	<0.001
Liver Stiffness >21.1 kPa	14/58 (24%)	31/38 (82%)	<0.001
HVPG (mmHg)	7 ± 6	17 ± 8	<0.001
Prothrombin index (%)	86 ± 15	65 ± 17	<0.001
Platelet count (10^3/mm^3)	197 ± 88	127 ± 56	<0.001
Serum albumin (g/L)	39 ± 8	30 ± 7	<0.001
Serum bilirubin (μmol/L)	36 ± 78	92 ± 140	0.02
Serum sodium (mmol/L)	138 ± 4	135 ± 3	<0.001
γGT (UI/L)	193 ± 290	271 ± 237	n.s.
AST (UI/L)	104 ± 283	122 ± 153	n.s.
ALT (UI/L)	116 ± 292	89 ± 175	n.s.
Serum creatinine (μmol/L)	82 ± 15	81 ± 29	n.s.
Cirrhosis (%) (n = 65)	45.7	92.6	<0.001
Child-Pugh score	6.7 ± 2.4	8.3 ± 1.9	0.0006
MELD	9.6 ± 6.2	13.9 ± 7.2	0.001

* LS was measured in 96 patients.

Table 4. Comparison of demographic, clinical, and laboratory characteristics of patients with cirrhosis between those who experienced or not PHT related complications.

	Cirrhotic patients without PHT complication (n = 47)	Cirrhotic patients with PHT complication (n = 18)	*p* value
Sex: Males-Female (%)	26 (72.2)-21 (72.4)	10 (27.7)-8 (27.6)	n.s.
Age (years)	59.4 ± 12.4	59.2 ± 9.7	n.s.
BMI (kg/m^2)	24.6 ± 4.3	25.8 ± 3.6	n.s.
Liver Stiffness (kPa)* n = 62	36.7 ± 24.7	57.6 ± 19.4	0.001
Liver Stiffness <21.1 kPa, n = 62	18/44 (41%)	0/18 (0%)	0.02
HVPG (mmHg)	13.9 ± 7.8	17.5 ± 4.5	0.01
Prothrombin index (%)	72 ± 18	63 ± 17	n.s.
Platelet count (10^3/mm^3)	145 ± 64	136 ± 70	n.s.
Serum albumin (g/L)	32 ± 9	30 ± 6	n.s.
Serum bilirubin (μmol/L)	75 ± 134	88 ± 115	n.s.
Serum sodium (mmol/L)	136 ± 5	135 ± 3	n.s.
γGT (UI/L)	246 ± 318	283 ± 288	n.s.
AST (UI/L)	132 ± 295	136 ± 206	n.s.
ALT (UI/L)	108 ± 282	123 ± 261	n.s.
Serum creatinine (μmol/L)	85 ± 26	69 ± 19	0.006
Child-Pugh score	7.3 ± 2.4	8.4 ± 1.7	0.05
MELD	11.9 ± 7.4	12.9 ± 6.3	n.s.

Parameters associated with PHT related complications

The next objective was to determine which clinical parameters could predict the development of PHT related complications. PHT related hemorrhage and/or ascites were observed in patients with higher LS value, higher HVPG, lower prothrombin index, lower platelet count, lower albumin concentration, lower sodium, lower creatinine, higher Child–Pugh and MELD scores. Mean values of HVPG in patients with or without PHT related complications were 17.5 mmHg [10–30] and 9.6 mmHg [0–36], respectively (p <0.001). Corresponding mean values of LS were 57.6 kPa [21.3–75] and 24.5 kPa [3.8–75], respectively (p <0.001). None of the patients with LS <21.1 kPa developed PHT related complications. In multivariate analysis, LS was independently associated with PHT complications (p = 0.01) only after excluding HVPG, and conversely (p = 0.01). The correlation between these two parameters was confirmed (r = 0.803; p <0.001).

When considering only PHT related events in cirrhotic patients, a significant association was found in patients displaying higher LS, HVPG, and Child–Pugh score and lower serum creatinine (Table 4). As in the whole sample, LS was, in multivariate analysis, independently associated with PHT complications (p = 0.01) only after excluding HVPG and conversly (p = 0.01).

Performances of LS and HVPG for predicting the risk of clinical decompensation

Performances are listed in Table 5. The AUROC of HVPG and LS values for predicting clinical complications were 0.815 [0.727–0.903] and 0.837 [0.754–0.920], respectively (Fig. 1). No statistically significant difference could be observed between these values.

According to the presence or the absence of significant PHT (HVPG ⩾10 mmHg), the actuarial rates of remaining free of any

Table 5. Performances of HVPG and LS in predicting clinical decompensation and PHT related complications in all patients.

	AUROC*	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
All complications					
HVPG ≥10 mmHg	0.815 [0.727-0.903]	82.9	71.2	66.7	85.7
LS ≥21.1 kPa	0.837 [0.754-0.920]	81.6	75.9	68.9	86.3
PHT related complications					
HVPG ≥10 mmHg	0.830 [0.751-0.910]	100	59.8	35.3	100
LS ≥21.1 kPa	0.845 [0.767-0.923]	100	65.4	40.0	100

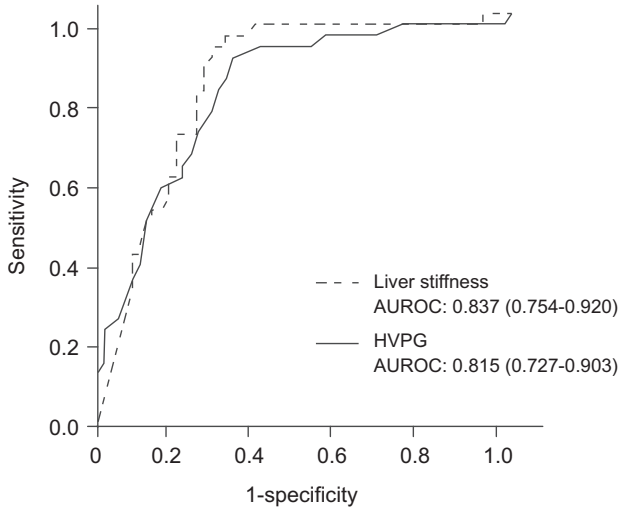

Fig. 1. Performance of liver stiffness and HVPG for the prediction of liver related complications.

liver related complication were 32.2% and 84.1%, respectively (Log Rank p <0.001) (Fig. 2A).

The actuarial rates of remaining free of any complication related to the liver disease were 29.5% and 85.4%, respectively, if LS was ⩾21.1 kPa or <21.1 kPa (Log Rank p <0.001) (Fig. 2B).

Performance of LS and HVPG in predicting the risk of PHT related complications

The AUROC of HVPG and LS values in predicting PHT related complications were 0.830 [0.751–0.910] and 0.845 [0.767–0.923] (Fig. 3A). When considering only cirrhotic patients, HVPG and LS had similar performances, AUROC values being 0.725 [0.602–0.849] and 0.734 [0.609–0.859], respectively. (Fig. 3B).

According to the presence or the absence of significant PHT (HVPG ⩾10 mmHg), the actuarial rates of remaining free of PHT complications were 51.3% and 100%, respectively (Log Rank p <0.001) (Fig. 4A). In fact, none of the patients with a HVPG <10 mmHg developed PHT related complications. In the subgroup of cirrhotic patients, the HVPG with a 10 mmHg threshold had a sensitivity of 100%, a specificity of 36.1%, a PPV of 37.5%, and a NPV of 100%. In this subgroup, the actuarial rates of remaining free of PHT complications with a HVPG ⩾10 mmHg or <10 mmHg were 47.8% and 100%, respectively.

When LS value was ⩾21.1 kPa or <21.1 kPa, the actuarial rates of remaining free of PHT related complications were 47.5% and 100%, respectively (Log Rank p <0.001) (Fig. 4B). No patient with a LS value <21.1 kPa experienced PHT related complications. For the subgroup of patients with cirrhosis, LS with a 21.1 kPa cutoff had a 100% sensitivity, 41% specificity, 41% PPV, and 100% NPV. The actuarial rates of remaining free of PHT complications with LS ⩾21.1 kPa or <21.1 kPa were 47% and 100%, respectively.

Discussion

The present study shows a strong relationship between LS and the risk of decompensation in patients with chronic liver disease, regardless of the presence of cirrhosis.

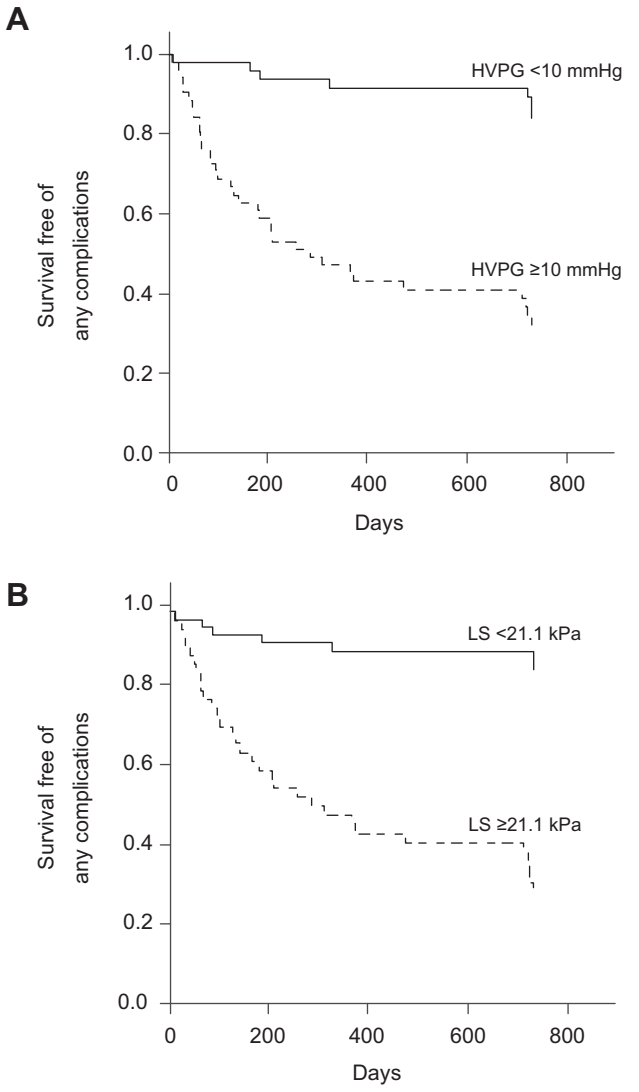

Fig. 2. Risk of liver related complications according to HVPG or liver stiffness. (A) Probability of remaining free of liver related complications according to the 10 mmHg-threshold for HVPG. (B) Probability of remaining free of liver related complications according to the 21.1 kPa-threshold for liver stiffness.

To the best of our knowledge this is the first study that prospectively assessed the performance of LS for predicting clinical complications and that compared it with HVPG measurement. HVPG is a well established index in different clinical settings for patients with cirrhosis [2,3]. However, the only available method to assess HVPG is a direct measurement of pressure in a hepatic vein. This method is not available in all medical centers and is considered invasive, cost-ineffective, and hardly reproducible by most authors [18]. Until now, most non-invasive approaches for assessing short-term prognosis in patients with chronic liver disease have proved inaccurate. The need for prospective longitudinal studies to assess new non-invasive procedures was recommended at the Baveno IV Consensus Conference [19].

Foucher *et al.* have previously found a correlation between LS and severity of cirrhosis [20]. However, in this study, PHT complications were retrospectively assessed as a history of ascites or

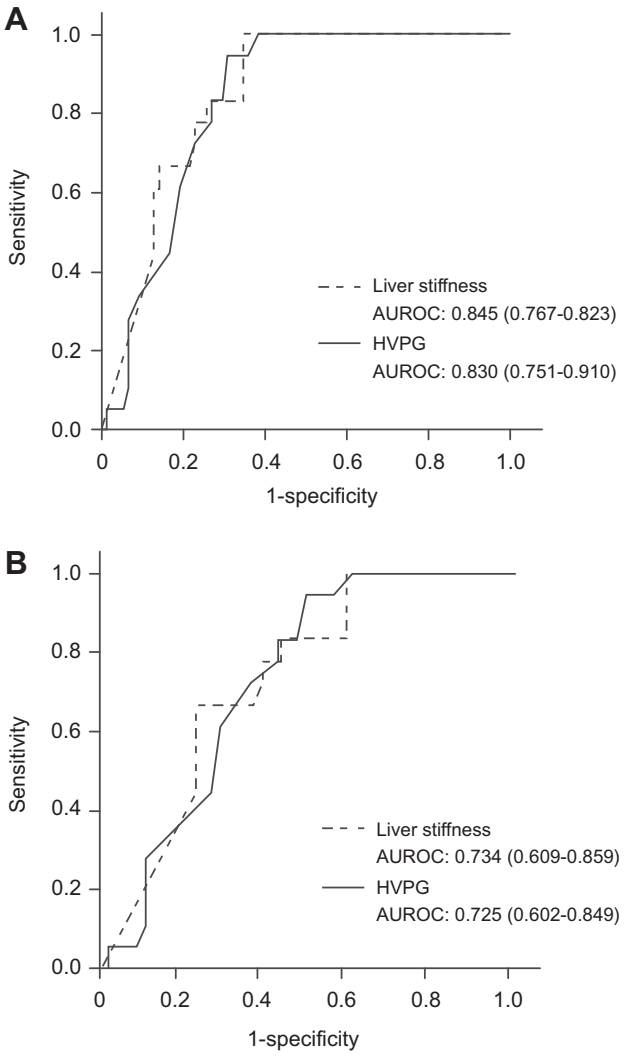

Fig. 3. Performance of liver stiffness and HVPG for the prediction of portal hypertension related complications. (A) All patients and (B) patients with cirrhosis.

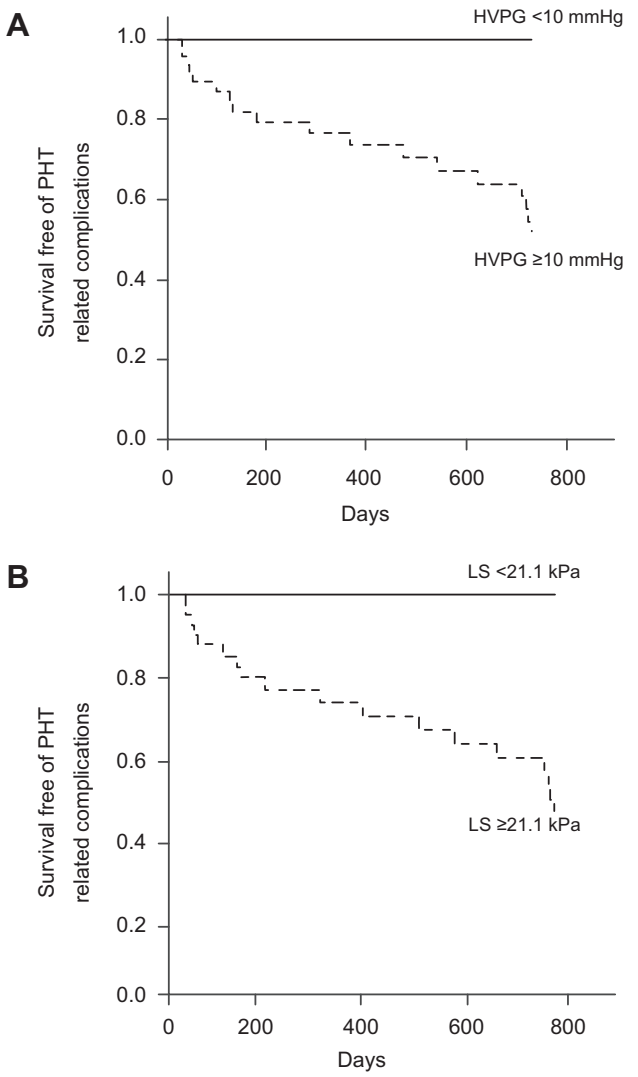

Fig. 4. Risk of portal hypertension related complications according to HVPG or liver stiffness. (A) Probability of remaining free of portal hypertension related complications according to the 10 mmHg-threshold for HVPG. (B) Probability of remaining free of portal hypertension related complications according to the 21.1 kPa-threshold for liver stiffness.

variceal bleeding. LS was also found to be correlated with the grade of esophageal varices [20,21]. Our group previously showed that a LS value higher than 21.1 kPa is predictive of clinically significant PHT [12]. In the present study, we found that this cut-off value can predict decompensation in a population of patients with chronic liver disease of whom 65% proved to have cirrhosis on liver biopsy. Non cirrhotic patients were included since at the present time not all patients have a liver biopsy but quite a few are assessed using non-invasive procedures. Furthermore, LS is used at least in part to avoid such an invasive procedure as a liver biopsy. Finally, owing to sampling errors, cirrhosis can be misclassified by biopsy [22]. One can hypothesize that in the near future, patients will be screened using non-invasive techniques whether or not they might have cirrhosis of the liver. The purpose for investigating the PHT related complications in the entire patient population was to validate the predictive value of LS and HVPG in a non-selected population that represents the future target of non-invasive procedures. Transjugular or percutaneous routes are systematically proposed in our center to every patient who has an indication for liver biopsy. As such, the transjugular route is not restricted to patients presenting with either coagulation disorders or ascites. In the present study, only 12 patients had a contra-indication to percutaneous liver biopsy ($\leqslant$50,000 platelets in 2 patients and prothrombin time index $\leqslant$50% in 10 patients). For the majority of our patients, liver biopsy was performed for fibrosis staging and, only in a few patients liver biopsy was performed for liver abnormalities of unknown etiology or hemodynamic evaluation. Therefore, we believe that this gave us a rare opportunity to measure HVPG in patients with compensated liver disease. Some patients displayed markers of liver dysfunction, but according to D'Amico's classification, all of the cirrhotic patients in our study belonged to compensated liver cirrhosis stage 1 or 2. However, in a prospective study with more recently selected patients with compensated cirrhosis, Ripoll *et al.* [3] reported a rate of complications of 29%, lower than in the population of our study. Furthermore, the prevalence of

varices in our sample is higher than expected in fully compensated patients. It could suggest a selection bias. Nevertheless, the NPV in predicting PHT related complications was 100%. Thus, inclusion of less severe patients should result in lower rates of clinical events and consequently NPV should not be lowered. According to the present study, the main interest of LS is to avoid invasive procedures in low-risk patients. Our interests are corroborated with the exceptional NPV we found in our study.

Using multivariate analysis, in the entire patient population included, platelet count only was found independently associated with the risk of clinical decompensation. This finding is not surprising, as the presence of thrombocytopenia is a sign of advanced liver disease [6,23]. Furthermore, thrombocytopenia was found to be associated with high HVPG [24].

Sepsis was included in the definition of complications since the immune system is often impaired in patients with chronic liver disease and the risk of infections is therefore increased. Moreover, PHT related complications are often triggered by sepsis [25]. It is noteworthy that 5 out of the 6 patients who were misclassified by LS (using the cut-off value of 21.1 kPa) experienced sepsis. Thus, by including sepsis in our definition of complications, the performance of LS could have been underestimated.

The performances of LS were found to be better when considering only PHT related complications. Others, as well as our group, have previously shown that LS is highly correlated with HVPG [11–15]. Thus, the prognostic value of LS could be the result of a strong association between HVPG and LS. It is noteworthy that no patient with a LS value below 21.1 kPa experienced ascites or PHT related bleeding at two-year follow-up (NPV = 100%). The lowest LS value associated with a PHT complication was 21.3 kPa. Both our previous study and the present one suggest that a 21.1 kPa threshold could help identifying patients with chronic liver disease at low risk to experience a complication within 2 years. In these selected patients, unnecessary and invasive procedures such as hepatic vein catheterization or endoscopic screening could be avoided.

As expected, most complications occurred in patients with cirrhosis (87.5% of patients with decompensation). It is to be noted that the performances of LS and HVPG remained similar in the subgroup of patients with cirrhosis. Nevertheless, over HVPG, LS holds the major advantage of being non-invasive and easy to repeat during patients' follow-up.

The present investigation provides several important data. It is the first longitudinal and prospective study demonstrating that LS can be as effective as HVPG for the prediction of clinical complications in patients with chronic liver disease. In our cohort, the HVPG with a 10 mmHg threshold was confirmed as a good predictor of clinical decompensation and PHT related complications, as demonstrated [2,3]. Moreover, the LS cutoff of 21.1 kPa had the same performance as HVPG in predicting clinical decompensation and PHT related complications. An important aspect of the present study is that those results were obtained in non selected patients with chronic liver disease. Based on these findings, LS could be used as a screening test for clinical outcome in patients with chronic liver disease. The 100% NPV of LS with a 21.1 kPa threshold emphasizes the potential usefulness of this non-invasive screening test to rule out PHT related complications in patients with cirrhosis.

However, it must be kept in mind that LS value is influenced by several specific conditions such as acute hepatitis [26,27], cholestasis [28], or heart failure [29,30]. Therefore, results must be interpreted with caution in those conditions. In the present cohort, 6 patients had acute hepatitis (3 patients with acute alcoholic hepatitis and 3 with auto-immune hepatitis) and at least 5 of these patients had chronic liver disease since fibrosis was found to be F3 or F4 and, F0 in only one patient. Interestingly, the patient with acute hepatitis and F0 stage of fibrosis had a LS value equal to 10 kPa. The LS value was greater than 12 kPa in all remaining patients. When the analysis was performed after excluding patients with acute hepatitis, the results were unchanged. Only 2 patients in our cohort had an acute hepatitis and a LS value below 21 kPa. Hence, it is difficult to draw a definitive conclusion from this subgroup of patients.

The sample size in the present study is not large enough for definitive conclusions to be drawn and extrapolated to all subgroups of patients, according to liver disease severity or etiology. In our study, all patients with PHT had an intra-hepatic block so that these results may not apply to patients with extra hepatic PHT. Furthermore, other non-invasive markers, in particular biochemical tests, were not assessed in the present study.

In conclusion, in the present study, LS proved to be as accurate as HVPG for selecting patients at low-risk of clinical decompensation and PHT related complications. These results warrant external validation in fully compensated patients and further studies are needed with other non invasive markers of liver fibrosis.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References

[1] Thalheimer U, Leandro G, Samonakis DN, Triantos CK, Patch D, Burroughs AK. Assessment of the agreement between wedge hepatic vein pressure and portal vein pressure in cirrhotic patients. Dig Liver Dis 2005;37:601–608.
[2] Bosch J, Abraldes JG, Berzigotti A, Garcia-Pagan JC. The clinical use of HVPG measurements in chronic liver disease. Nat Rev Gastroenterol Hepatol 2009;6:573–582.
[3] Ripoll C, Groszmann R, Garcia-Tsao G, Grace N, Burroughs A, Planas R, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology 2007;133:481–488.
[4] Kalambokis G, Manousou P, Vibhakorn S, Marelli L, Cholongitas E, Senzolo M, et al. Transjugular liver biopsy-indications, adequacy, quality of specimens, and complications – a systematic review. J Hepatol 2007;47:284–294.
[5] D'Amico G, Morabito A. Noninvasive markers of esophageal varices: another round, not the last. Hepatology 2004;39:30–34.
[6] de Franchis R. Non-invasive (and minimally invasive) diagnosis of oesophageal varices. J Hepatol 2008;49:520–527.
[7] Castera L, Forns X, Alberti A. Non-invasive evaluation of liver fibrosis using transient elastography. J Hepatol 2008;48:835–847.
[8] Ziol M, Handra-Luca A, Kettaneh A, Christidis C, Mal F, Kazemi F, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. Hepatology 2005;41:48–54.
[9] Poynard T, Morra R, Ingiliz P, Imbert-Bismut F, Thabut D, Messous D, et al. Assessment of liver fibrosis: noninvasive means. Saudi J Gastroenterol 2008;14:163–173.
[10] Alisi A, Pinzani M, Nobili V. Diagnostic power of fibroscan in predicting liver fibrosis in nonalcoholic fatty liver disease. Hepatology 2009;50:2048–2049.
[11] Vizzutti F, Arena U, Romanelli RG, Rega L, Foschi M, Colagrande S, et al. Liver stiffness measurement predicts severe portal hypertension in patients with HCV-related cirrhosis. Hepatology 2007;45:1290–1297.
[12] Bureau C, Metivier S, Peron JM, Selves J, Robic MA, Gourraud PA, et al. Transient elastography accurately predicts presence of significant portal hypertension in patients with chronic liver disease. Aliment Pharmacol Ther 2008;27:1261–1268.

[13] Lemoine M, Katsahian S, Ziol M, Nahon P, Ganne-Carrie N, Kazemi F, et al. Liver stiffness measurement as a predictive tool of clinically significant portal hypertension in patients with compensated hepatitis C virus or alcohol-related cirrhosis. Aliment Pharmacol Ther 2008;28:1102–1110.
[14] Kazemi F, Kettaneh A, N'kontchou G, Pinto E, Ganne-Carrie N, Trinchet JC, et al. Liver stiffness measurement selects patients with cirrhosis at risk of bearing large oesophageal varices. J Hepatol 2006;45:230–235.
[15] Castéra L, Le Bail B, Roudot-Thoraval F, Bernard PH, Foucher J, Merrouche W, et al. Early detection in routine clinical practice of cirrhosis and oesophageal varices in chronic hepatitis C: comparison of transient elastography (FibroScan) with standard laboratory tests and non-invasive scores. J Hepatol 2009;50:59–68.
[16] Kettaneh A, Marcellin P, Douvin C, Poupon R, Ziol M, Beaugrand M, et al. Features associated with success rate and performance of FibroScan measurements for the diagnosis of cirrhosis in HCV patients: a prospective study of 935 patients. J Hepatol 2007;46:628–634.
[17] Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology 1996;24:289–293.
[18] Thalheimer U, Mela M, Patch D, Burroughs AK. Targeting portal pressure measurements: a critical reappraisal. Hepatology 2004;39:286–290.
[19] de Franchis R. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol 2005;43:167–176.
[20] Foucher J, Chanteloup E, Vergniol J, Castéra L, Le Bail B, Adhoute X, et al. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. Gut 2006;55:403–408.
[21] Kazemi F, Kettaneh A, N'Kontchou G, Pinto E, Ganne-Carrie N, Trinchet JC, et al. Liver stiffness measurement selects patients with cirrhosis at risk of bearing large oesophageal varices. J Hepatol 2006;45:230–235.
[22] Bedossa P, Dargere D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. Hepatology 2003;38:1449–1457.
[23] Peck-Radosavljevic M. Thrombocytopenia in liver disease. Can J Gastroenterol 2000;14:60D–66D.
[24] Qamar AA, Grace ND, Groszmann RJ, Garcia-Tsao G, Bosch J, Burroughs AK, et al. Incidence, prevalence, and clinical significance of abnormal hematologic indices in compensated cirrhosis. Clin Gastroenterol Hepatol 2009;7:689–695.
[25] Cazzaniga M, Dionigi E, Gobbo G, Fioretti A, Monti V, Salerno F. The systemic inflammatory response syndrome in cirrhotic patients: relationship with their in-hospital outcome. J Hepatol 2009;51:475–482.
[26] Arena U, Vizzutti F, Corti G, Ambu S, Stasi C, Bresci S, et al. Acute viral hepatitis increases liver stiffness values measured by transient elastography. Hepatology 2008;47:380–384.
[27] Coco B, Oliveri F, Maina AM, Ciccorossi P, Sacco R, Colombatto P, et al. Transient elastography: a new surrogate marker of liver fibrosis influenced by major changes of transaminases. J Viral Hepat 2007;14:360–369.
[28] Millonig G, Reimann FM, Friedrich S, Fonouni H, Mehrabi A, Büchler MW, et al. Extrahepatic cholestasis increases liver stiffness (Fibroscan) irrespective of fibrosis. Hepatology 2008;48:1718–1723.
[29] Lebray P, Varnous S, Charlotte F, Varaut A, Poynard T, Ratziu V. Liver stiffness is an unreliable marker of liver fibrosis in patients with cardiac insufficiency. Hepatology 2008;48:2089.
[30] Millonig G, Friedrich S, Adolf S, Fonouni H, Golriz M, Mehrabi A, et al. Liver stiffness is directly influenced by central venous pressure. J Hepatol 2010;52:206–210.