Diagnosis of clinically significant portal hypertension by transient elastography in patients with compensated cirrhosis and potentially resectable hepatocellular carcinoma

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Abstract

Background/aim: Patients with cirrhosis and small hepatocellular carcinoma (HCC), with normal bilirubin and hepatic venous pressure gradient (HVPG) < 10 mmHg have low risk of descompensation and over 70% survival after hepatic resection. On the contrary, patients with HVPG ≥ 10 mmHg (clinically significant portal hypertension, CSPH) frequently develop decompensation following surgery, with <50% survival. Therefore, practice guidelines recommend measuring the HVPG before indicating surgery. Liver stiffness (LS) evaluation by transient elastography (TE; FibroScan®) might non-invasively identify CSPH. We investigated the usefulness of TE for predicting CSPH in patients with compensated cirrhosis and potentially resectable HCC.

Patients and methods: 70 consecutive Child Pugh A patients with potentially resectable HCC referred to our unit for HVPG measurement were prospectively evaluated. In fasting condition all received a LS measurement before the hemodynamic study. The overall correlation between LS and HVPG was assessed, and the performance of 2 previously published cut-offs of LS (13.6 and 21 kPa) in predicting CSPH was analysed.

Results: HVPG could be measured in all patients, whereas in 10 (14%) obese patients LS could not be measured. In the 60 patients with valid TE, mean HVPG was 8.7 ± 4.5 mmHg; 25 (41.7%) had CSPH. Mean LS was 18.6± 12.7 kPa (<13.6 kPa: 37%; 13.6-21 kPa: 38%; >21 kPa: 25.0%). LS showed a moderate direct correlation with HVPG (r=0.522; p < 0.001). Sensitivity and specificity of the two LS cut-offs for CSPH prediction was: 13.6 kPa: Se 92%, Sp 57% and 21 kPa: Se 52%, Sp 94%.

Conclusion: TE was not feasible in 14% of patients with potentially resectable HCC. When feasible, values of LS below 13.6 kPa rule-out CSPH, while values over 21 kPa confirm CSPH. However over a third (38%) of patients belong to a “grey zone” having LS between 13.6 and 21 kPa. Our results suggest that HVPG measurement cannot be replaced by the non-invasive assessment of LS.

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Hepatocellullar carcinoma (HCC) is the most frequent primary malignant hepatic neoplasia, showing a high incidence in patients with liver cirrhosis. Patients with a single nodule and in an early stage, compensated disease (stage 0), can be effectively treated with resection [1,2]. In western countries the selection of optimal candidates for surgery is based on the assessment of portal hypertension. Studies from our group have shown that in compensated patients, a normal serum bilirubin and the absence of clinical significant portal hypertension (CSPH) (hepatic venous pressure gradient, HVPG < 10 mmHg) are the best predictors of excellent outcomes after surgery even if limiting resection to Child-Pugh A patients[3]. Five-year survival of patients with normal bilirubin and HVPG< 10 mmHg is > 70% [4]. In contrast, patients with CSPH will frequently decompensate after surgery and have < 50% five-year survival [4]. These data have been confirmed by a recent study in Japan[5]. Therefore, measurement of HVPG is a key step in the evaluation of candidates for resection[1].

Measurement of the HVPG is the gold standard to assess the presence of CSPH. However, HVPG measurements are invasive, relatively expensive and available only in a few centers. For these reason, it has been suggested that non-invasive methods might be used to predict the presence of portal hypertension. Transient elastography (TE, FibroScan ®) has been introduced as a rapid and non-invasive technique that measures liver stiffness (LS)[6]. Recent studies have suggested that TE can predict cirrhosis and its complications including the presence of esophageal varices[7,8] and variceal bleeding[7]. In a cohort of patients with HCV infection recurrence after a liver transplantation[9] LS showed a good correlation with HVPG, and some authors hypothesised that TE could be used as a non-invasive alternative to HVPG measurements to assess the presence of CSPH. In the study by Vizzutti and co-workers[10], performed in patients with HCV-related cirrhosis, a strong correlation between LS and HVPG measurements was found ($r=0.81$, $p< 0.0001$), especially below the threshold of 10 mmHg. The AUROC of LS for predicting CSPH was 0.99 and a cut-off value of 13.6 kPa, having 97%

sensitivity and 92% specificity, was chosen. In the study by Bureau and co-workers[11] patients with all cirrhosis of any etiology were included. As in the previous study HVPG correlated strongly with LS (r=0.858; p>0.001). Regarding CSPH, AUROC of LS was 0.945. In this study a cut-off value of 21KPa was set, having 89.9% sensitivity and 93.2% specificity for predicting CSPH.

Given these observations, the aim of our study was to evaluate if transient elastography is able to predict CSPH in patients with potentially resectable HCC so non-invasively identifying the best candidates for resection.

Patients and methods

Seventy consecutive Child Pugh A cirrhotic patients with a potentially resectable hepatic nodule referred to our unit for HVPG measurements from June 2007 to December 2009 and were included in this prospective study. All patients had a previous diagnosis of cirrhosis on the basis of histological results or unequivocal clinical and imaging data. Patients' history and routine laboratory tests were obtained at inclusion. Severity of liver disease was assessed by Child-Pugh {Child, 1964 1872 /id} and MELD scores {Kamath, 2001 1963 /id}.

The study protocol was approved by the Ethics Committee of Hospital Clinic. The nature of the study was explained to the patients, and an informed consent was obtained in each case, according to the principles of the Declaration of Helsinki (revision of Edinburgh 2000).

Transient elastography

In all patients TE was used to assess LS before the hemodynamic procedure in fasting condition. The operator was blinded to clinical data, and was not allowed to perform the hepatic vein catheterization. Measurements of liver stiffness were performed on the right lobe of the liver through intercostal spaces on patients lying in the dorsal decubitus position with the right arm in maximal abduction. The tip of the probe transducer was placed on the skin between the ribs at the level of the right hepatic lobe. The operator, assisted by an ultrasonic time-motion image, located a liver portion of at least 6 cm thick free of large vascular structures. 10 successful measurements were performed on each patient. Success rate was calculated as the ratio of the number of successful measurements over the total number of acquisitions. Only liver stiffness measurements with a success rate of at least 60% and an interquartile range

lower than 30% were considered reliable. The results are expressed in kilopascal (kPa) and median value was kept as representative of liver stiffness. The whole examination duration was less than 5 minutes.[12,13]. According to previous published data (Vizzutti y Bureau) two cut-offs of LS, namely 13.6 and 21 kPa, were tested for predicting CSPH.

HVPG measurement

Immediately after TE examination patients underwent hepatic vein catheterisation. Under local anaesthesia, a 8F venous catheter introducer (Axcess; Maxxim Medical, Athens, TX, USA) was placed in the right internal jugular vein using the Seldinger technique. Thereafter, a 7F balloon-tipped catheter (Edwards Lifesciences, Irvine, CA, USA) was advanced into the right hepatic vein to measure wedged and free hepatic venous pressures (WHVP and FHVP, respectively) by the connection to external electro-mechanical transducer and polygraph (Mac-Lab®, GE Healthcare, Freiburg, Germany). Hepatic venous pressure gradient was calculated as the difference between wedged and free hepatic venous pressure, as previously described (Bosch Seminars 2006). All measurements were performed in triplicate, and permanent tracings were recorded.

Clinically significant portal hypertension was defined as HVPG $\geq$ 10 mmHg [14] . The operator was blinded to transient elastography results.

Statistical analysis

The SPSS 15.0 package (SPSS Inc, Chicago, IL) was used to perform the analysis. Data are reported as means with standard error deviation of the mean. Correlation of LS with HVPG was performed by Pearson's test. HVPG was dichotomized in < 10 mmHg an $\geq$ 10 mmHg as previously defined[14]. Linear regression was calculated according to the least squared methods in order to calculate correlation between HVPG and LS. Sensitivity, specificity, positive predictive value, negative predictive value and positive and negative likehood ratios for CSPH diagnosis were then calculated for the pre-established cut-off values of LS. Significance was established at $p<0.05$.

Results

Table 1 summarises the clinical characteristics of the population of the study. Fourty-six (76.7%) were male and mean age was 62 (SD 11) years. The etiology of cirrhosis was HCV infection in 63% of the patients. In the remaining, cirrhosis was due to HBV infection (8%), alcohol (8%) and other causes (12%).
As for the nodule dimension, X were below 2 cm, X below 3 cm, X between 3 and 5 cm, and X over 5 cm.

HVPG could be obtained in all the patients. On the other hand, in 10 (14%) obese patients LS could not be measured.
Thus, the agreement between HVPG and LS could be studied in sixty patients. In this population mean HVPG was 8.7 (SD 4.5) mmHg; 25 patients (41.7%) had CSPH.
Mean LS was 18.6 (SD 12.8) kPa; 22/60 patients (36.7%) had LS <13.6 kPa; 15/60 (25.0%) patients had LS >21 kPa, and 23/60 (38.3%) had intermediate values.
LS showed a moderate direct correlation with the HVPG ($r=0.522$; $p < 0.001$) (Figure 1). When we separately analysed the subgroup of patients with HCV–related cirrhosis (n=38) the correlation slightly improved ($r=0.607$; $p< 0.001$) (Figure 2).
Tables 2 and 3 show the performance of the previously reported LS cut-offs for the diagnosis of CSPH. As shown, the 13.6 kPa value had a high sensitivity but a low specificity (92% and 57%, respectively), which did not improve in the subgroup of HCV-infected patients (sensitivity 89%, specificity 58%). Conversely, the 21 kPa value had a low sensitivity and a high specificity for the detection of CSPH (52% and 94% respectively). Specificity further improved in the subgroup of patients with HCV-related cirrhosis (specificity 100%; sensitivity 42%).
Given these results, a LS value $\leq$ 13.6 would rule out clinically significant portal hypertension and a value $\geq$ 21 kPa would confirm clinically significant portal hypertension. Nonetheless, up to 23 out of 60 (38%) patients had a LS value between 13.6 kPa and 21 kPa, which was not informative on CSPH presence or absence (indeterminate findings, “grey zone”) (Figure 3).

According to the results of LS, two patients with LS below 13.6 kPa were misclassified as not having CSPH while they had, and two patients with LS over 21 kPa were misclassified as having CSPH while they had not.

Discussion

Hepatocellular carcinoma is the sixth most common neoplasm in the world, with more than half a million new cases annually (Parkin et al. 2005), and the main cause of death among patients with cirrhosis (Sangiovanni et al 2004). In this population, prognosis is not only due to tumor-related factors, but also to factors related to the underlying liver disease, such as liver function and presence of portal hypertension. Therefore, the Barcelona-Clínic Liver Cancer Group (Llovet Seminars 1999; Forner Seminars 2010) (BCLC) suggests taking into account these factors when planning treatment strategy. In patients with preserved hepatic function, single nodules below 2 cm (very early HCC) or up to 3 cm (early HCC) are potential candidates for surgical resection. Within this population, those patients with CSPH have an increased risk of post-surgical decompensation, and other therapeutic options should be considered. In those patients without esophageal varices the diagnosis of CSPH requires the invasive measurement of the HVPG. In this setting non-invasive methods able to predict the presence of CSPH would represent a major progress. LS well correlated with the HVPG in previous studies[10,11].

This is the first study evaluating the performance of TE as a non-invasive technique to predict CSPH in patients with hepatic nodules who were candidates for surgical resection. Our results suggest that in this population the correlation between LS and HVPG is only moderate ($r=0.522$; $p < 0.001$), even in the subgroup of patients with HCV-related cirrhosis ($r=0.607$; $p< 0.001$), and much weaker than what observed in patients without HCC in previous studies[10,11].

By applying the previously described LS cut-offs for CSPH prediction (Vizzutti y Bureau) we observed that the value of 13.6 KPa had a good sensitivity and high negative predictive value to detect CSPH, both in the entire population (92%) and in the subgroup with VHC related cirrhosis (89%). This is in agreement to what observed by Vizzutti and colleagues[10]. Nonetheless, in our patients the specificity and positive predictive value of this cut-off were very low. From a

clinical point of view the application of this cut-off only would result in a large number of false positive results (patients in whom surgery would not be indicated despite a low risk of post-surgical decompensation).

On the other hand, the LS cut-off of 21 KPa had a high specificity for CSPH diagnosis (92% in the whole population and 100% in HCV positive patients, respectively) and high PPV (87 % and 100%, respectively), similar to those described in the paper by Bureau et al. (CITA), but low sensitivity and NPV. Therefore, from a clinical point of view the application of this cut-off alone would result in a large number of false negative results (patients in whom surgery would eventually be indicated despite a high risk of post-surgical decompensation).

Given these results, it can be suggested that both cut-offs could be used, the first to rule-out CSPH (LS < 13.6 kPa) and the second to diagnose CSPH (LS > 21 kPa). Since approximately 40% of patients show values between these cut-offs, which cannot be non-invasively classified (indeterminate or in a “grey zone”), it could be speculated that HVPG measurement could be saved in more than a half of patients by LS assessment. Nonetheless, 4 patients (7%) were misclassified, 2 (9%) of those with LS < 13.6 kPa, and 2 (13%) of those with LS > 21 kPa.

All these data suggest that in real-life scenarios LS is not accurate enough to diagnose or rule-out CSPH in the individual patient with a potentially resectable hepatic nodule.

The reason for the different performance of LS in our patients with HCC as compared to previous series might have different explanations. First, we included only patients with cirrhosis, since this is the population in which the use of HVPG as a prognostic factor is validated. Both in Vizzutti’s and in Bureau’s papers also patients with less severe liver disease were included, and it has been shown that LS better correlates with HVPG when CSPH has not yet developed (Vizzutti). So, this might partly explain the worse correlation of LS with HVPG in our patients. Also, we included patients with different etiologies, while one of the used cut-offs was developed in patients with HCV-related

cirrhosis. On the other hand, our results slightly, but not substantially improved in the subgroup of patients with HCV-related cirrhosis.

Another finding regards the applicability of TE; in our study LS measurements could not be performed due to obesity in 14% of the patients initially included. Even if this is a well-known limitation of TE, it is particularly relevant in this cohort, since the association of obesity and HCC is well established and a relevant proportion of patients with HCC are overweight or obese (CITA); unfortunately, the specifically designed Fibroscan® probe for obese patients is not still available in our center, and we cannot report on its usefulness in these cases. Furthermore, TE only allows a blinded measurement, and we cannot exclude that the hepatic nodule was placed in the measurement area. This limitation of TE, which possibly explains the high values of LS observed in 2 patients with HVPG<10 mmHg, might be overcome by newer methods for LS measurement in real time, such as ARFI (Friedrich-Rust), which also allows a standard ultrasound examination of the liver.

In conclusion, LS could not be measured in 14% of the population of this study due to its technical limitations. In those patients in whom TE was feasible, values over 21 kPa suggest CSPH, while values below 13.6 kPa rule-out CSPH with acceptable accuracy. Nonetheless, over a third (38%) of patients has LS between 13.6 and 21 kPa, “grey zone” in which the diagnosis of CSPH cannot be done non-invasively. Finally, our results suggest that HVPG measurement for the diagnosis of CSPH in patients with potentially resectable liver nodules cannot be replaced by the non-invasive assessment of LS.

Table 1. Clinical and laboratory characteristics of the population of the study.

Age (y)	62 (SD 11)
Sex (M/F) (%)	76.7/23.3
Etiology	
HCV	38 (63.3%)
Alcohol	5 (8.3%)
HBV	5 (8.3%)
Other	12 (13.6%)
AST (UI/L)	76 (56)
ALT (UI/L)	86 (62)
GGT (UI/L)	126 (187)
Alcaline phosphatase (UI/L)	214 (85)
Bilirubin (mg/dl)	0.9 (0.4)
Albumin (g/l)	41 (7.2)
Prothrombin activity (%)	85 (11)
INR	1.1 (0.9)
Platelet count, n3/ml	162 (68)
Spleen diameter (cm)	12 (2.3)
Hepatic nodule size (cm)	
Hepatic nodule site	
HVPG (mmHg)	8.7 (4.5)
HVPG≥10 mmHg, n (%)	25 (41.7)
LS (kPa), mean (SD)	18.6 (12.8)
Median (range)	17.3 (3-63.9)

Table 2. Performance of the previously reported LS cut-offs for the diagnosis of CSPH in the whole population (n=60).

	13.6 kPa	**21 kPa**
Sensitivity (%)	92%	52%
Specificity (%)	57%	94%
Positive predictive value (%)	61%	87%
Negative predictive value (%)	91%	73%
+ Likelihood ratio	2.15	9.00
– Likelihood ratio	0.14	0.51

Table 3. Performance of the previously reported LS cut-offs for the diagnosis of CSPH in VHC related cirrhosis.

	13.6 kPa	**21 kPa**
Sensitivity (%)	89%	42%
Specificity (%)	58%	100%
Positive predictive value (%)	68%	100%
Negative predictive value (%)	85%	63%
+ Likelihood ratio	2.13	-
– Likelihood ratio	0.18	0.58

Figure 1. Linear regression analysis between HVPG and LS in the whole population of the study (n=60).

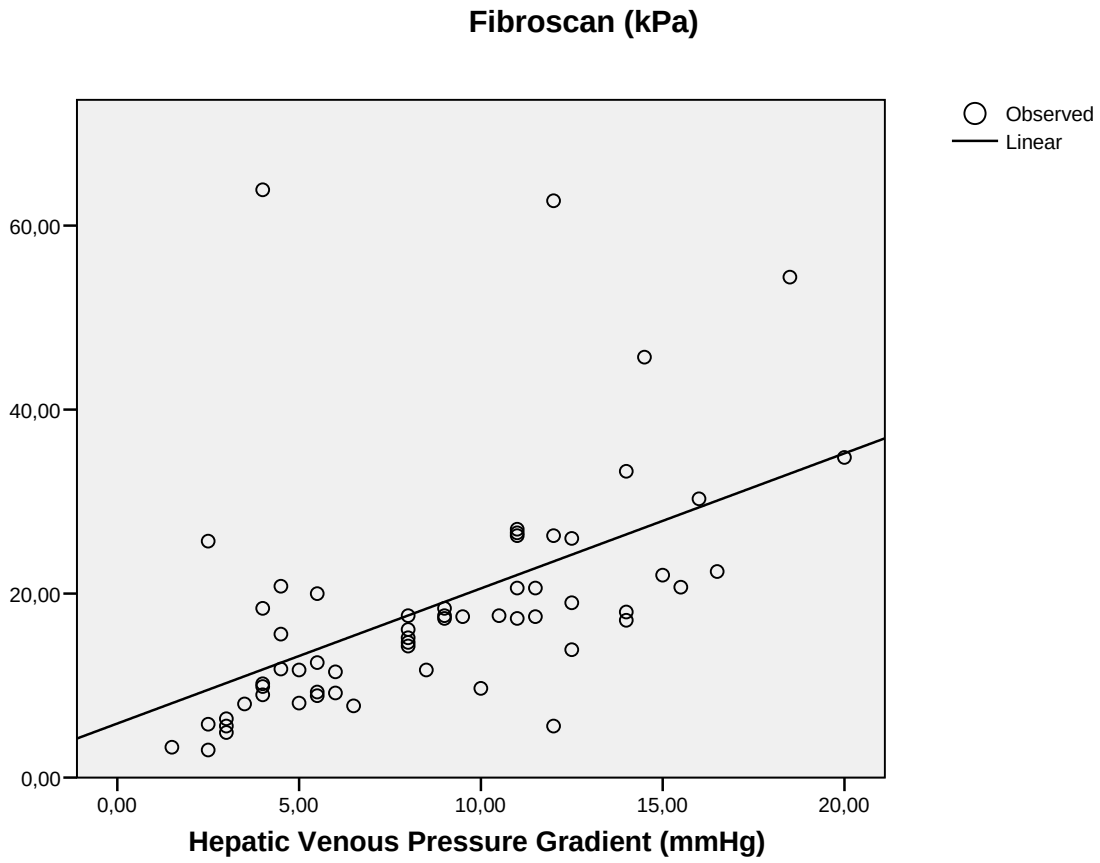


Figure 2 Linear regression analysis between HVPG and LS in the subgroup of patients with HCV-related cirrhosis (n=38).

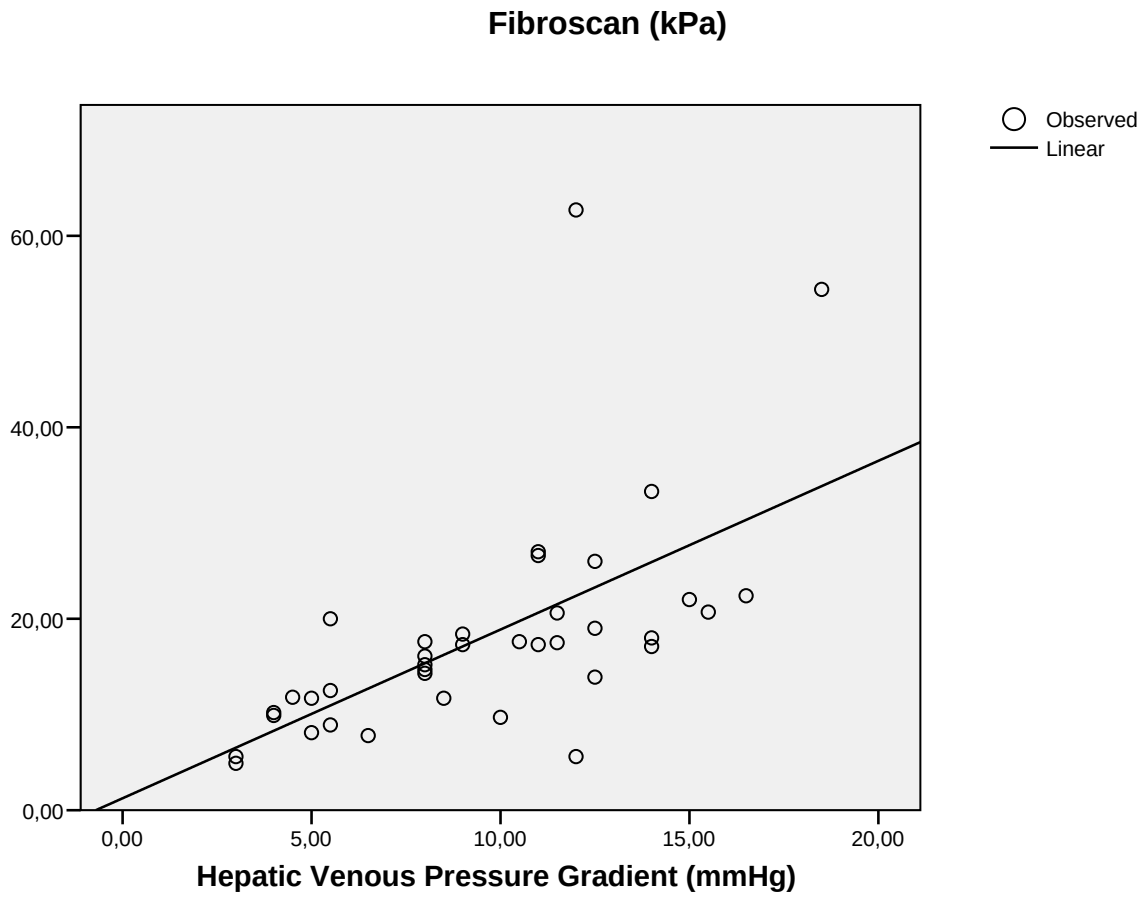
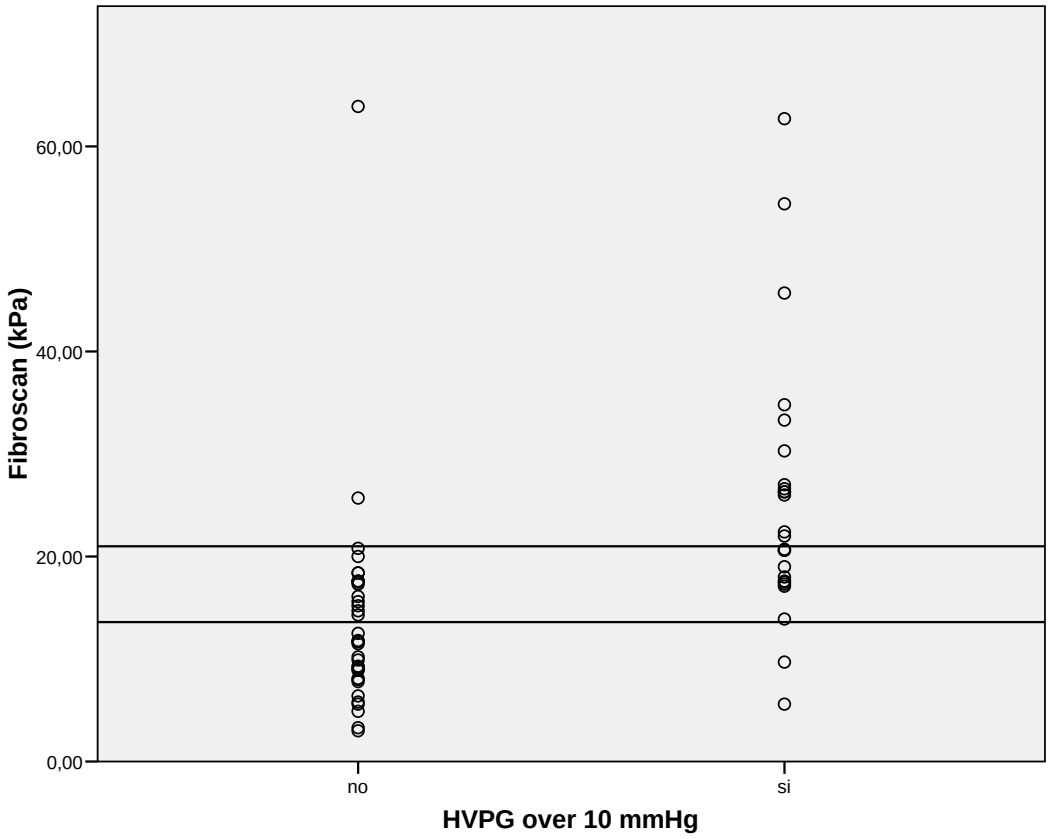


Figure 3. LS values according to the presence or absence of CSPH (HVPG≥10 mmHg) in the whole population of the study (A) and in patients with HCV-related cirrhosis (B). As shown, values between 13.6 and 21 kPa give no information on the presence or absence of clinically significant portal hypertension, so constituting a ‘grey zone’ for CSPH prediction in patients with potentially resectable hepatic nodules.

A)



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