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Good performance of liver stiffness measurement in the prediction of postoperative hepatic decompensation in patients with cirrhosis complicated with hepatocellular carcinoma

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Abstract:

The evaluation of patients with early hepatocellular carcinoma (HCC) referred for liver resection is still a matter of debate. **Aims:** 1) to compare liver stiffness measurement (LSM) by transient elastography with hepatic venous pressure gradient (HVPG) in the prediction of decompensation after liver resection in patients with cirrhosis and early HCC; 2) to identify which definition for posthepatectomy liver failure is better associated with survival. **Material and methods:** Fifty-one patients (MELD score of 10±3) were included. In this group, 34 patients underwent HVPG measurement, of which 13 (38%) had clinically significant portal hypertension (CSPH) and 35 patients underwent LSM (21.8±17.9 kPa). The study's end-points were: posthepatectomy liver failure (PHLF) defined according to International Study Group of Liver Surgery criteria and 3-month decompensation defined as de novo ascites, variceal bleeding, jaundice, hepatic encephalopathy and acute kidney injury. The performance of LSM compared to HVPG in predicting the end-points were assessed by AUROC curves and accuracy. **Results:** Twenty (39%) patients developed PHLF and 15 (29%) developed decompensationat 3 months. Three-month decompensation tended to be better correlated with survival. LSM performed well in predicting decompensation at 3 months (AUROC=0.78, 95%CI: 0.63-0.94; p=0.01), comparable with HVPG (AUROC=0.89, 95%CI: 0.79-1.00; p<0.01) (DeLong test p=0.21). LSM was not sufficiently accurate to predict PHLF. **Conclusion:** LSM has a similar performance to HVPG in predicting decompensation at 3 months in patients with early HCC submitted to liver resection. Three-month decompensation is better associated with survival.

Keywords: clinical significant portal hypertension; hepatic venous pressure gradient; prognosis; liver resection; liver elastography

Introduction

The evaluation and management of patients with early hepatocellular carcinoma (HCC) and portal hypertension (PHT) referred for surgical resection is a matter of debate. The current recommendation is that patients with early HCC, Barcelona-Clinic Liver Cancer (BCLC) stage 0 and A without PHT should undergo liver resection when possible [1-2]. The main concern in patients with PHT remains the occurrence of post-hepatectomy liver failure (PHLF) although there is no consensus regarding its definition. The gold standard method to assess PHT is hepatic venous pressure gradient (HVPG) measurement [3] which is not widely available and is considered invasive [4]. When unavailable, surrogate markers of PHT (esophageal varices, splenomegaly and low platelet count) are recommended for

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patient selection for surgery [1], but their accuracy is inadequate [5].

Presently there is no consensus regarding the assessment of post-hepatectomy complications but two main perspectives on this issue are prevalent. Some studies calculate a short-term in-hospital prognosis based mainly on the "50-50 criteria" on the 5th postoperative day (increase of bilirubin >50 mmol/L, equivalent of 3 mg/dl, and decrease of prothrombine index to less than 50%) [6-7], while others determine a mid-term prognosis (at 3 months), assessing complications related to PHT such as ascites or PHT-related bleeding [8-9].

In the last decade liver stiffness measurement (LSM) by transient elastography has proven to be very well correlated with HVPG [4] and presently is recommended for the selection of patients at risk of clinical significant PHT (CSPH) [3], defined as HVPG ≥10 mmHg and which implies an increased risk of decompensation in patients with cirrhosis [10].

Although there are 8 studies that have validated the use of LSM in the prediction of PHLF [11-18], only one compared LSM with the direct intraoperative measurement of the portal pressure [18]. The direct comparison between LSM and HVPG in this clinical scenario was performed in 97 patients and confirmed the good ability of LSM to identify patients with CSPH, but in this report the patients with CSPH were excluded from hepatic resection [19].

The primary aim of our observational study was to compare LSM with HVPG in the prediction of PHLF and 3 months decompensation in patients with cirrhosis and early HCC treated by hepatic resection. The secondary aim was to analyze which end-point (PHLF and 3 months decompensation) is better associated with survival.

Material and methods

Patients

Between May 2016 and February 2018, 169 patients with HCC were diagnosed in our tertiary healthcare center. Among them 68 (40%) were diagnosed with early HCC (BCLC A) and were considered for percutaneous ablation or potential candidates for liver resection. As recommended by the current guidelines [1], a multidisciplinary team establishes the allocation for different treatment options according to the BCLC stage, number and localization of the tumors and presence of PHT (HVPG or surrogate markers as presence of esophageal varices). HVPG and LSM were done during the initial evaluation, before treatment allocation. In our center HVPG is not systematically used for selecting patients for surgery, but together with tumor size and localization, may contribute to reject patients from resection. After this assessment, 51 patients were referred for liver resection and were included in this observational study.

The Ethics Committee of our institution approved the study protocol (No. 69/2016) and an informed consent was obtained in each case, according to the principles of the Declaration of Helsinki (revision of Edinburgh, 2000).

HVPG measurement

Under local anesthesia and ultrasonographic guidance, a 9F venous catheter introducer (St. Jude Medical, Minnesota, 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). HVPG was calculated as the difference between WHVP and FHVP and measured in triplicate. Clinically significant portal hypertension was defined as HVPG ≥10mmHg [10]. The operator was blinded to transient elastography results.

Liver stiffness measurement by Transient Elastography

During the same hospitalization, after an overnight fast, measurements of liver stiffness were performed on the right lobe of the liver through intercostal spaces on patients lying supine with the right arm in maximal abduction. The tip of the probe was placed on the skin on an intercostal space at the level of the right hepatic lobe under ultrasound guidance (to locate the liver and avoid large vessels). Ten successful measurements were performed on each patient. A success rate of 60% and an interquartile range lower than 30% were considered reliable. The investigator was blind to the HVPG result.

Surgical resection

Surgery was performed within a maximum 30 days after initial evaluation and the treatment allocation by the multidisciplinary team. Two types of resection were performed: minor hepatic resection (≤2 segments resected) and major hepatic resection (>2 segments resected) depending on the localization, number and size of tumors. All the procedures were anatomical resections performed mainly by open surgery (only a small minority were laparoscopic). In selected cases intraoperative ultrasound was performed to assess the vascular relation with the tumor or the section plane.

End-points of the study

In the present study two end points were considered: PHLF and 3-month decompensation.

Post-hepatectomy liver failure (PHLF) was defined and graded according to the International Study Group of Liver Surgery (ISGLS) criteria [7]. ISGLS criteria are based on the ability of the liver to preserve its synthetic, excretory, and detoxifying functions, and rely mainly by an increased INR and hyperbilirubinemia after postoperative day 5. The PHLF is graded as follows: grade A (abnormal laboratory parameters but requiring no change in the clinical management of the patient); grade B (deviation from the regular clinical management but manageable without invasive treatment) and grade C (deviation from the regular clinical management and requiring invasive treatment). However, according to ISGLS recommendations, diuretic treatment or vasoactive drugs are also included in "deviation from regular clinical management" and, therefore, patients who had decompensated ascites without "50-50 criteria" were still considered to have PHLF. The end-point of the study was grade B and C PHLF.

Three-month decompensation was defined as de novo ascites, PHT-related bleeding, jaundice (serum bilirubin >3 mg/dl), hepatic encephalopathy and acute kidney injury occurring during the first 3 months after surgery [8-9].

Statistical analysis

Quantitative variables were expressed as mean and standard deviation (SD), whereas qualitative variables as absolute and relative frequencies. For comparison of quantitative variables, Student's t or Mann-Whitney test (when appropriate) were used, whereas for the qualitative variables Chi square or Fisher's test were used. Correlations between variables were computed using the Spearman Rho coefficient. To assess the performance of LSM and HVPG sensitivity (Se), specificity (Sp), positive and negative likelihood ratios (LR), accuracy and receiver operating characteristic curve (AUROC) were calculated. The diagnostic accuracy is defined asthe number of well-classified patients. The AUROC graphics and comparison between ROC curves was done using Stata version 12 (StataCorp LP, Texas, United States). The McNemar test was used in the 2×2 contingency table for assessing differences in the proportion of misclassified patients at risk for 3-month decompensation. The statistical analysis was performed using the SPSS software version 20 (SPSS Inc., USA).

Results

Patient characteristics

The baseline characteristics of the study group are presented in Table I. Eighteen patients (35%) had major liver surgery (resection of ≥2 segments) and only a minority (3 patients, 6%) had laparoscopic surgery. The mean duration of surgery was 110±42 minutes. HVPG measurement was performed in 34 patients of whom 13 (38%) had CSPH; 35 patients were screened for esophageal varices (EV), which were found in14 patients (40%).

Table I. Patient's characteristics

Variable	
Sex (m)	38 (74.5)
Etiology	
alcohol	12 (23.5)
virus	33 (64.7)
others	6 (11.8)
AST (U/L)	56±61
ALT(U/L)	51±81
Bilirubin (mg/dl)	1.1±0.7
Platelets count *10^3/L	150±71
Albumin g/L	34±15
MELD	10±3
HVPG (mmHg)	10±6
CSPH	13 (38)
Liver stiffness kPa	21.8±17.9
Esophageal varices	14 (40)
Splenomegaly+platelets count <10^5	20 (50)

Data are expressed as mean±SD or count (%); MELD = Model for End stage Liver Disease, AST = aspartate aminotransaminase, ALT = alanine aminotransaminase, HVPG = hepatic venous pressure gradient, CSPH = clinical significant portal hypertension (HVPG≥10 mmHg)

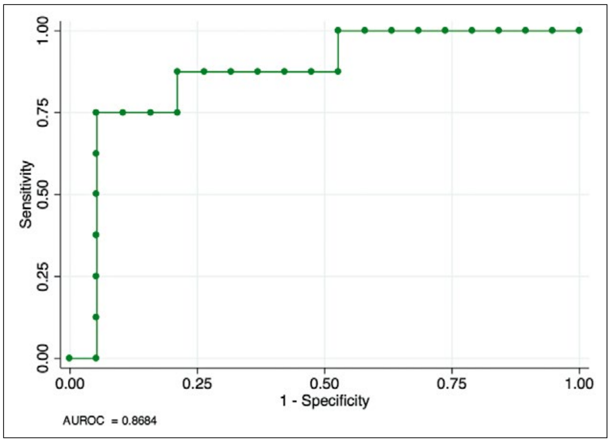

Fig 1. The performances of LSM in predicting CSPH

LSM was performed in 35 patients and reliable results were obtained in 32 patients, with a median value of 15.7 (70.3) kPa.

A good correlation between LSM and HVPG (Rho=0.610, p=0.001) was found and LSM performed well in identifying the patients with CSPH (AUROC=0.86, 95%CI: 0.70-1.00; p=0.004) (fig 1), with 19 kPa as the best cut-off according to the Youden index (Se=87%; Sp=79%; positive LR=4.16; negative LR=0.16, accuracy=81.4%).

End-points

During hospitalization 20 (39%) patients developed PHLF (15 patients class B and 5 class C) as follow: PI below 50% (11 patients), ascites (12 patients), acute kidney injury (10 patients), variceal bleeding (3 patients) and increased bilirubin >3mg/dl (4 patients).

The factors associated in univariate analysis with PHLF were HVPG, AST, bilirubin, PI and the MELD score. In multivariate analysis the only independent variable associated with the development of PHLF was HVPG (OR=1.32, 95%CI: 1.08-1.62, p=0.007).

Among the included patients 15 (29%) patients presented 3 months decompensation as follow: 12 patients had ascites, 3 patients variceal bleeding, 3 patients hepatic encephalopathy and 10 patients acute kidney injury of whom 3 met the hepato-renal syndrome diagnostic criteria. In univariate analysis only HVPG and LSM were associated with 3-month decompensation. In multivariate analysis HVPG was the only variable associated with decompensation (OR=1.44, 95%CI: 1.07-1.95).

During a mean follow-up of 14.5±10.2 months, 9 (17.6%) patients died and among them 5 (56%) had PHLF and 4 (44%) 3-month decompensation. None of the study end points was significantly associated with mortality. However, 26% of patients with 3-month decompensation died in comparison with only 9% of patients without decompensation (Fischer's Exact test, p=0.11). PHLF was less associated with survival: 25% of patients with PHLF died in comparison with 16% of patients without PHLF (Fischer's Exact test, p=0.48).

When Kapplan-Meier curves were analyzed, 3-month decompensation proved to have better discriminative power for survival (Log rank p=0.06) than PHLF (Log rank p=0.27) (fig 2).

The performance of LSM in the prediction of the end-points

LSM was not sufficiently accurate to predict PHLF (AUROC=0.60, 95%CI: 0.38-0.81; p=0.3) but was able to fairly predict 3-month decompensation (AUROC=0.78, 95%CI: 0.63-0.94; p=0.01) (fig 3).

Contrary to LSM, HVPG was able to accurately predict both end-points: PHLF (AUROC=0.85, 95%CI: 0.71-0.99; p=0.01) and 3-month decompensation (AUROC=0.89, 95%CI: 0.79-1.00; p<0.01). When the analysis was performed only in patients with both LSM and HVPG (n=27), there was no difference between LSM and HVPG for the prediction of 3-month decompensation, DeLong test p=0.21 (fig 4).

Using the 21 kPa Baveno VI recommended cut-off to rule-in CSPH [3], the accuracy for the prediction of 3-month decompensation was good: 71% (p=0.08) and not significantly different from HVPG which had 79% accuracy (p=0.005) (the McNemar test for assessing differences in the proportion of misclassified patients at risk, p=0.68). None of the patients with LSM <13.6 kPa (the cut-off of rule-out CSPH) decompensated at 3 months,

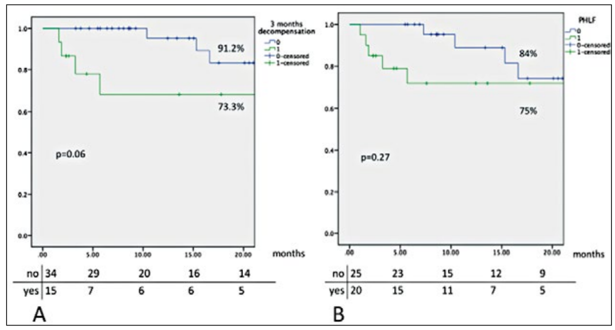

Fig 2. The survival of patients with and without 3-months decompensation (A); the survival of patients with and without PHLF (B)- Kapplan-Meier analysis

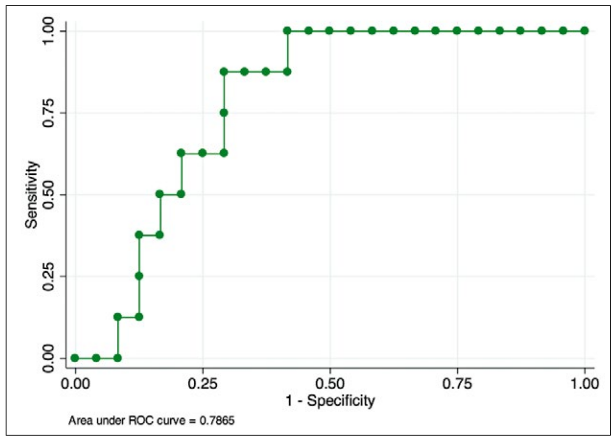

Fig 3. The performances of LSM in predicting 3-months decompensation.

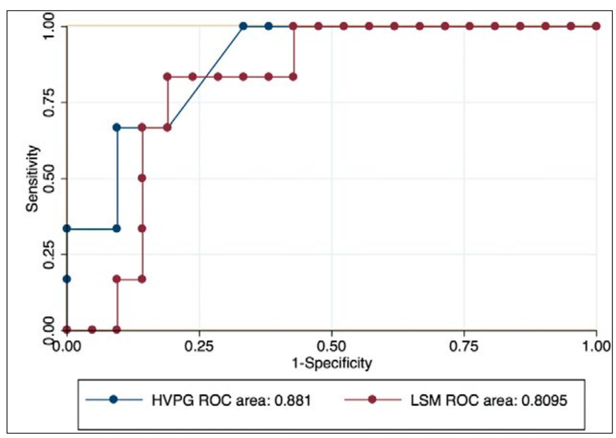

Fig 4. The comparison of LSM and HVPG AUROC curves in predicting 3-months decompensation

while 3 of the 8 patients in the "grey zone" (between 13.6 kPa and 21 kPa) decompensated.

Surrogate markers for CSPH (the presence of EV or splenomegaly and low platelet count <100.000/L) have an accuracy in identifying patients at risk for PHLF and 3-month decompensation lower than that of HVPG and LSM (58% and 52%, respectively).

Discussions

In the present study we found that LSM had a similar accuracy to HVPG measurement in selecting patients with cirrhosis complicated with HCC referred for liver resection who were at risk to develop posthepatectomy decompensation. The management of patients with early HCC is still a matter of debate. While the present guidelines recommend HVPG measurement whenever possible to identify patients at risk of complications after resection [1], some groups use a more permissive policy using the liver function assessment by MELD score rather than the PHT assessment by HVPG [20]. According to Cucchetti et al the HVPG-based selection of potential candidates for liver resection (using 10 mmHg as cut-off) excludes almost 25% of patients that would benefit from resection without PHLF [20]. This is somehow in contrast with the current recommendations [1] which are based mainly on the evidence generated by the BCLC group [8,9]. A possible explanation for these differences may lay in different end-points. While in the BCLC group the end-point was 3-month persistent decompensation [8] in the Cucchetti's et al study the end-point was PHLF according to the ISGLS criteria [20] which are mainly based on the "50-50 criteria" in the 5^{th} postoperative day and, thus, implies a more rapid censoring of patients. In our study we compared the two end-points from the survival perspective and we found no difference. However, the 3-month decompensation seems to be better correlated with survival, as may be seen from the Kapplan Meier curves, and the explanation of non-statistical significance lies in the low number of patients. When we analyzed strictly the "50-50 criteria" (increase of bilirubin >50 mmol/L, equivalent of 3mg/dl, and decrease of prothrombine index to less than 50%) which are the basis of PHLF diagnosis, there was no discriminative power for survival (83% in patients without *vs* 80% in patients with "50-50 criteria", Log rank p=0.66). The increased performance of PHLF (according to the ISGLS recommendations) is explained by the inclusion of patients with ascites, leading to a very good (86%) concordance between both end points. Although the data were not statistically significant, due to the low number of patients included, we believe that PHT-related decompensation is a more appropriate end-point for patients referred for liver resection.

Despite the current recommendations, in our center patients with CSPH may still benefit from surgery if the tumor size and localization is favorable. This is in concordance with the experience of other centers in which up to two thirds of resected patients do not meet the guideline resection criteria [21]. Moreover, resection in patients outside the resectability criteria has a better prognosis when compared to embolization or other treatments but a lower survival rate than transplantation or percutaneous ablation [21]. Interestingly, in this study the presence of portal hypertension was not significantly correlated with survival but it should be stressed that PHT was estimated only by the presence of its surrogate markers (EV or splenomegaly associated with low platelet count). In a recent meta-analysis surrogate markers, although significantly associated with prognosis, had a lower prediction power than HVPG [5]. In our study, surrogate markers were not significantly associated with both end-points and, therefore, were unable to select patients at risk for decompensation.

Because HVPG measurement is not widely available and is an invasive technique, non-invasive methods that may overcome the disadvantages of surrogate markers are needed. Among all non-invasive methods, LSM proved to be the most validated method able to assess the risk of CSPH in patients with advanced liver disease. Recently its role in risk assessment was endorsed by the Baveno VI recommendation [3] and LS values of more than 21 kPa are able to rule-in CSPH. The performance of LSM in the prediction of PHLF were good in the previous studies [11-18], with AUROCs ranging from 0.79 [13] to 0.86 [12], but none of the studies compared LSM with HVPG and the great majority used end-points based on the "50-50 criteria". The only study that used invasive measurement of portal pressure (intraoperatory measurement by direct puncture of the portal vein) and 3-months decompensation as end-point, found that LSM is slightly better than portal pressure measurement in prognosis assessment, with an AUROC of 0.81 for LSM *vs* 0.71 for direct portal pressure measurement [18]. However, in this study only 50% of the patients had cirrhosis and probably only they would benefit from portal pressure measurement, while LSM is more useful for fibrosis staging which is also correlated with prognosis. In a subgroup of patients with available LSM, Cucchetti et al found similar performances for LSM and HVPG in PHLF prediction, 0.81 and 0.79, respectively [20]. In our cohort, HVPG was the only variable associated with both end points while LSM was associated only with 3-month decompensation.

The small number of patients included represents the main drawback of the study. Despite this, we believe that the results are convincing because we used HVPG, which is the “gold standard” to assess portal hypertension and because we compared our end points with survival. Another limitation is the lack of homogeneity in the management of patients with early HCC which are outside the BCLC resection criteria, since this management is usually based on liver resection. However, as previously mentioned, this tendency is very frequent in many centers [21] and in our center is partially explained by the limited access to liver transplantation.

Conclusions

LSM had a similar performance to HVPG in predicting 3-month posthepatectomy decompensation in patients with early HCC suitable for liver resection. Three-month decompensation tended to be better correlated with the survival in this clinical scenario. More studies are required to confirm these findings.

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