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Similar performance of liver stiffness measurement and liver surface nodularity for the detection of portal hypertension in patients with hepatocellular carcinoma

Authors

Alexandra Souhami¹ MD ; Riccardo Sartoris¹ MD; Pierre-Emmanuel Rautou^{2,3,4} MD PhD; François Cauchy⁵ MD; Mohamed Bouattour² MD ; François Durand^{2,3} MD PhD; Valerio Gianelli² MD ; Elia Gigante² MD; Laurent Castera² MD PhD ; Dominique Valla^{2,3} MD PhD; Olivier Soubrane⁵ MD PhD; Valérie Vilgrain^{1,3,6} MD PhD; Maxime Ronot^{1,3,6} MD PhD.

Affiliations

1. Department of Radiology. APHP. University Hospitals Paris Nord Val de Seine. Beaujon, Clichy, France
2. Service d'Hépatologie, DHU Unity, DMU Digest, Hôpital Beaujon, AP-HP, Clichy, France
3. Université de Paris, Centre de recherche sur l'inflammation, Inserm, U1149, CNRS, ERL8252, F-75018 Paris, France
4. Centre de Référence des Maladies Vasculaires du Foie, French Network for Rare Liver Diseases (FILFOIE), European Reference Network on Hepatological Diseases (ERN RARE-LIVER)
5. Department of Hepatobiliary Surgery. APHP. University Hospitals Paris Nord Val de Seine. Beaujon. Clichy, France
6. INSERM U1149. CRI. Paris, France

Corresponding author

Prof. Maxime Ronot MD, PhD.

Department of Radiology.

Beaujon Hospital. AP-HP. 100 Boulevard du Général Leclerc. 92118 Clichy, France.

E-mail: maxime.ronot@aphp.fr.

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ABSTRACT

Background & Aims: To compare the performance of liver surface nodularity (LSN) and liver stiffness measurements (LSM) using transient elastography (TE) for the detection of clinically significant portal hypertension (CSPH) in patients with cirrhosis and hepatocellular carcinoma (HCC).

Materials: All patients with cirrhosis and HCC who underwent computed tomography (CT), LSM and hepatic venous pressure gradient (HVPG) measurements within 30 days between 2015-2018 were included. The estimation of CSPH by LSN, LSM, and the LSM-spleen-size-to-platelet-ratio score (LSPS) were evaluated and compared.

Results: 140 patients were included (109 men [78%], mean age 63±9 years-old), including 39 (28%) with CSPH. LSN measurements were valid in 130 patients (93%) and significantly correlated with the HVPG ($r=0.68$; $P<.001$). Patients with CSPH had higher LSN measurements than those without (3.1 ± 0.4 vs. 2.5 ± 0.3 , $p<0.001$; AUROC: 0.87 ± 0.31). LSM and LSPS were valid in 132 patients (94%) and significantly correlated with HVPG ($r=0.75$, $P<.001$; AUROC 0.87 ± 0.04 and $r=0.68$, $P<.001$; AUROC 0.851 ± 0.04 , respectively). There was no significant difference in the diagnostic performance between LSN and LSM-LSPS (DeLong, $P=0.28$, 0.37 and 0.65 , respectively) in patients with both valid tests ($n=122$). LSN <2.50 had 100% negative predictive value for CSPH. A two-step algorithm combining LSN and LSPS for the diagnosis of CSPH classified 108/140 patients (77%) with an 8% error.

Conclusion: The diagnostic performance and feasibility of LSN measurements were similar to those of LSM for the detection of CSPH in patients with compensated cirrhosis and HCC. Combining LSN and LSPS accurately detects CSPH in more than 75% of patients. This could be useful in centers where the HVPG measurement is unavailable.

Lay summary

The diagnostic performance and feasibility of the quantification of LSN on routine abdominal CT was similar to that of LSM for the detection of CSPH in patients with compensated cirrhosis. Thus, LSN could be an option for the preoperative detection of CSPH in patients with HCC. Combining LSN with LSPS results in accurate detection of CSPH in more than three quarters of patients, thus limiting the need for HVPG measurements.

Highlights

- The feasibility and diagnostic performance of Liver Surface Nodularity (LSN) is similar to that of Liver Stiffness Measurements (LSM) for the diagnosis of clinically significant portal hypertension (CSPH) in patients with cirrhosis and HCC
- LSN could be useful for the preoperative detection of CSPH in patients with HCC and compensated cirrhosis.
- The combination of LSN as the first line non-invasive test and LSPS accurately detects CSPH in more than three quarters of patients, thus limiting the need for HVPG measurements.

INTRODUCTION

The development of clinically significant portal hypertension (CSPH), defined as a hepatic venous pressure gradient ≥ 10 mm Hg, is a turning point in the progression of chronic liver disease and is associated with the development of gastric and esophageal varices and the first sign of clinical decompensation in patients with no varices [1]. In addition, the assessment of CSPH plays a critical role in the management of patients with cirrhosis and primary liver tumors, especially when major liver resection is the only potential curative treatment. CSPH is associated with an increase in perioperative morbidity of 22 to 50% in these cases [2]. Moreover, European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) guidelines consider portal hypertension (PHT) to be a major factor in the indication for resection of liver tumors [3,4]. Therefore, preoperative screening for CSPH is highly important.

Measurement of the hepatic venous pressure gradient (HVPG) by right hepatic vein catheterization is the reference technique to assess CSPH. This method is invasive, and can often only be performed in expert centers, limiting its availability. To overcome these limitations, several non-invasive methods have been developed. The most frequently used technique is liver stiffness measurement (LSM), using transient elastography (TE) which has been shown to be strongly correlated to the HVPG and to be useful for the detection of CSPH, including in patients in whom liver resection is indicated [5-7]. LSM-derived scores, such as the LSPS (liver stiffness to spleen size/platelet count score) - combining liver stiffness, spleen diameter and platelet count, have been shown to improve the detection of CSPH [8]. Nevertheless, LSM has certain well-known limitations, in particular, the rate of unreliable examinations [9].

Our group recently showed that the diagnostic performance of the quantification of liver surface nodularity (LSN) on routine computed tomography (CT) was good for detecting CSPH and was better than numerous other non-invasive tests [10,11]. The quantification of LSN is easy to obtain and can be retrospectively derived from routine CT, which is especially convenient in patients in whom liver resection is being considered.

The aim of the present study was to compare the performance of LSM using TE and the quantification of LSN from CT for the diagnosis of CSPH, and to evaluate whether the combination of these two techniques could improve the determination of CSPH.

METHODS

Study Population

This retrospective study, together with protocol review, was approved by the institutional review board and the requirement for written informed consent was waived. The study cohort included all patients with histologically proven compensated cirrhosis and HCC who underwent measurement of the HVPG during the work-up for liver surgery between January 2015 and July 2018 at Beaujon University Hospital (Clichy, France). Patients underwent a HVPG measurement and transient elastography measurement of the liver on the same day, and a preoperative abdominal contrast enhanced CT examination within 30 days before or after the HVPG measurement. At our center, tumor size *per se* does not represent a contraindication to surgery and liver resection is considered in cirrhotic patients with large-sized lesions only if: (i) a future liver remnant of at least 40% (with adequate inflow, outflow and biliary drainage) is secured. This may require a combination of preoperative transarterial chemoembolization and preoperative liver volume

modulation using portal vein with or without hepatic vein embolization; (ii) no clinically significant portal hypertension (as evaluated using HPVG or indirect signs) is present. Clinical data, results of laboratory tests performed within 1 week before the HVPG measurement and hemodynamic data were prospectively collected. Patients with a prior history of surgery, without a CT scan performed within 30 days before surgery and those with portal vein thrombosis were not included. It is important to note that 48 patients included in the present study were part of a population included in a previously published study by our group [10].

Analysis Derived from CT Images

LSN quantification was performed on portal venous phase CT images using semiautomated CT software (Liver Surface Nodularity Software, version 0.88; Liver Nodularity llc) by two abdominal radiologists (AS and RS) blinded to clinical data and HVPG results. Radiologists drew a region of interest of 1–2 cm in diameter across the margin of the left liver surface on portal venous phase CT images. The software automatically detected the liver edge compared to adipose tissue on the selected section and on upward and downward continuous sections by propagating the painted region of interest. The software automatically generated a smooth polynomial line to mimic the expected normal liver surface. The distance between the detected liver margin and the polynomial line was measured on a pixel-by-pixel basis, expressed in tenths of a millimeter. A series of 10 valid margin measurements were obtained according to previous studies [10-12]. The software calculated the arithmetical mean of the measurements. Fewer than ten valid measurements were arbitrarily considered to have be invalid measurements.

Additional CT-derived data including the size and location of HCC lesions along with the largest spleen diameter were analyzed and collected.

Liver stiffness measurement (LSM) by transient elastography (TE) and derived scores

TE was performed by hepatology nurses with an experience of more than 500 procedures, according to the instructions provided by the manufacturer. Reliable LSM were defined as the median value of 10 consecutive measurements with a success rate >60% and an interquartile range <30% of the median of measurements. The measurement was expressed in kilopascals (kPa). LSPS, which combines LSM, platelet count and spleen diameter was calculated as described previously: $LSM \text{ (by TE in kPa)} \times \text{spleen diameter (cm)} / \text{platelet ratio (10}^9\text{/L)}$ [8].

Hepatic venous pressure gradient

HVPG measurements were performed under local anesthesia as previously described [13]. A catheter was introduced under ultrasound guidance using the Seldinger technique, then a 7-French balloon catheter was inflated in the right or median hepatic vein to measure the wedged hepatic venous pressure. Occlusion was then confirmed by injection of 5 to 10 mL of iodinated contrast. The free hepatic venous pressure was then obtained. Finally, HVPG was calculated as the difference between wedged and free hepatic venous pressures.

Statistical Analysis

Continuous variables are expressed as means and standard deviations or medians and ranges, and compared using the Student t-test or Mann-Whitney test, when

appropriate. Gaussian distribution was tested using the Kolmogorov-Smirnov test. Comparisons between categorical variables were performed using the Chi-2 test or the Fisher exact test, when appropriate. Correlations were computed with the Pearson correlation coefficient. The discriminative value of LSN and LSM – alone or in combination - for the identification of CSPH was assessed by measuring the area under the receiver operating characteristic (AUROC) curve provided with the corresponding standard deviation. Optimal cut-off values were identified using the Youden index and associated sensitivities, specificities, and positive and negative predictive values (with 95% confidence intervals [CI]) were determined. Comparison between AUROCs was performed by using the DeLong method [14]. Net Classification Index Improvement (NRI) analysis was performed for LSN and LSPS, with LSM as a reference [15]. NRI quantifies how well a new model correctly reclassifies subjects. NRI provides separated indices for patients with and without CSPH, and estimates the overall proportion of correct reclassifications in each group. The performance of non-invasive methods to confirm or exclude CSPH was assessed using previously published cut-off values for the LSN score (exclude <2.50 and rule-in ≥ 3.10) and for LSPS (rule-out <1.08 and rule-in ≥ 2.06) and TE (rule-out <13.6 kPa and rule-in ≥ 21.0 kPa) [8,10,14]. Analyses were performed both on an intention-to-diagnose (including the entire cohort) and per-protocol (including only patients with valid LSM and LSN score) basis. All tests were two-sided and a p value <0.05 was considered to be statistically significant. Statistical analyses and figures were performed by using the SPSS statistical package software (version 24.0; SPSS, Chicago, Ill, USA), GraphPad Prism software (version 7; GraphPad Software, La Jolla, Ca, USA) and Tableau V10.2.0 (Tableau Software Inc, Seattle, Wa, USA).

RESULTS

Study Population

The flowchart of the population is provided in **Figure 1**. One hundred and forty patients underwent both LSN and LSM (109 men [78%], mean age 63±9 years old), including 39 (28%) with CSPH. Most patients had chronic viral hepatitis infection (50 with hepatitis C virus [36%]; 30 with hepatitis B virus [21%]), or alcoholic cirrhosis (47 [34%]).

The LSN score was reliable in 130/140 (93%) patients. LSN measurements were unsuccessful in 10 patients because of patient-related issues in 8 (insufficient adipose tissue to delineate the liver surface in 3 patients and HCC leading to left lobe capsular bulging in 5), or software-related issues (errors in reading the Digital Imaging and Communications in Medicine header with the LSN software in 2 patients). LSN measurements took a mean 165±55 seconds to perform. LSM was reliable in 132/140 patients (94%). Overall, 122/140 patients (87%) had reliable LSN and LSM (91 men [75%], mean age 63±10 years old) measurements, including 36 (30%) with CSPH, and constituted the per-protocol cohort. The characteristics of the intention-to-diagnose and per-protocol populations are provided in **Table 1** and **Supplemental Table 1**, respectively. The characteristics of the excluded patients are provided in **Supplemental Table 2**,

Performance of LSN, LSM and LSPS for assessment of CSPH in the per-protocol cohort

Table 2 and **Figure 2** describe the diagnostic performance of LSN, LSM and LSPS for the diagnosis of CSPH. The mean LSN score in the per-protocol cohort was 2.7±0.4. It was higher in patients with CSPH than in those without, resulting in an

AUROC of 0.87 ± 0.31 (95% CI: 0.80 to 0.93) for the detection of CSPH. The diagnostic performance of LSN was also assessed in the 92 patients who were not included in the previous study by our group, resulting in a similar diagnostic performance [10] (**Supplemental Table 3**).

Median LSM was 14.1 (range 3.2-75.0) kPa. It was higher in patients with CSPH than in those without, resulting in an AUROC of 0.83 ± 0.04 (95% CI: 0.75 – 0.89) for the detection of CSPH.

The mean LSPS value was 1.80 ± 1.50 and it was higher in patients with CSPH than in those without, resulting in an AUROC of 0.85 ± 0.04 (95% CI: 0.78 – 0.91).

Pairwise comparison of AUROCs of LSN, LSM and LSPS for the diagnosis of CSPH showed no significant difference (p values ranging from 0.28 to 0.65). Results were found consistent when focusing on the 83 patients with HCC in Milan (**Table 2**).

Using LSM as the reference for patient classification, the overall NRI for LSN and LSPS was +0.05 and -0.01, respectively. The NRI of patients with CSPH was +0.25 and + 0.06 for LSN and LSPS, respectively. The NRI of patients without CSPH was - 0.20 and -0.07 for LSN and LSPS, respectively.

Although tumor location (i.e. right or left liver) did not significantly influence LSN, LSM or LSPS values in the overall per-protocol population (p=0.06 to 0.53; **Supplemental Table 4**), median LSM values tended to be higher when HCC were located in the right liver lobe (p=0.06). We therefore performed a more detailed analysis presented in **Supplemental Figure 1** and **Supplemental Table 4** and found that in the 13 patients with HCC ≥ 10 cm, CSPH was correctly assessed in 12 (92%) patients with LSN, and in only 5 (38%) patients with LSM and LSPS (p=0.011). The other eight patients were misclassified as having CSPH because of elevated LSM or LSPS values (all > 55 kPa or > 1.5 , respectively). It is interesting to note that all tumors

were located in the right liver (**Supplemental Figure 1**). Detailed comparison of LSN, LSM and LSPS values according to HCC size (i.e. $<$ or ≥ 10 cm) and location, and to the presence of CSPH is provided in **Supplemental Table 4**.

Value of LSN, LSM and LSPS to rule-in or rule-out CSPH in the intention-to-diagnose cohort

In the intention-to-diagnose cohort, the previously proposed LSN cut-off values < 2.5 [10] ruled out the presence of CSPH in 52 patients with a negative predictive value of 100%, and ≥ 3.10 ruled-in CSPH in 25 patients with a positive predictive value of 72% (18/25 patients with CSPH). A total of 63 patients (45%) had either an unreliable or intermediate LSN score (LSN value ≥ 2.5 and < 3.1). These rule-in and rule-out thresholds resulted in 70/140 (50%) correctly classified patients with an error of 9%.

The previously proposed [16] LSM cut-off values < 13.6 kPa ruled-out the presence of CSPH in 63 patients with a negative predictive value of 93% (59 without CSPH), and ≥ 21 kPa ruled-in CSPH in 43 patients with a positive predictive value of 60% (26 with CSPH). A total of 34 patients had either an unreliable or intermediate value (LSM value ≥ 13.6 and < 21 kPa). Rule-in and rule-out thresholds resulted in 85/140 (61%) patients correctly classified with an error of 20%.

The previously proposed [8] LSPS cut-off values < 1.08 ruled-out the presence of CSPH in 69 patients with a negative predictive value of 91% (63 without CSPH), and ≥ 2.06 ruled-in CSPH in 33 patients with a positive predictive value of 70% (23 with CSPH). A total of 38 patients had an unreliable or intermediate LSPS score (LSPS value ≥ 1.08 and < 2.06). Rule-in and rule-out thresholds resulted in 86/140 (61%) patients correctly classified with an error of 15%.

Performance of the combination of LSN and LSPS for estimating CSPH in the intention-to-diagnose cohort

Combining the rule-in and rule-out thresholds for both LSN and LSPS [8,10] successfully stratified patients with an increasing risk of CSPH (**Figure 3**). This combination was chosen because LSPS has been shown to outperform LSM alone for patient classification. Briefly, of the 27 patients with both $LSN \geq 2.50$ and $LSPS \geq 2.06$, 23 (85%) had CSPH. On the other hand, none of the 52 patients with LSN values <2.50 had CSPH, regardless of LSPS values.

Based on these observations, a two-step diagnostic algorithm applying first LSN and then LSPS in the subset of 88 patients with either $LSN \geq 2.5$ or an unreliable LSN was designed. In the latter group ($n=88$), a $LSPS <1.08$ ruled-out CSPH in 39 patients with a negative predictive value of 85% (33 patients without CSPH), while a $LSPS >2.06$ ruled-in CSPH in 27 patients with a positive predictive value of 85% (23 patients with CSPH). Therefore, applying the LSPS score after the LSN measurement correctly reclassified 56/88 patients (64%). Overall, this two-step algorithm had an AUROC of 0.874 (95% CI 0.760-0.949) for the diagnosis of CSPH, and resulted in 108/140 correctly classified patients (77%) with an error of 8% (**Figure 4**). Applying this algorithm to the subset of 91/140 patients with HCC in Milan correctly classified 65/91 (71%) patients with 10% error (AUROC 0.851 [95%CI 0.760-0.942]). Details about the calibration of this model are provided as **Supplemental Material**.

DISCUSSION

The aim of the present study was to compare the diagnostic performance of the quantification of LSN on CT images and LSM measured by TE - alone or in a derived

score - for the diagnosis of CSPH in patients with cirrhosis during the initial preoperative work-up for HCC surgery. Our results show that the feasibility and diagnostic performance of LSN and LSM are similar. Moreover, the combination of tests correctly classified approximately three quarters of the patients as with or without CSPH, and had clinically acceptable error rates.

LSN was initially developed as a non-invasive test for the diagnosis and prognosis of cirrhosis [17,18] with an excellent reproducibility and interobserver agreement [12].

This score reflects the major architectural changes that occur during the development of cirrhosis, including progressive liver fibrosis and the formation of regenerative nodules in the liver [19]. Our group extended the field of application and showed the high diagnostic performance of LSN for detecting CSPH [10]. The present results further validate the diagnostic performance of LSN. Indeed, using the same rule-in and rule-out thresholds (i.e. LSN <2.50 and ≥ 3.10 , respectively) we correctly classified 50% of the patients with 9% error, which is comparable to the 58% of correctly classified patients and the 5% error in the initial publication [10].

While our previous study also showed that the performance of LSN was better than numerous other non-invasive tests, it was not compared to LSM or its derived scores. Several studies have reported that the performance of LSM - measured by transient elastography – is good for the detection of CSPH, with sensitivities and specificities ranging between 88% and 98%, and between 50% and 73%, respectively when applying cut-off values of around 21 kPa (19.0-21.8 kPa) [20-22]. On the other hand, Vizutti et al. also showed a strong correlation between the absence of portal hypertension and LSM < 13.6 kPa (AUROC: 0.99) [23]. LSPS was initially developed for the prediction of high-risk esophageal varices [24]. This simple score using three parameters (LSM, spleen size and platelet count) was proposed to increase the

diagnostic performance of these separate parameters, merging different aspects of the pathogenesis of portal hypertension, including fibrosis, vascular congestion and portal hypertension-induced splenic sequestration. The performance of this score has been shown to be better than LSM alone (AUROC 0.95 vs. 0.88, $p < 0.001$) for the detection of CSPH [25]. Berzigotti et al. proposed comprehensive rule-in and rule-out thresholds for both LSM and LSPS in patients with compensated cirrhosis [8]. It is important to note that the diagnostic performance and feasibilities in the present study were similar between LSN and LSM or LSPS. Thus, in practice we believe that the choice of LSN or LSM/LSPS for the diagnosis of CSPH should be based on the context rather than the diagnostic performance.

CT is not routinely recommended in patients with cirrhosis and LSM/LSPS is more frequently performed. On the other hand, in patients with HCC, cross-sectional imaging, and especially CT, is systematically performed and results show that LSN is a valuable, easy to use tool to estimate CSPH, which may also be determined retrospectively. Although the population in this study only included patients with HCC before resection, we believe it is also representative of patients with compensated cirrhosis, allowing our results to be extrapolated to this group.

Hepatic resection in patients with cirrhosis and portal hypertension is associated with significantly increased mortality and morbidity. [2,7]. Thus, a preoperative evaluation of portal hypertension is recommended, and has been included in the preoperative workup of expert teams [26]. Although measurement of the hepatic venous pressure gradient by invasive transjugular catheter is the reference method, numerous other non-invasive tests are available, which could lead to confusion and a non-standardized approach. The advantage of LSN is that it can be quickly and easily quantified on routine abdominal CT-scan, to be used as a first-line triage test,

allowing further more specific examinations in selected patients. Moreover, LSN had excellent negative predictive value. This justifies our proposal of a two-step algorithm with LSN as the first step. It suggests that patients with low LSN values (i.e. <2.50) may not require additional examinations to exclude CSPH. Applying LSPS to others (i.e. unreliable LSN or $LSN \geq 2.50$) could help identify patients with suspected (LSPS ≥ 1.08) or nearly certain (LSPS ≥ 2.06) CSPH that would require further testing with an HVPG measurement. This algorithm had good performance, but appeared better at ruling-out than at ruling-in CSPH. This should be acknowledged before implementing it in practice. Importantly, results were consistent when focusing on patients with HCC in Milan only, reinforcing its clinical value.

LSN measurements were found to be unreliable in 7% of cases, which is similar to previous studies [10,17,18]. In particular, the presence of exophytic HCC in the anterior left liver lobe resulted in five (4%) unreliable LSN evaluations in our study, but did not affect the LSM measurement. On the other hand, LSM values were significantly increased in patients with large HCC (i.e. $\geq 10\text{cm}$) located in the right liver, resulting in a significant overestimation of CSPH, while LSN was not affected and corrected classified most of these patients. $HCC \geq 10\text{ cm}$ in the right liver lobe should be added to the list of potential causes of false positives of LSM. This suggests that an LSM-based strategy might not be reliable in patients with such large right-sided HCC. In these patients, LSN should probably be favored.

This single center study has certain limitations. First and foremost, its retrospective design comes with possible selection bias. For instance, LSM values were in the lower bound of reported values in cirrhotic patients. Because we included patients with compensated cirrhosis undergoing hepatic resection only. Then, we did not analyze the predictive role of the LSN score for portal hypertension-related

complications such as esophageal varices bleeding or death and post-operative morbidity or mortality because this was beyond the scope of the study. Noticeably, in our group recently showed that preoperative LSN value was associated with severe complication, post-operative liver failure, and clinically significant post-operative liver failure in patients with HCC undergoing resection [27]. Also, there was no external validation cohort. Nevertheless, our study further validates the results of Sartoris et al. [10]. Finally, no sample size calculation was performed.

In conclusion, LSN determined on routine CT scan may be useful for the preoperative detection of CSPH in patients with HCC and compensated cirrhosis. A combination of LSN and LSPS could improve the non-invasive classification of these patients. LSN is probably more relevant in clinical practice as a first-line triage test.

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Tables

Table 1. Intention-to-diagnose study population (n=140)

	Total (n=140)	No CSPH (n=101)	CSPH (n=39)	P Value
Gender (%)				
<i>Male</i>	109 (78)	76 (75)	33 (85)	.23
<i>Female</i>	31 (22)	25 (25)	6 (15)	.23
Mean Age ± SD				
<i>Overall</i>	63 ± 9	63 ± 10	63 ± 9	.91
<i>Male</i>	62 ± 10	62 ± 10	62 ± 9	.87
<i>Female</i>	67 ± 7	67 ± 7	67 ± 4	.94
BMI (kg/m²)	28.9 ± 6.9	29.5 ± 8.2	27.2 ± 3.9	.10
Child-Pugh score (%)				
<i>A</i>	133 (95)	97 (96)	36 (93)	.40
<i>B</i>	7 (5)	4 (4)	3 (7)	
Cause of cirrhosis*				
<i>Hepatitis C virus infection</i>	50 (36)	31 (31)	19 (49)	.05
<i>Hepatitis B virus infection</i>	30 (21)	21 (21)	9 (23)	.76
<i>Alcohol</i>	47 (34)	35 (35)	12 (31)	.67
<i>Nonalcoholic fatty liver disease</i>	25 (18)	19 (19)	6 (15)	.64
Duration between HPVG-LSM and CT (days)	15 ± 11	15 ± 12	14 ± 10	.41
HVPG (mm Hg)	8 ± 4	6 ± 2	14 ± 3	<.001
Hepatocellular carcinoma				
<i>Mean size ± SD (mm)</i>	51 ± 27	57 ± 28	38 ± 19	<.001
<i>Right liver</i>	98 (70)	70 (70)	28 (72)	0.84
<i>Left Liver</i>	42 (30)	31 (30)	11 (28)	
Barcelona Clinic Liver Cancer stage				
<i>Stage 0</i>	26 (19)	14 (14)	12 (31)	.022
<i>Stage A</i>	114 (81)	87 (86)	27 (69)	
Laboratory				
<i>INR</i>	1.1 ± 0.1	1.1 ± 0.1	1.2 ± 0.1	<.001
<i>Serum creatinin (μmol/L)</i>	80 ± 18	80 ± 20	78 ± 13	.59
<i>Serum bilirubin (μmol/L)</i>	14 ± 6	14 ± 7	15 ± 5	.56
<i>Platelet count (G/L)</i>	193 ± 58	211 ± 59	146 ± 38	<.001
<i>Serum albumin (g/L)</i>	35 ± 7	36 ± 6	33 ± 7	.004
<i>Serum AST (x ULN)</i>	1.8 ± 1.1	1.6 ± 1.0	1.8 ± 1.4	.35
<i>Serum ALT (x ULN)</i>	1.6 ± 1.2	1.6 ± 1.3	1.5 ± 1.0	.60
<i>γ-glutamyl transferase (x ULN)</i>	3.5 ± 2.9	3.3 ± 3.0	3.8 ± 3.9	.42
<i>Alcaline phosphate (x ULN)</i>	1.2 ± 0.7	1.1 ± 0.6	1.6 ± 1.1	.002
Non-invasive tests				
<i>Liver surface nodularity</i>	2.68 ± 0.4	2.50 ± 0.3	3.14 ± 0.4	<.001
<i>Largest spleen size (cm)</i>	11.5 ± 1.6	11.1 ± 1.4	12.6 ± 1.5	<.001
<i>Platelets/spleen size</i>	17.7 ± 6.5	20.0 ± 6.4	12.2 ± 4.0	<.001

<i>LSM kPa median (range)</i>	14.2 (3.3-75.0)	10.6 (3.3-75.0)	29.5 (8.8-75.0)	<.001
<i>LSPS</i>	1.78 ± 1.50	1.03 ± 0.76	3.62 ± 2.21	<.001

AST/ALT aspartate aminotransferase/alanin aminotransferase; CSPH: Clinically significant portal hypertension; BMI: Body mass index; HVP: hepatic venous pressure gradient; CT: computed tomography; INR: international normalized ratio; LSM liver stiffness measurement; LSPS: Liver stiffness*(spleen size/platelet count), ULN: upper limit of normal values. Values are expressed as mean and standard deviation unless specified.

* some patients had several causes of cirrhosis

Table 2. Performance of Liver Surface Nodularity (LSN), Liver Stiffness measurement (LSM), and LSPS for the diagnosis of clinically significant portal hypertension in the per-protocol population (n=122) and in patients with HCC in Milan (n=83).

	AUROC	Cut-off values		Se (%) [95%CI]	Sp (%) [95%CI]	PPV (%) [95%CI]	NPV (%) [95%CI]	LR+ (%) [95%CI]	LR- (%) [95%CI]	No. Correctly classified
Per-protocol										
LSN	0.871±0.03	Optimal ^a	> 2.57	100 [91, 100]	63 [50,73]	54 [44, 61]	100 [93, 100]	2.70 [1.82-3.70]	0 [0-0.18]	90/122 (74%)
		Se ≥ 90%	> 2.60	94 [77,99]	66 [52,74]	54 [41,67]	97 [88,99]	2.64 [1.09-3.81]	0.09 [0.01-0.44]	91/122 (75%)
		Sp ≥ 90%	> 2.96	60 [40,77]	90 [81-95]	70 [51,85]	84 [75,91]	6.00 [5.00-15.4]	0.44 [0.24-0.74]	98/122 (80%)
LSM	0.825±0.04	Optimal ^a	> 21.5 kPa	68 [61, 83]	88 [80, 93]	70 [62, 81]	87 [78, 94]	3.09 [3.05-11.9]	0.36 [0.18-0.49]	97/122 (80%)
		Se ≥ 90%	> 13.7 kPa	91 [77,98]	63 [52,73]	49 [37,62]	93 [83,98]	2.46 [1.60-3.63]	0.14 [0.03-0.44]	85/122 (70%)
		Sp ≥ 90%	> 33.0 kPa	46 [29,63]	91 [83,96]	64 [43,82]	79 [70,87]	5.44 [4.14-15.8]	0.59 [0.39-0.86]	93 /122 (76%)
LSPS	0.851±0.04	Optimal ^a	> 1.34	75 [64, 82]	78 [69, 86]	59 [50, 67]	88 [81, 94]	3.40 [2.06-5.86]	0.32 [0.21-0.52]	95/122 (78%)
		Se ≥ 90%	> 0.88	91 [77,98]	60 [49,71]	49 [36,61]	94 [85,99]	2.28 [1.51-3.38]	0.15 [0.03-0.47]	84/122 (69%)
		Sp ≥ 90%	> 2.29	57 [39,74]	91 [83,96]	70 [51,85]	84 [75,91]	6.33 [2.29-18.5]	0.47 [0.270.73]	98/122 (80%)
In Milan										
LSN	0.866±0.04	Optimal ^a	> 2.57	100 [89,100]	65 [52,77]	63 [49-75]	100 [90,100]	2.22 [1.85-4.35]	0 (0-0.21)	65/83 (78%)
		Se ≥ 90%	> 2.66	92 [79,97]	62 [47,75]	67 [54,78]	90 [75,97]	2.42 [1.49-3.88]	0.13 [0.04-0.45]	63/83 (76%)
		Sp ≥ 90%	> 3.10	55 [38,71]	90 [79,95]	77 [65,86]	77 [57,90]	5.50 [1.81-14.2]	0.50 [0.31-0.78]	64/83 (77%)
LSM	0.880±0.04	Optimal ^a	> 21.0 kPa	65 [47,79]	90 [79,95]	81 [69,89]	80 [61,91]	6.5 [2.23-15.8]	0.39 [0.22-0.67]	67/83 (81%)
		Se ≥ 90%	> 10.0 kPa	90 [74-97]	53 [40-66]	51 [39-65]	90 [75-97]	1.91 [1.23-2.20]	0.40 [0.05-0.90]	55/83 (66%)

		Sp ≥ 90%	> 21.0 kPa	65 [47,79]	90 [79,95]	81 [69,89]	80 [61,91]	6.5 [2.23-15.8]	0.39 [0.22-0.67]	67/83 (81%)
LSPS	0.886±0.04	Optimal ^a	> 1.38	74 [57-86]	90 [79-95]	82 [64-92]	85 [73-92]	7.40 [2.71-17.2]	0.32 [0.15-0.54]	69/83 (83%)
		Se ≥ 90%	> 0.86	92 [78-97]	61 [46-74]	64 [51-76]	90 [75-97]	2.24 [1.44-3.73]	0.13 [0.04-0.48]	61/83 (73%)
		Sp ≥ 90%	> 1.38	74 [57-86]	90 [79-95]	82 [64-92]	85 [73-92]	7.40 [2.71-17.2]	0.32 [0.15-0.54]	69/83 (83%)

95% CI. 95% confidence interval; AUROC: Area under receiver operating characteristic; LR+/- Positive / negative likelihood ratios; LSPS: Liver stiffness*(spleen size/platelet count); PPV/NPV positive/negative predictive value; Se/Sp sensitivity/specificity.

^a to maximize the Youden index,

Figure legends

Figure 1: Flowchart of population study. HVPG: Hepatic venous pressure gradient; HCC: Hepatocellular carcinoma; CT: computed tomography; LSN: Liver surface nodularity; LSM: liver stiffness measurement.

Figure 2 Plot of sensitivities and specificities associated with Liver Stiffness Measurement (LSM), Liver Surface Nodularity (LSN) and LSPS for the diagnosis of Clinically Significant Portal Hypertension (CSPH) in the 122 patients with available LSN, LSM and LSPS. Potatoids are centered by couples of sensitivities and specificities associated with optimal diagnostic cut-off values for each test. The cut-off values are indicated in italic. Their shapes represent the associated 95% confidence intervals.

Figure 3: Performance of the combination of Liver Surface Nodularity (LSN) and Liver Stiffness Platelet count to Spleen size ratio (LSPS) for the diagnosis of clinically significant portal hypertension (CSPH). Figure 3A: Performance in the intention-to-diagnose cohort and per-protocol cohort. Figure 3B: Performance of rule-in and rule-out cut-offs of non-invasive variables (LSN, LSM, LSPS) for predicting CSPH. LSN: Liver surface nodularity; LSM: Liver stiffness measurement; CSPH: clinically significant portal hypertension.

Figure 4: Two-step algorithm with liver surface nodularity (LSN) as first step and LSPS as second step in the intention-to-diagnose cohort to rule-in and rule-out patients with clinically significant portal hypertension (CSPH).

303 patients with histologically proven compensated cirrhosis with HVPG measurements performed before liver surgery for HCC from January 2015 to July 2018

Excluded patients: 163

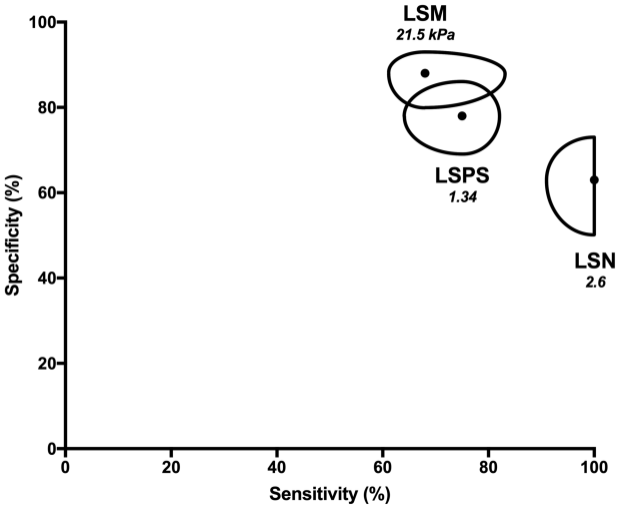
- History of previous major liver surgery: 13
- No Transient Elastography and CT within 30 days: 147
- Portal Vein thrombosis on CT: 3

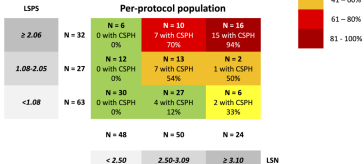
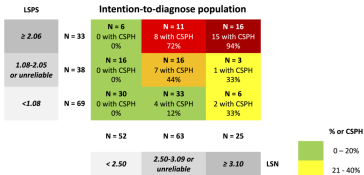
140 patients with HVPG, LS, and CT within 30 days
Intention-to-diagnose population

130 patients with
valid LSN

132 patients with
valid LS

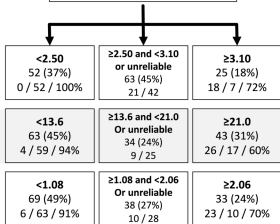
122 patients with both valid LSN and LS
Per-protocol population



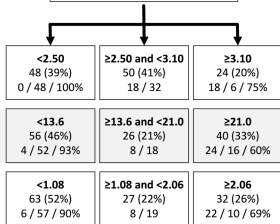


Intention-to-diagnose population

N = 140
CSPH = 39 (28%)

**Per-protocol population**

N = 122
CSPH = 36 (30%)

*Legend*

LSN – LSM – LSPS Value

N of patients (%)

N patients with CSPH / without CSPH / % correctly classified

Intention-to-diagnose population
N=140

1st step - LSN

LSN <2.50
N=52
CSPH=0 (0%)

LSN ≥2.50 or non reliable LSN
N=88
CSPH=39 (44%)

2nd step - LSPS

LSPS <1.08
N=39
CSPH=6 (15%)

LSPS ≥1.08 and <2.06
N=22
CSPH=10 (45%)

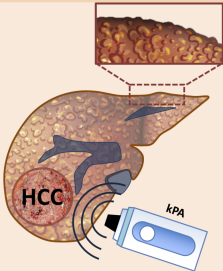
LSPS ≥2.06
N=27
CSPH=23 (85%)

To rule-out CSPH
85/91 (93%)

To rule-in CSPH
23/27 (85%)

N° of correctly classified patients
108/140 (77%)

**140 patients with cirrhosis undergoing hepatic resection for HCC
39 (28%) with Clinically Significant Portal Hypertension**



*Liver Surface Nodularity
on CT images*

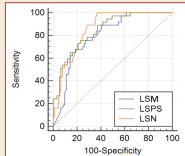
93%

Similar Feasibility

94%

*Liver Stiffness Measurement
By transient Elastography*

Similar performance to detect CSPH



**Combining LSN and LSPS
correctly classified
108/140 (77%)
with 7% error**