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

Alexandra Souhami, Riccardo Sartoris, Pierre-Emmanuel Rautou, François Cauchy, Mohamed Bouattour, François Durand, Valerio Gianelli, Elia Gigante, Laurent Castera, Dominique Valla, Olivier Soubrane, Valérie Vilgrain, Maxime Ronot

Table of contents

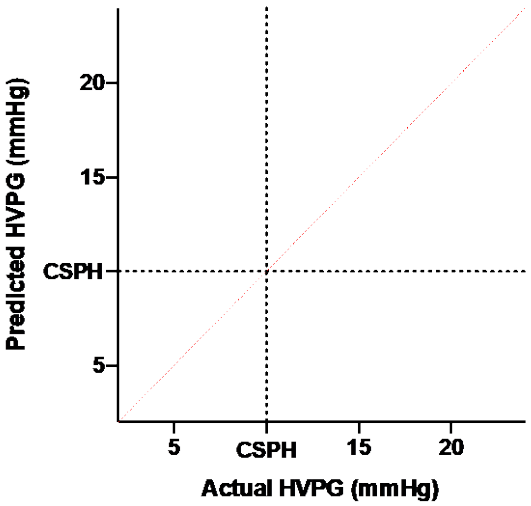
**Supplementary methods**

**Calibration of the two-step algorithm**

The two-step algorithm is not a linear model *per se.* Indeed, the algorithm provides three possible outputs:
- no CSPH
- inconclusive
- CSPH
Therefore, no calibration plot can be provided.

Nevertheless, adopting a different approach, we performed a multiple linear regression using HVPHG as continuous dependent variable, and LSN and LSPS as variables in the model. The resulting equation for 'predicting HVPG' is:
Predicted HVPG = 3.83*LSN + 0.97*LSPS – 3.94.

This model is well calibrated (goodness of fit p=0.52), as shown by the following plots.



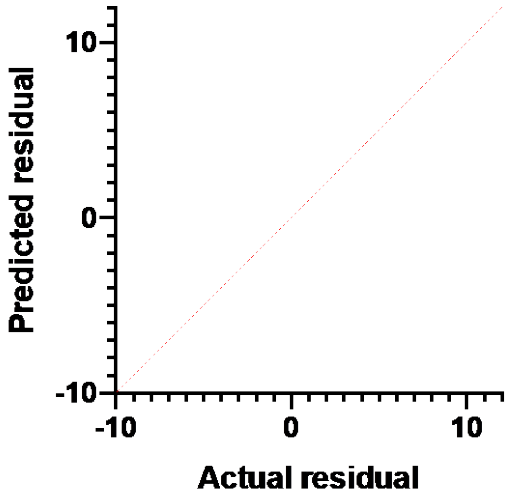



**Table S1. Per-protocol study population (n=122)**

| | Total (n=122) | No CSPH (n=86) | CSPH (n=36) | P Value |
|---|---|---|---|---|
| **Gender (%)** | | | | |
| *Male* | 91 (75%) | 61 (71%) | 30 (83%) | .15 |
| *Female* | 31 (25%) | 25 (29%) | 6 (17%) | .15 |
| **Mean Age ± SD** | | | | |
| *Overall* | 63 ± 10 | 63 ± 10 | 62 ± 9 | .56 |
| *Male* | 61 ± 10 | 62 ± 10 | 61 ± 10 | .84 |
| *Female* | 67 ± 7 | 67 ± 8 | 67 ± 4 | .94 |
| **BMI (kg/m$^2$)** | 27.3 ± 5.0 | 27.3 ± 5.3 | 27.3 ± 4.0 | 1.0 |
| **Child-Pugh score (%)** | | | | |
| *A* | 117 (96) | 84 (98) | 34 (95) | 0.58 |
| *B* | 5 (4) | 2 (2) | 2 (5) | |
| **Duration between HPVG-LSM and CT (days)** | 15 ± 11 | 15 ± 12 | 14 ± 10 | .66 |
| **HVPG (mm Hg)** | 8 ± 4 | 6 ± 2 | 14 ± 3 | <.001 |
| **Hepatocellular carcinoma** | | | | |
| *Mean size ± SD (mm)* | 50 ± 27 | 56 ± 28 | 37 ± 19 | <0.001 |
| *Right Liver* | 92 (75) | 65 (76) | 27 (75) | 0.52 |
| *Left Liver* | 20 (25) | 31 (24) | 9 (25) | |
| **Laboratory** | | | | |
| *INR* | 1.1 ± 0.1 | 1.1 ± 0.1 | 1.2 ± 0.1 | <.001 |
| *Serum creatinin (µmol/L)* | 80 ± 18 | 81 ± 21 | 78 ± 13 | .46 |
| *Serum bilirubin (µmol/L)* | 14 ± 6 | 14 ± 7 | 15 ± 5 | .57 |
| *Platelet count (G/L)* | 193 ± 59 | 213 ± 60 | 146 ± 36 | <.001 |
| *Serum albumin (g/L)* | 38 ± 6 | 39 ± 6 | 35 ± 7 | <.001 |
| *Serum AST (x ULN)* | 1.9 ± 1.3 | 1.6 ± 0.8 | 1.7 ± 2.5 | .74 |
| *Serum ALT (x ULN)* | 1.4 ± 0.9 | 1.3 ± 0.8 | 1.5 ± 0.9 | .24 |
| *γ-glutamyl transferase (x ULN)* | 3.2 ± 2.6 | 3.0 ± 2.4 | 3.7 ± 2.0 | .20 |
| *Alcaline phosphate (x ULN)* | 1.2 ± 0.7 | 1.1 ± 0.6 | 1.5 ± 1.0 | .01 |
| **Non-invasive tests** | | | | |
| *Liver surface nodularity* | 2.69 ± 0.4 | 2.5 ± 0.3 | 3.15 ± 0.4 | <.001 |
| *Largest spleen size (cm)* | 11.5 ± 1.6 | 11.1 ± 1.4 | 12.6 ± 1.4 | <.001 |
| *Platelets/spleen size* | 17.6 ± 6.6 | 19.9 ± 6.5 | 12.2 ± 4.0 | <.001 |
| *LSM kPa median (range)* | 14.1 (3.2-75.0) | 10.6 (3.2-75.0) | 29.5 (8.8-75.0) | <.001 |
| *LSPS* | 1.80 ± 1.50 | 1.07 ± 0.78 | 3.52 ± 2.06 | <.001 |

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

**Table S2. Comparison of included (n=140) and excluded (n=147) patients. Excluded patients did not undergo transient elastography for Liver stiffness Measurement or CT examination within 30 days before or after the Hepatic Venous Pressure Gradient measurement.**

| | Included (n=140) | Excluded (n=147) | P Value |
|---|---|---|---|
| **Gender (%)** | | | |
| *Male* | 109 (78) | 109 (74) | .43 |
| *Female* | 31 (22) | 38 (26) | |
| **Mean Age ± SD** | | | |
| *Overall* | 63 ± 9 | 59 ± 11 | **.001** |
| **BMI (kg/m$^2$)** | 28.9 ± 6.9 | 27.1 ± 7.2 | .03 |
| **Child-Pugh score (%)** | | | |
| *A* | 133 (95) | 141 (96) | .68 |
| *B* | 7 (5) | 6 (4) | |
| **Barcelona Clinic Liver Cancer stage** | | | |
| *Stage 0* | 26 (19) | 35 (24) | .31 |
| *Stage A* | 114 (81) | 112 (76) | |
| **Cause of cirrhosis*** | | | |
| *Hepatitis C virus infection* | 50 (36) | 68 (46) | **.009** |
| *Hepatitis B virus infection* | 30 (21) | 24 (16) | .28 |
| *Alcohol* | 47 (34) | 56 (38) | .48 |
| *Nonalcoholic fatty liver disease* | 25 (18) | 15 (10) | .05 |
| **HVPG (mmHg)** | 8 ± 4 | 9 ± 5 | .06 |
| **Laboratory** | | | |
| *Platelet count (G/L)* | 193 ± 58 | 179 ± 68 | .06 |
| *Serum albumin (g/L)* | 35 ± 7 | 34 ± 8 | .26 |
| *Serum AST (x ULN)* | 1.8 ± 1.1 | 1.7 ± 1.5 | .52 |
| *Serum ALT (x ULN)* | 1.6 ± 1.2 | 1.8 ± 1.6 | .23 |
| *γ-glutamyl transferase (x ULN)* | 3.5 ± 2.9 | 3.4 ± 2.7 | .76 |
| *Alcaline phosphate (x ULN)* | 1.2 ± 0.7 | 1.2 ± 0.4 | 1.0 |

AST/ALT aspartate aminotransferase/alanin aminotransferase; BMI: Body mass index; HVPG: hepatic venous pressure gradient; CT: computed tomography; ULN: upper limit of normal values. Values are expressed as mean and standard deviation unless specified.
* some patients had several causes of cirrhosis

**Table S3. Analysis of the 92 patients who were not included in the previous study by Sartoris et al. [1]**

| LSN | < 2.5 (N=26) | ≥ 2.5 and < 3.10 (N=48) | ≥ 3.10 (N=20) |
|---|---|---|---|
| **No CSPH (N=66)** | 26 | 34 | 7 |
| **CSPH (N=26)** | 0 | 12 | 13 |
| **Correctly classified** | 26 (100%) | | 13 (65%) |

LSN: Liver surface nodularity; CSPH: Clinically significant portal hypertension.

**Table S4.** LSN, LSM, and LSPS values according to the size and location of hepatocellular carcinoma and to the presence of CSPH in the 122 patients with available LSN, LSM and LSPS

| | **LSN** | | | **LSM (kPa)** | | | **LSPS** | | |
|---|---|---|---|---|---|---|---|---|---|
| **HCC location** | **Left Liver** (N=30) | **Right Liver** (N=92) | **P value** | **Left liver** (N=30) | **Right Liver** (N=92) | **P value** | **Left Liver** (N=30) | **Right Liver** (N=92) | **P value** |
| **Overall** | 2.68 ± 0.55 | 2.69 ± 0.52 | 0.91 | 10.6 (7.2-20.1) | 14.4 (8.8-32.0) | 0.06 | 1.38 ± 1.87 | 1.89 ± 2.10 | 0.24 |
| *HCC < 10 cm* | 2.68 ± 0.55 (n=30) | 2.73 ± 0.55 (n=79) | 0.58 | 10.6 (7.2-20.1) (n=30) | 10.5 (6.8-15.9) (N=79) | 0.36 | 1.38 ± 1.87 (n=30) | 1.72 ± 2.12 (N=79) | 0.46 |
| *HCC ≥ 10 cm* | - | 2.44 ± 0.21 (n=13) | - | - | 72.0 (38.3-75.0) (N=13) | - | - | 2.88 ± 1.77 (N=13) | - |
| *p-value < vs. ≥ 10cm* | - | 0.061 | | - | **<0.001** | - | | 0.07 | |
| **CSPH (N=36)** | 3.26 ± 0.49 (N=9) | 3.11 ± 0.51 (N=27) | 0.45 | 27.0 (12.0-39.4) (N=9) | 34.4 (19.1-52.3) (N=27) | 0.32 | 3.04 ± 2.77 (N=9) | 3.68 ± 2.66 (N=27) | 0.53 |
| *HCC < 10 cm* | 3.26 ± 0.49 (N=9) | 3.16 ± 0.52 (N=24) | 0.48 | 27.0 (12.0-39.4) (N=9) | 31.6 (18.3-47.0) (N=24) | 0.37 | 3.04 ± 2.77 (N=9) | 3.39 ± 2.48 (N=24) | 0.42 |
| *HCC ≥ 10 cm* | - | 2.69 ± 0.10 (N=3) | - | - | 72.0 (20.5-75.0) (n=3) | - | - | (N=3) | - |
| *p-value < vs. ≥ 10cm* | - | 0.10 | | | 0.24 | | | 0.85 | |
| **No CSPH (N=86)** | 2.43 ± 0.35 (N=21) | 2.52 ± 0.42 (N=65) | 0.38 | 8.0 (6.9-15.6) (N=21) | 11.2 (6.9-19.9) (N=65) | 0.07 | 0.68 ± 0.49 (N=21) | 1.20 ± 1.28 (N=65) | 0.07 |
| *HCC < 10 cm* | 2.43 ± 0.35 (N=21) | 2.55 ± 0.45 (N=55) | 0.31 | 8.0 (6.9-15.6) (N=21) | 10.5 (6.8-15.9) (N=55) | 0.52 | 0.68 ± 0.49 (N=21) | 0.84 ± 0.82 (N=55) | 0.24 |
| *HCC ≥ 10 cm* | - | 2.36 ± 0.18 (N=10) | - | - | 72.80 (46.0-75.0) (N=10) | - | - | 2.72 ± 1.65 (N=10) | - |
| *p-value < vs. ≥ 10cm* | - | 0.22 | | - | **<0.001** | **-** | | **<0.001** | |

HCC: Hepatocellular carcinoma; LSM: Liver Stiffness Measurement; LSN: Liver surface nodularity; LSPS: Liver stiffness*spleen size/platelet count.
CSPH: Clinically significant portal hypertension.
Significant p values are bold
LSM is provided as median and IQR, LSN and LSPS are provided as means and standard deviations

**Fig. S1. LSN, LSM and LSPS values according to the size and location of HCC, and to the presence of CSPH.**

Each graph plots LSN (A), LSM (B) and LSPS (C) values (y-axis) according to the size of HCC (x-axis). HCC location is represented by different forms. Presence of CSPH is shown by large forms, and absence of CSPH by small ones. Graph A shows that LSN values are not affected by the size or location of HCC, whatever the CSPH status. Graph B and C show that among patients with HCC ≥ 10cm located in the right liver (n=13), a subset have high LSM (> 55 kPa) and LSPS values (> 1.50) (n=10, circle). In this subgroup, 8/10 (80%) patients without CSPH are misclassified as having CSPH.

HCC: Hepatocellular carcinoma; LSM: Liver Stiffness Measurement; LSN: Liver surface nodularity; LSPS: Liver stiffness*spleen size/platelet count. CSPH: Clinically significant portal hypertension. Optimal cut-off values are shown by the horizontal dashed lines. Only the largest tumor per patient is considered here.

**Fig. S1A**

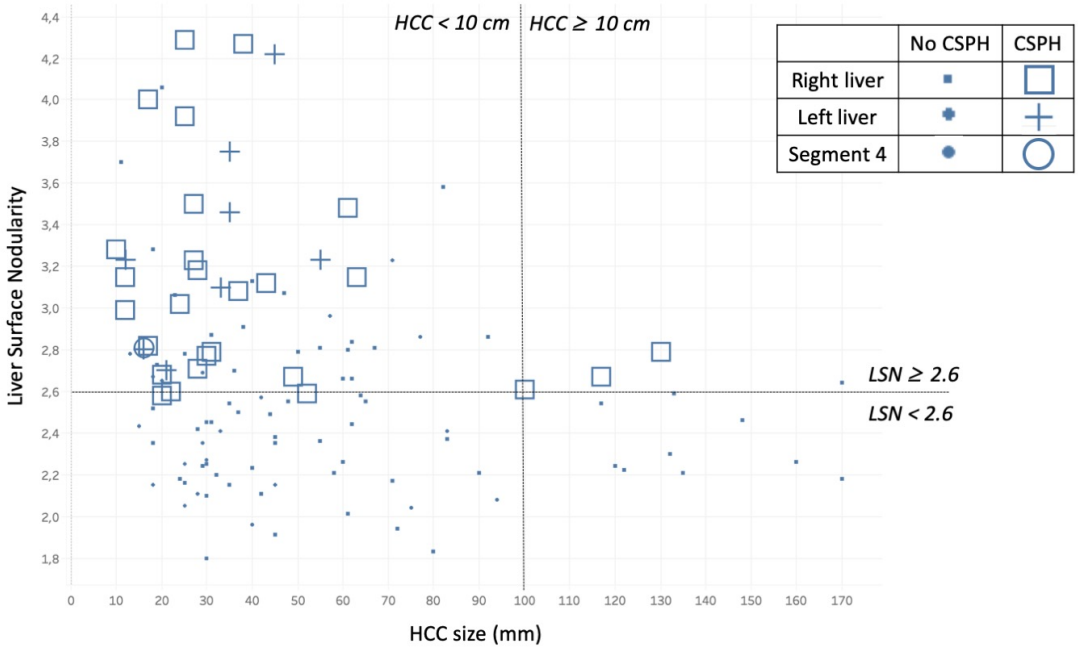


**Fig. S1B**

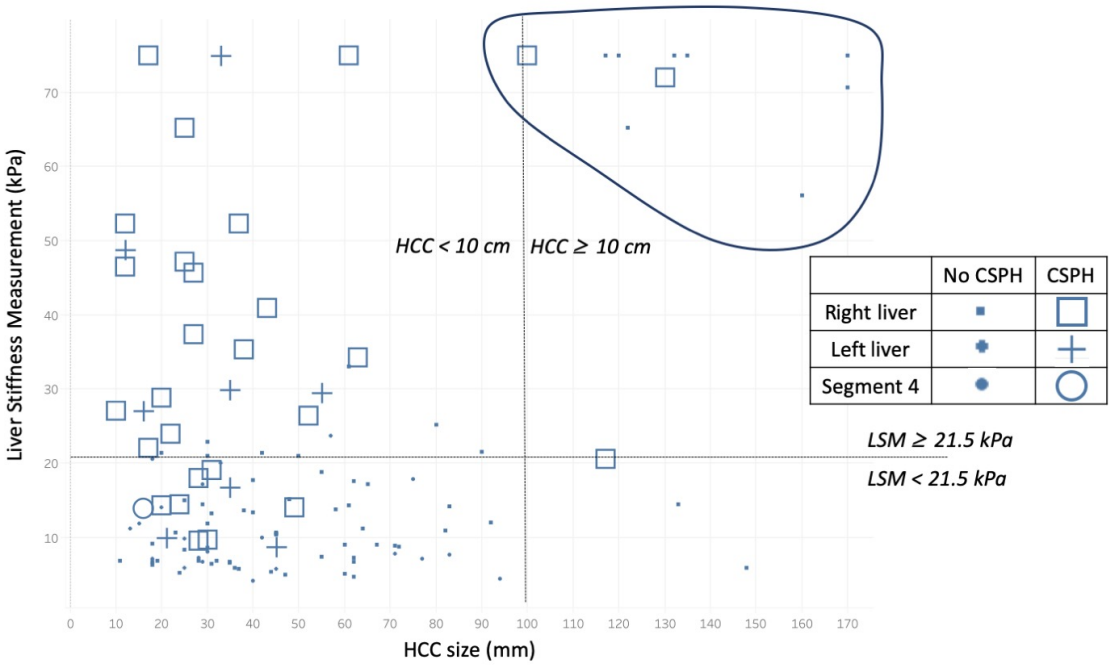
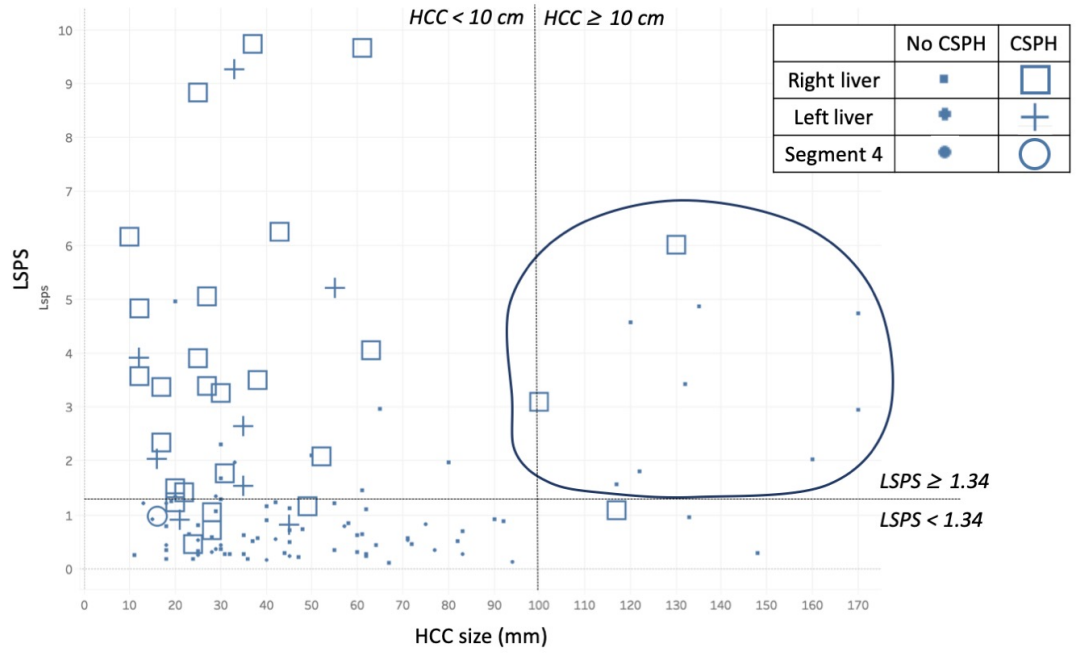



**Fig. S1C**



**REFERENCE**

1. Sartoris R, Rautou PE, Elkrief L, Pollorsi G, Durand F, Valla D, et al. Quantification of Liver Surface Nodularity at CT: Utility for Detection of Portal Hypertension. Radiology 2018;289:698–707. doi:10.1148/radiol.2018181131.