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Spleen Volumetry and Liver Transient Elastography: Predictors of Persistent Post-hepatectomy Decompensation in Patients with Hepatocellular Carcinoma

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E. Vibert: Concept and Design. Writing of Article.

ABSTRACT

Background: Post-hepatectomy decompensation (PHD) remains a frequent and poor outcome after hepatectomy, but its prediction is still inaccurate. Liver Stiffness Measurement (LSM) can predict PHD, but there is a so-called “grey zone” that requires another predictor. Because splenomegaly is an objective sign of portal hypertension, we hypothesized that spleen volumetry (SV) could help in the better identification of patients at risk.

Methods: Patients with hepatocellular carcinoma who underwent hepatectomy in our tertiary center between August 2014 and December 2017 were reviewed. The primary endpoint was to determine if the SV and LSM were independent predictors of PHD, and secondarily, to determine if they were synergistic through a theoretic predictive model.

Results: One hundred and seven patients were included. The median follow-up time was 3 months [3-5]. Postoperative 90-day mortality was 4.7%. By multivariate analysis, LSM and SV predicted PHD. The LSM had a cut-off point of 11.6kPa (area under receiver operating curve [AUROC] = 0.71 CI 95% 0.71-0.88, Sensitivity: 89%, Specificity: 47%). The SV cut-off point was 381.1cm³ (AUROC = 0.78 CI 95% 0.77-0.93, Sensitivity: 55%, Specificity: 91%). The SV improved prediction of PHD, because use of the SV increased sensitivity (from 62% to 97%) and NPV (from 96 to 100%) along with a negligible decrease in specificity (from 96.7 to 93.4) and PPV (from 64 to 59%), (p=0.003).

Conclusions: An SV (>380cm³) and LSM (>12kPa) are non-invasive, independent, and synergistic tools that appear to be able to predict PHD. The importance of this finding is that these measurements may help to anticipate PHD and possibly be used to direct alternative treatments to resection.

Key words: *liver failure; volumetry; liver stiffness; spleen volumetry; hepatocellular carcinoma*

INTRODUCTION

Hepatocellular carcinoma (HCC), is the most common primary neoplasm of the liver, can be managed via many different treatment modalities.(1) Operative treatment that includes either liver resection and transplantation, is the most effective treatment; however, these options may not be applicable, appropriate, or safe in all patients. The biologic behavior of neoplasm and the patients' own clinical characteristics play a preeminent role in the selection process (i.e. tumor burden, liver function, degree of portal hypertension, and patient performance status).(1,2)

Although current perioperative management protocols of HCC have decreased the post-operative mortality rates to levels <5%.(3,4), morbidity after a hepatectomy remains a major concern, especially liver failure.(5,6) Amongst the definitions of post-hepatectomy liver failure (PHLF), the most commonly used are the ISGLS consensus(7) and the "50:50 criteria"(8). Depending on the definition and grading, the presence of PHLF can lead to death in of up to 60%of such patients with postoperative liver failure.(4) Clinical manifestations (i.e. ascites, jaundice, or encephalopathy) that develop or persist more than 3 months postoperatively after liver surgery are known as persistent post-hepatectomy decompensation (PHD)(9) and can appear even in the absence of early post-operative PHLF criteria. The incidence of PHD in patients with HCC who undergo liver resection is about 18%.(9) depending on the severity of underlying liver disease or the extent of resection Regardless of its cause, hepatic decompensation is a crucial event in the history of cirrhotic patients, which negatively impacts their survival and involves a mortality rate that can vary from 20% to 75%.(10)

Of relevant implication, PHD is more frequent in patients with clinically important portal hypertension(11) and is a well-known risk factor of morbidity and mortality after hepatic

resection(12). The preoperative measurement of hepatic venous pressure gradient (HVPG) is the gold standard to diagnose this entity and values <10mmHg are considered appropriate for resection(13). Currently, the presence of clinically important portal hypertension as a contraindication for hepatectomy h is a subject of considerable debate(14–18) and its sole presence should not preclude liver resection(1,17,19). Multiple studies have demonstrated that patients with clinically important portal hypertension can be operated with comparable rates of morbidity and mortality to those without clinically important portal hypertension (20–22). Nevertheless, HPVG remains the gold standard for careful patient selection.

Liver Stiffness Measurement (LSM) by Transient Elastography (TE) is a recognised, non-invasive test for the diagnosis of cirrhosis that has been proposed to predict PHLF(23) and PHD.(24,25) But there is a so-called “grey zone” (12 to 22kPa), where the prediction of outcomes remains challenging and requires the addition of another predictor of PHD. Splenomegaly is a clinical sign of portal hypertension(26–28) that is associated with hemodynamic changes in the portal territory, cytokine release(29), liver fibrosis, and decreased functional reserve. Therefore, a reliable, non invasive measure of portal hypertension and cirrhosis could help in identifying patients classified as “*borderline compensated*”. In these patients, additional stress factors such as a hepatectomy become the trigger for decompensation. Thus, we hypothesized that the measurement of spleen volume for the prediction of PHD could improve the accuracy of LSM alone in these cases.

This study had the objective of assessing this predicament. First, we attempted to determine if the spleen volume (SV) and LSM were independent predictors of PHD, and then, through a theoretic predictive “decision tree” model, to establish if these factors could have a synergistic effect and decrease this “grey zone”.

PATIENTS AND METHODS

We reviewed all patients with a diagnosis of HCC who underwent a hepatectomy between August 2014 and December 2017 at our tertiary centre. Operative variables (intraoperative data and TE results) were collected prospectively. Epidemiologic and biologic variables as well as SV data were abstracted retrospectively into a database. Patients with lacking data (particularly TE, computed tomography of the abdomen, and preoperative biologic tests) were excluded. Nine patients were excluded, because LSM was not accurate because the liver parenchyma was replaced by a large tumor in the region of interest. Informed consent was signed by all patients in compliance with the Helsinki declaration. All cases were included notwithstanding their liver status (presence or absence of cirrhosis) nor the operative approach (open or laparoscopic surgery).

We specifically analysed the following parameters: the LSM, the controlled attenuation parameter (CAP), and the SV. Post-operative variables were collected until postoperative (POD) 90, and the last follow-up was recorded on July 2018.

Spleen Volumetry

All patients included in this study had a pre-operative computed tomography (CT) or magnetic resonance imaging (MRI) performed within a three-month period prior to operation. These images were stored in the DICOM format and were exported retrospectively from the imaging archives to the Myrian[®] volumetry software (Intrasense, Montpellier, France). The portal phase was preferred to determine the spleen volume, and the region of interest was semi-automatically delimited (see **Figure 1a-b**). When the semi-automatic delimitation of the region of interest extended beyond the spleen, a single operator (RF) corrected the region

of interest manually. The dedicated software returned the volumetry in cubic centimetres (cm³).

Transient Elastography

All the reported patients underwent a TE that was performed by either a radiologist or a dedicated nurse. The patients were placed in the supine position with maximum abduction of the right arm with the intention of better evaluating the right liver through the intercostal space and obtaining a thicker cut (6cm minimum) void of large vessels or neoplasm. From each patient, 10 successful measurements were obtained, and the median value was logged. The equipment used for this study was the FibroScan Touch502 with M/XL probes (Echosens, Paris, France) and the results were expressed in kilopascals (kPa). All patients underwent operation within two weeks from when the measurements were performed. The resulting LSM determined the parenchymal fibrosis.

The Controlled Attenuation Parameter (CAP), another modality obtained by Transient Elastography and used to determine the grade of steatosis, was collected systematically and analysed (results expressed in dB/m).

Hepatectomy

All patients had a preoperative liver function assessment, (i.e. Child-Pugh Score, MELD score), imaging, and TE. Determined on a case-by-case decision during multi-disciplinary sessions, a few patients were considered to generally not candidates for operative intervention when any of the following items were found: platelet count of <80,000/mm³, MELD score >12, >2 HCCs, portal vein tumor thrombosis (macrovascular), ICG-R15>15%, or a poor general overall physical status. In rare and selected cases, these thresholds could have been crossed.

If a patient did not have a sufficient liver remnant, a portal vein embolization (PVE) was performed(30). Patients for whom tumors were superficially located in the inferior-medial or lateral sections preferentially underwent laparoscopic surgery, whereas patients with large tumors (>5cm), when the tumour was located more deeply, or when it was in the posterior-superior segments, usually underwent open surgery.

The abdominal cavity was carefully explored to rule out the presence of extrahepatic disease. An intraoperative ultrasonography was performed routinely; and intermittent pedicle clamping was performed in the majority of cases. For parenchymal transection, different energy devices were used, such as bipolar forceps, ultrasonic dissector (CUSA Excel+, Valley Lab Inc, Boulder, USA), and the Ligasure (Medtronic, USA) or the Thunderbeat® (Olympus, Tokyo, Japan) for laparoscopic approach. The goal of the liver resection was to obtain a clean operative margin of at least 2cm,(31) or a full anatomic resection when possible(32). The first control (CT) was performed on POD 7. Minor hepatectomies are defined as resection of ≤ 2 segments.

Follow-up

Morbidity and mortality were recorded throughout the 90 days of follow-up, which was discontinued when the patient did not exhibit any of the symptoms throughout the 90 days or if the patient returned to her/his primary care provider. If hepatic decompensation was present after POD 90, it was considered a PHD. PHLF was defined by the “50:50 criteria”(8) (serum bilirubin $>50\mu\text{mol/L}$ and prothrombin time $<50\%$ on POD 5); post-hepatectomy decompensation was defined by the presence of any of the following signs: ascites (determined clinically or detected by ultrasonography or CT), jaundice (determined clinically) or encephalopathy. Follow-up CTs were obtained at 1- and 3-months post resection

simultaneously with the measurements of alpha fetoprotein (AFP). Patients who exhibited ascites during the post-operative period were managed medically with aldactone \pm furosemide and albumin infusion as deemed necessary; if these measures were not effective, a paracentesis was performed until all the ascitic fluid was drained. These patients were followed-up every 2 weeks. Liver transplant was considered when there was no resolution of the decompensation after 6 months, unless the transplantation procedure was contraindicated.

Statistical analysis.

The continuous variables were reported as median (range) and categorical variables as counts (percentage). Variables with missing data were excluded from analysis. The Mann-Whitney U test was used for the analysis of continuous variables. The Chi-Square or Fisher's exact tests (when appropriate) were used for qualitative variables.

Parameters with a $p < 0.05$ were included for binary logistic regression (backward elimination) to determine independent factors of PHD. Receiver operating characteristic (ROC) analysis was performed to determine the cut-off points of statistically significant variables ($p < 0.05$) along with their respective sensitivity, specificity, anerepositive and negative predictive values (PPV and NPV, respectively).

As secondary endpoint, a decision tree model was proposed (using clinically relevant variables) after sampling through the bootstrap technique (random of 1000 repetitions). Afterwards, the data was divided into two groups: a training group (with 70% of all cases) and a validation group (remaining 30%) following Pareto's Principle(33,34). The decision tree method is a predictive model used widely for classification purposes. It is a non-parametric classification method composed of two parts: the nodes (input variables) and the rules (decision outcomes)(35,36). The concept of this method of machine learning is to draw a

flowchart with a root node on top with a determining question (variable value) and two branches (yes or no). If a given value satisfies a new question, then a node is created. This arrangement repeats itself until the leaf node is determined (final result). This method was selected due to its advantages compared to conventional methods(37) that can be used in a complementary fashion to logistic regression as well (38). The decision tree provides an easy interpretation and flexibility at the time of capturing and classifying the nonlinear behaviors of the data, which are more frequent in daily clinical practice.

Finally, the values of sensitivity, specificity, and PPV and NPV were obtained from the validation group. In order to obtain the differences in the diagnostic ability of the model with and without spleen volumetry, the ROC curves were obtained and compared. In this setting, the sensitivity, specificity, and PPV and NPV were obtained, and the ROC curves were compared using De Long's test. The data were analysed using the following statistical software applications: SPSS v21.0 (IBM Corp, NY, USA) and R (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Preoperative and operative characteristics (Table 1).

Among the 208 patients resected for HCC during the study period, 107 patients had complete data and were included in the analysis. Of these, 84 were male and 23 were female, with a median age of 68 (31-87) years. Fifty-eight percent of patients were Child-Pugh A. The median MELD score was 8 [6-20]; 68 had a score between 6 and 8 points. Viral hepatitis (B and/or C) was the most common cause of chronic liver disease. Before hepatectomy, 10 patients (9.3%) underwent PVE.

The median LSM was 12kPa [3.4-69], and the median spleen volume was 186cm³ [53.9-1,528]. Laparoscopic resections were performed in 34.6% of patients (n=37) and minor hepatectomies were performed in 80 patients (74.7%). Specifically, partial hepatectomies were completed in 33 patients, anatomic segmentectomies, bi-segmentectomies and left lateral sectionectomies were accomplished in 32, 14 and one patient respectively (n=80). The median follow-up time was 3 months [3-5]. Barring the deceased patients, the postoperative follow-up extended beyond 90 days.

Pathologic and postoperative outcomes (Table 2).

The median number of HCC tumors was 1 (1-6) and the average tumour size was 3.5cm [0.7–32]; METAVIR scores of F0-F2 and F3-F4 were present in 32.7% and 67.3% of cases respectively (formal cirrhosis F4 in 57.3%). The median duration of hospital stay was 7 days [6- 11]. Severe morbidity (Clavien-Dindo \geq III) was observed in 18 patients (16.8%). Twenty-four patients (22.4%) developed hepatic decompensation during the hospital stay, four (3.7%) of whom fitted the “50:50 criteria” for PHLF, 9 patients (8.4%) persisted after three months with HD. Of note, only one of these patients had PHLF.

There were five postoperative deaths before POD 90 (4.7%); two of these patients had evident hepatic decompensation. The first patient had ascites followed by an anastomotic leak of an ileocolic anastomosis that resulted in peritonitis; and the second patient had ascites, jaundice, and encephalopathy followed by pneumonia and respiratory failure. The other 3 patients died with causes unrelated to hepatic decompensation. One patient suffered of decompensated chronic kidney disease and died after being discharged from a geriatric center, a second patient went into cardiogenic shock with subsequent multi-organ failure ,and the third patient died of an undetermined cause (a cardiac event is suspected).

All patients who developed with PHD (n=9) had a METAVIR score of F3-F4. Major hepatectomies were performed in three of these 9 patients. Ascites, the most common manifestation that categorized the designation of PHD was managed with diuretics and albumin. It was noteworthy that three of them required draining paracentesis, another required placement of a drain because of infection of the ascitic fluid. One patient required a repeat laparotomy because of suspicion of peritonitis. Two patients developed jaundice that resolved with supportive measures and one patient was diagnosed with encephalopathy that resolved after 6 days with clinical management that included lactulose enemas. Of the 9 patients diagnosed with PHD, only one received a liver transplant.

Postoperative events, such as a greater hospital stay and hospital readmissions, were more likely to occur in patients with PHD. Of particular importance, none of the patients discharged without evidence of any hepatic decompensation developed PHD afterwards. Other comparative postoperative outcomes are presented in **Table 3**.

Predictors of PHD (Table 4).

Univariate analysis determined that the following markers were potential risk factors for PHD: hemoglobin, platelet count, total bilirubin, LSM, and SV. The etiology of HCC was not a risk factor for PHD ($p=0.504$) nor previous PVE ($p=0.138$)

Hemoglobin, LSM, and SV were identified as preoperative risk factors of PHD by binary logistic regression analysis. The LSM had a cut-off point of 11.6kPa (AUROC 0.71 CI 95% 0.71-0.88), with a sensitivity of 89%, specificity of 47%, and a PPV of 14% and an NPV of 98% (**Fig. 2**). The SV showed a cut-off point of 381.1cm³ (AUROC 0.78 CI 95% 0.77-0.93), with a sensitivity of 55%, a specificity of 91%, and a PPV of 38.5% and NPV of 96% (**Fig. 3**). The CAP values were not an independent predictor for PHD ($p=0.984$).

The decision tree model was performed using SV and LSM; the ROC curves with SV (AUROC 0.983) and without SV (AUROC 0.889) were obtained (**Fig. 4**) and compared with the De Long's test ($p=0.003$). If SV was added in the model (**Table 5**), there was an increase in both the sensitivity (from 62% to 97%) and the NPV (from 96 to 100%) but with a small decrease in both specificity (from 96.7 to 93.4) and the PPV (from 64 to 59%); we maintain that these decreases might be interpreted as negligible if the gain of sensitivity is considered. Noteworthy, the hemoglobin level was not included in the decision tree, because many factors could have influenced this value (i.e chronic anemia, gastrointestinal bleeding of variceal origin, etc).

DISCUSSION

According to the presented data, Spleen Volumetry and Liver Stiffness Measurements appear to be potentially important, non-invasive tests with independent and synergistic ability to predict PHD with cut-off values of 380cm³ and 12kPa, respectively.

The present study shows the findings of a recent and prospectively followed cohort in a tertiary center that manages a high volume of patients with liver disease in which a wide array of therapies is available. Among them, laparoscopic liver resections (35% in the present cohort) are performed frequently, but neither laparoscopy nor minor resections prevented the occurrence of PHD. Of note, 2 of 3 patients who underwent major hepatectomy and developed PHD had both predictors (LSM and SV), while 5 of the other 6 patients who had a minor resection followed by PHD had both criteria.

All these patients were scheduled for hepatectomy after multi-disciplinary meetings and a case-by-case evaluation including when available the ICG clearance(39)., however, this variable had to be excluded from analysis due to the larger number of missing data points (not all patients had an ICG-R15 as part of their assessment) and in those patients who did have the test, it was part of the selection criteria for hepatectomy so its prognostic impact could not be assessed objectively (low range of ICR R15 values in the cohort). In spite of such a careful evaluation of patients and a discussion of their cases, nine patients developed PHD. This finding justifies our search of a new predictor (SV).

The inherent limitations of this study are related to the small number of patients who developed the primary end point of the study-PHD compounded by the careful patient selection using the standard criteria. This low prevalence also determined that laparoscopic and open approaches were analysed together despite the proven benefits of laparoscopic surgery in relation to ascites(22,40) and PHLF(41,42). Another limitation was that not all

patients had preoperative measurements of HPVG. Nevertheless, a previous study from our group reported a positive correlation between HPVG, ICG-R15, and LSM(24)

The LSM is a prognostic factor for outcomes after a liver resection for HCC. The mean cut-off predicting poor outcomes were 20–22 kPa in Europe(23–25) and 16 kPa in Asia.(43) Cescon et al. reported that patients had a greater risk of cirrhosis and PHLF when their LSM values were >13 and 20 kPa, respectively.(23) By considering the previous cut-off points described for LSM (22kPa), our group described a sensitivity of 43% and a specificity of 93%, and the wide “grey zone” of between 14 and 22kPa justified the present study. The threshold observed in the present study was decreased to 11.6kPa with a sensitivity of 89% and a specificity of 47% compared to the previous study by Rajakannu et al(24) where the cut-off from previous studies was used. CAP proved to be of no value in predicting PHD, probably because steatotic livers do not necessarily have concomitant fibrosis which is one of the main factors to develop PHD.

The spleen volume was demonstrated to be an independent risk factor for PHD as was LSM. Spleen volume is an objective and easy-to-use predictor because dedicated software can delimitate the region of interest and calculate spleen volumes accurately in a short time.

LSM is related to the degree of fibrosis and is a marker of the quality of the parenchymal architecture, while splenomegaly is a sign related to hemodynamic changes of the portal venous system. Abnormalities of liver stiffness and spleen volume are a result of a complex interaction of the etiology of liver disease,(44) hemodynamic changes(45), and molecular mediators(29). Chronicity of liver disease could play a role in this setting as well. Thus, splenomegaly portends hepatic decompensation after hepatectomy in cirrhotic patients, but splenomegaly is a clinical manifestation of other conditions that are not necessarily

related with clinically important portal hypertension (29,46–48). Even in cirrhosis, Kashani et al(44), have reported different spleen sizes according to aetiology.

Spleen stiffness has also been studied in the context of clinically important portal hypertension, but more studies are required to validate a wider use(49,50). Nonetheless, the data obtained has a good correlation with the degree of fibrosis and clinically important portal hypertension, depending on the etiology and technique applied(51,52). Of note is that recently, spleen stiffness and spleen volume have been also reported as predictors of PHLF as well(53).

In our proposed decision tree model, the SV associated with LSM offered a better sensitivity and specificity to predict PHD than using only the LSM. The prediction of PHD should improve the selection of patients in order to decrease severe morbidity rates (present in 8 of 11 patients with PHD), a greater duration of hospital stay, and a greater rate of re-admissions. Therefore, we maintain that patients with $LSM > 12\text{kPa}$ and $SV > 380\text{cc}$ should be offered less invasive treatments (i.e. ablation) that can provide almost comparable cure rates if the HCC is small, without putting the patient at a serious risk during the postoperative period. This selection could also influence the decision to proceed with liver transplantation (when applicable) instead of liver resection and prevent the development of PHD.

To the extent of our knowledge, this study is the first to present the association between SV and LSM for the prediction of PHD after 3 months. The accuracy of this non-invasive association could be used also in the setting of patients where the results of LSM are in the “grey zone”. LSM and SV are potentially important, non-invasive tests that should be used in association for predicting PHD and to determine high-risk patients for hepatectomy. Thus, these tests might enhance the selection of patients with HCC with or without chronic liver

disease who are fit for either resection or who should receive other therapies than hepatectomy.

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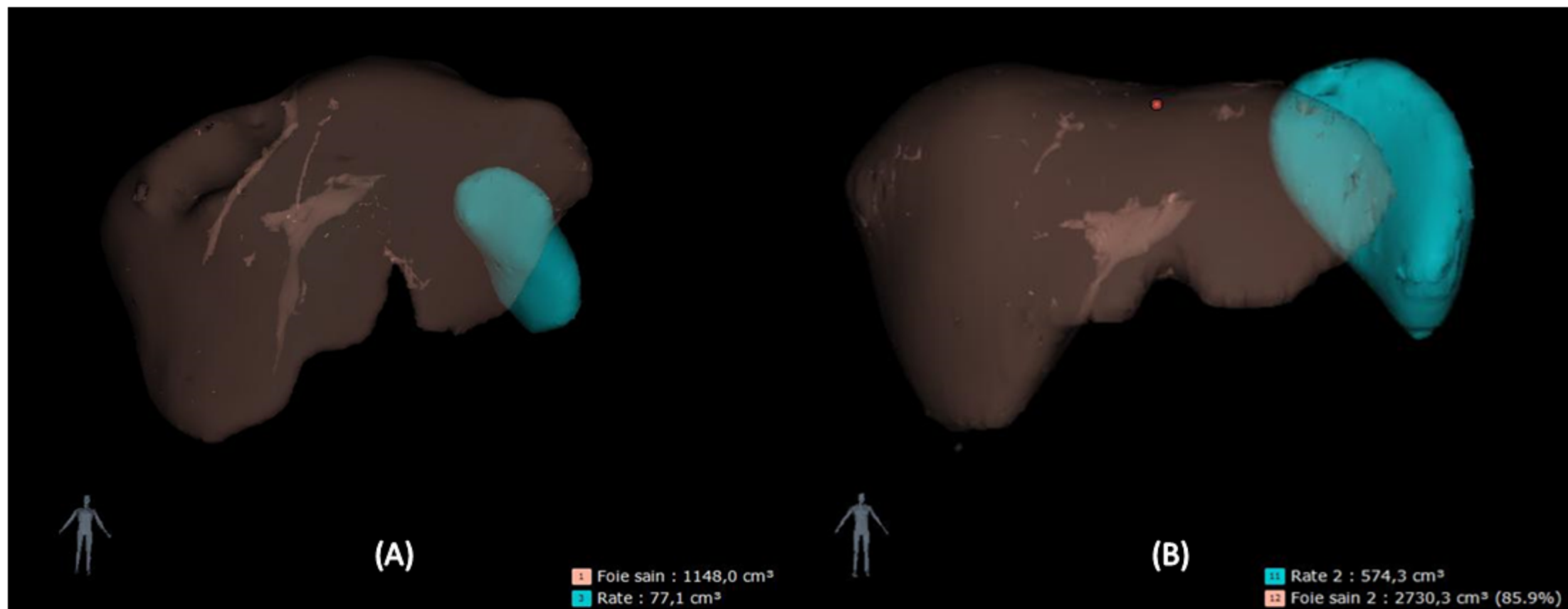
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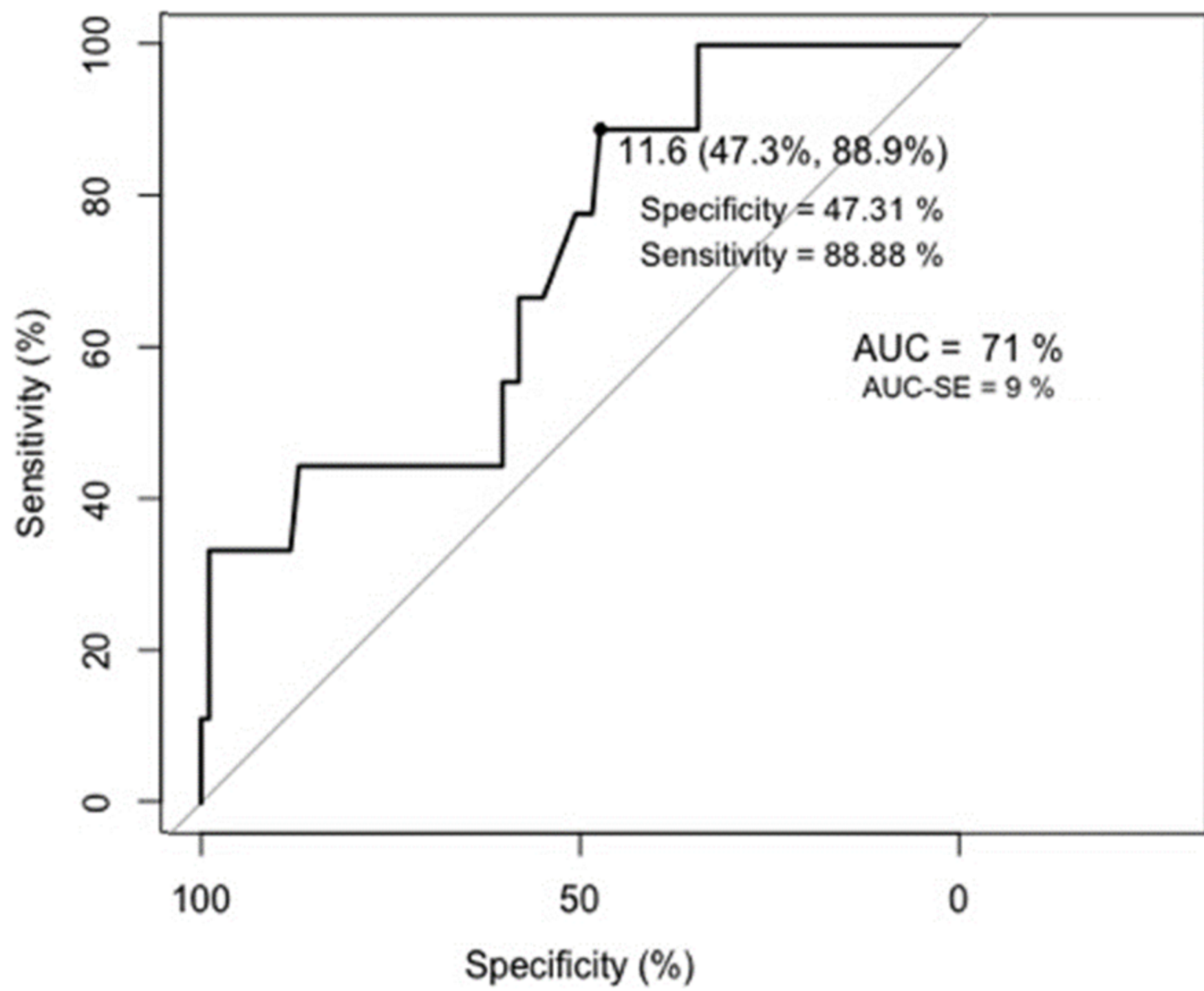
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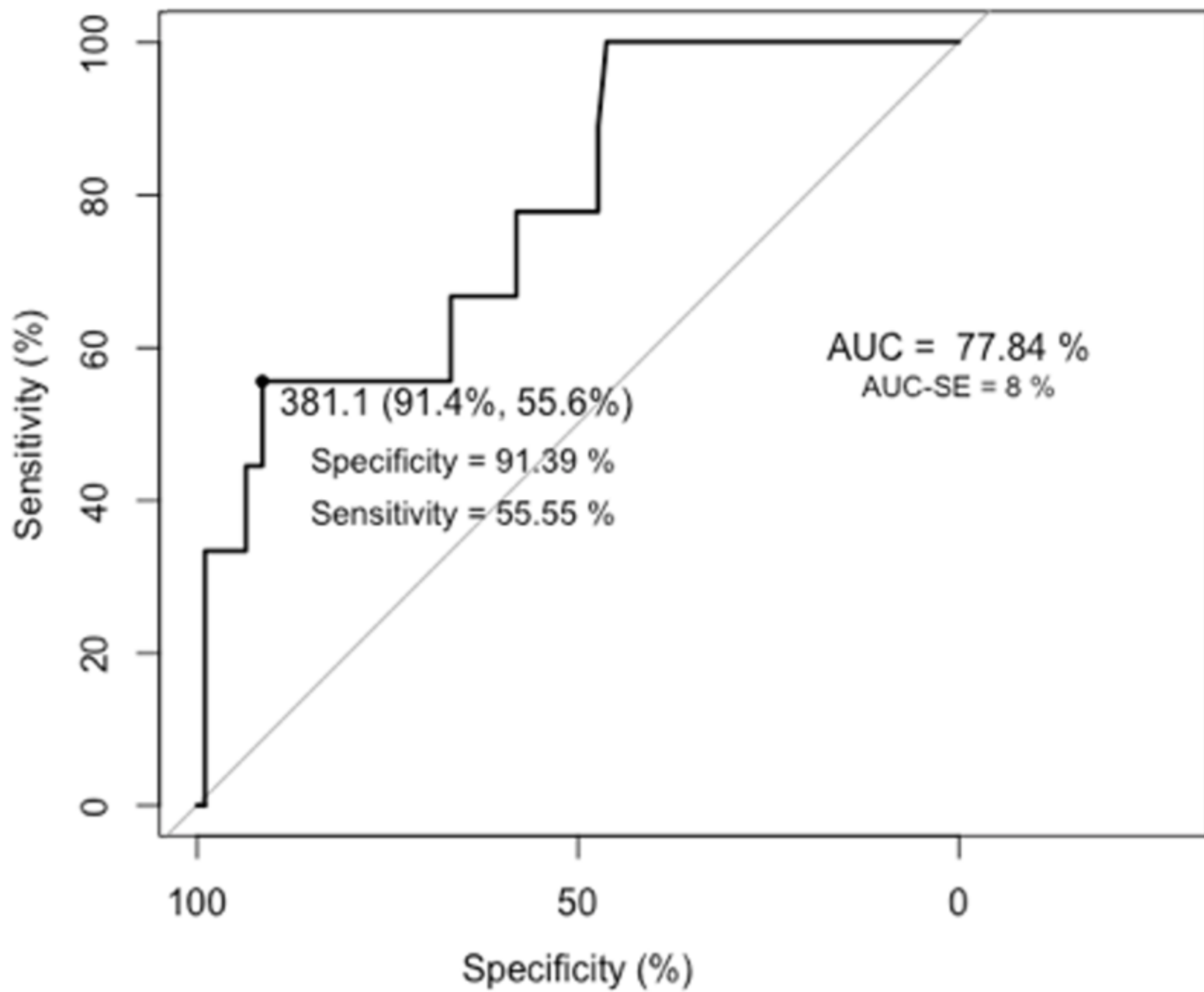
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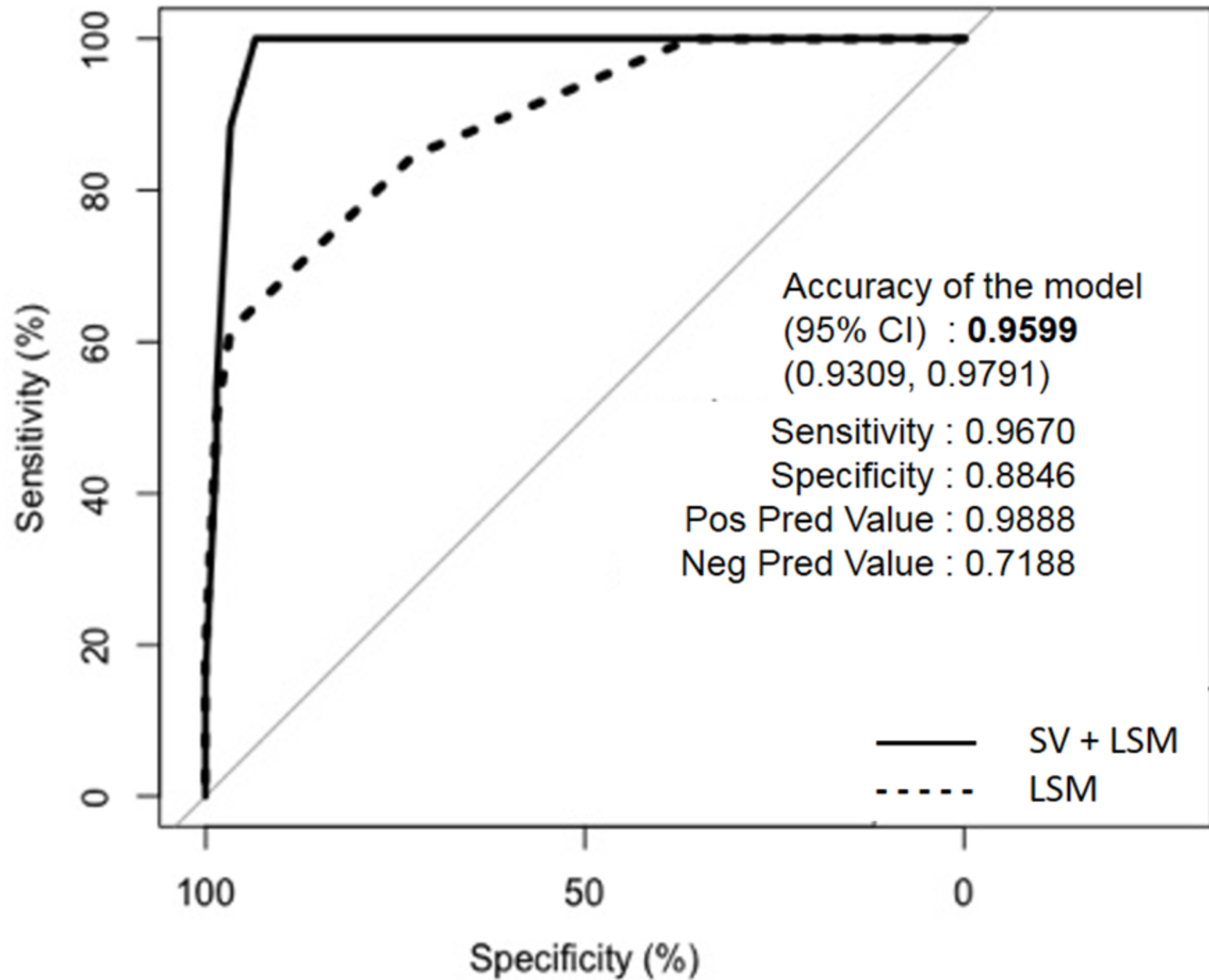


Table 1. Clinical, laboratory and operative patient characteristics

	n=107 (100%)
Patient demographics	
Age (y)	68 (31 - 87)
Sex, male: female	84 (78.5%) 23 (21.5%)
Body Mass Index (kg/m ²) median (range)	25.2 (15.2 - 42.2)
MELD score	8 (6 - 20)
Child - Pugh score	5 (5 - 8)
Main etiology of cirrhosis	
Viral Hepatitis (e.g. VHB, VHC)	42 (39.3%)
Non-alcoholic Fatty Liver Disease	25 (23.4%)
Alcohol	23 (21.5%)
Others (e.g. Hemochromatosis, Primary Biliary Cirrhosis)	4 (3.7%)
Unknown cause	13 (12.1%)
Laboratory tests	
Hemoglobin in g/L	13.7 (7.9 - 18.8)
Platelet count in 10 ⁹ /L	208 (34 - 477)
International Normalized Ratio	1.1 (0.9 - 1.6)
Prothrombin activity in %	83 (55 - 100)
Serum fibrinogen in g/L	3.7 (1.07 - 7.2)
Serum total bilirubin in μmol/L	10 (4 - 36)
Serum creatinine in μmol/L	74 (48 - 719)
Serum aspartate aminotransferase in IU/L	37 (14 - 178)
Serum alanine aminotransferase in IU/L	35 (10 - 218)
Serum g-glutamyl transpeptidase in IU/L	110 (18.3 - 2,400)
Serum alkaline phosphatase in IU/L	98.5 (37 - 414)
Serum albumin in g/L	36.9 (18.3 - 48.1)
Serum protein in g/L	74 (55 - 99)
Indocyanine green retention (ICG) at 15 min in %	12 (1 - 78.14)
Serum α-fetoprotein in ng/mL	8.8 (1.3 - 100,000)
Spleen volume (cm³)	186 (53.9 - 1,528)
Transient elastography	
Liver stiffness measurement (LSM) in kPa	12 (3.4 - 69.1)
Controlled Attenuation Parameter (CAO)	233 (100 - 400)
Operative characteristics	
Open resection/Laparoscopic resection	70 (65.4%)/37 (34.6%)
PVE before hepatectomy	10 (9.3%)
Minor hepatectomy (≤2 segments)	80 (74.7%)
Major hepatectomy (>2 segments)	27 (25.3%)
Blood loss (cc)	400 (50 - 4,500)

Continuous data are expressed as median (range).

Table 2. Pathologic and post-operative patient characteristics

	n=107 (100%)
Hepatocellular carcinoma characteristics	
Tumor number	1 (1 - 6)
Maximum diameter in cm	3.5 (0.7 - 32)
Tumor location, count (%)	
Right lobe	59 (56.2%)
Left lobe	40 (38.1%)
Bilobar	6 (5.7%)
Resection margin in cm	0.4 (0 - 6)
METAVIR fibrosis score in non-tumoral liver, count (%)	
F0	8 (7.5%)
F1	12 (11.2%)
F2	15 (14%)
F3	15 (14%)
F4	57 (53.3%)
Duration of Hospitalization stay, median (IQR)	7 (6 - 11)
Re-hospitalization (90 days), count (%)	8 (7.7%)
Complications	
Severe Morbidity (\geq III), count (%)	18 (16.8%)
Post-operative liver failure (50:50 criteria), count (%)	4 (3.7%)
Post-hepatectomy decompensation, count (%)	24 (22.4%)
Persistent Post-hepatectomy decompensation (at 3 months), count (%)	9 (8.8%)
Post-operative death (90 days), count (%)	5 (4.7%)

Continuous data are expressed as median (range).

Table 3. Comparison Characteristics of Patients with and without Persistent Post-hepatectomy DecompensatioPHD)

	No 93 (91.2%)	Yes 9 (8.8)	p value
Hepatocellular carcinoma characteristics			
Tumor number	1 (1 - 3)	1 (1 - 1)	0.193 ^φ
Maximum diameter in cm	4 (0.7 - 18)	2.5 (2 - 8)	0.073 ^φ
Right liver tumors, count (%)	52 (57.1%)	5 (55.6%)	0.789 ^χ
Resection margin in cm	0.4 (0 - 6)	0.4 (0 - 4)	0.544 ^φ
Fibrosis METAVIR scores			
F0-F2	33 (35.5%)	0	0.03^χ
F3-F4	60 (64.5%)	9 (100%)	
Hospitalization			
Hospitalization days	7 (0 -29)	10 (6 - 42)	0.042^φ
Re-hospitalization (90 days), count (%)	4 (4.4%)	4 (44.4%)	0.002^χ
Complications			
Severe Morbidity (Dindo-Clavien ≥III), count (%)	6 (6.5%)	7 (77.8%)	<0.001^χ
Post-hepatectomy liver failure(PHLF) , count (%)*	1 (1.1%)	1 (11.1%)	0.169 ^χ
PHD, count (%) ***			<0.001^χ
	No	-	
	90(77.6%)		
	Yes	9 (100%)	

*** Patients who developed PHD during hospitalization.

^φ Mann-Withney U test; ^χ Fisher's exact test

Continuous data are expressed as median (range).

*50:50 criteria

Table 4. Preoperative Independent Risk Factors for PHDat 3 months (n=107)					
Variables	Univariate analysis*		Multivariate analysis†		
	p value	p value	OR	CI 95%	
				Lower	Upper
Age in years, median ± SD	0.736 ^φ				
Sex					
Male	0.680 ^χ				
Female					
Body Mass Index (kg/m ²), median ± SD	0.770 ^φ				
MELD score (points), median ± SD	0.871 ^φ				
Hemoglobin preoperative, median ± SD	0.029 ^φ	0.004	2.47	1.342	4.546
Platelet count (mm ³), median ± SD	0.008 ^φ	0.215			
International Normalized Ratio, median ± SD	0.264 ^φ				
Prothrombin activity in %, median ± SD	0.340 ^φ				
Serum total bilirubin in μmol/L, median ± SD	0.047 ^φ	0.373			
Serum creatinine in μmol/L, median ± SD	0.373 ^φ				
Serum aspartate aminotransferase in IU/L, median ± SD	0.056 ^φ				
Serum alanine aminotransferase in IU/L, median ± SD	0.148 ^φ				
Serum g-glutamyl transpeptidase in IU/L, median ± SD	0.252 ^φ				
Serum alkaline phosphatase in IU/L, median ± SD	0.431 ^φ				
Serum albumin in g/L, median ± SD	0.962 ^φ				
Serum protein in g/L, median ± SD	0.920 ^φ				
LSMin kPa, median ± SD	0.038 ^φ	0.007	1.077	1.021	1.137
CAP, median ± SD	0.984 ^φ				
SVin cm ³ , median ± SD	0.006 ^φ	0.020	1.003	1.001	1.006

* Variables with a univariate p<0.05 were included for multivariate analysis and are marked in *italics*.

† Independent risk factors are defined by p<0.05 and shown with OR and CI at 95% (marked in **bold**).

^φ Mann-Withney U test; ^χ Fisher's exact test

Table 5. Area under the ROC Curve (AUROC), Sensitivity, Specificity, PPV, and NPV depending on whether SV is retained in the model

Endpoint	Model Without SV	Model With SV
PHD at 3 months AUROC (95%CI)	0.889 (0.88. 0.95)	0.983(0.98. 0.99)
Sensitivity	61.5	96.7
Specificity	96.7	93.4
PPV	64	59.1
NPV	96.4	100
(De Long's test)		0.0034

Fig. 1 Spleen volumetry (SV) obtained by dedicated software (Myrian®) Normal SV is observed (A). In (B) an enlarged spleen in relation with portal hypertension is observed.

Fig. 2. ROC curve for Liver Stiffness Measurements (LSM) for prediction of PHD

Fig. 3. ROC curve for Spleen Volumetry (SV) calculation for prediction of PHD.

Fig. 4. ROC curves and accuracy of the model comparing LSM *versus* LSM+SV.