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PhD thesis
in Advanced Biomedical and Surgical Therapies

Prognostic role of hepatic venous - portal pressure gradients vs indocyanine green retention test and liver stiffness on short- term surgical outcomes for HCC on liver cirrhosis: a multicenter prospective study.

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1- Introduction

Liver malignancies account for the fifth most common cancer worldwide and the fourth most common cause of cancer-related death(1). With an estimated incidence between 500,000 and 1 million per year, hepatocellular carcinoma (HCC) represents approximately 90% of liver tumors and it is associated with a poor prognosis(2). Nonetheless, when it is diagnosed in early stages, 5-year overall survival (OS) reaches 50-70%, thanks to advances in both surgical and medical fields(3).

HCC develops on an underlying chronic liver disease in over than 90% of cases, mainly of viral, metabolic, or alcoholic etiology, and in most cases over a liver cirrhosis(4). In these cases, the risks related to the underlying liver disease are added to the risks of mortality and morbidity linked to HCC(5).

Surgery represents the most effective treatment for HCC, as it has been shown to be safe and effective when using appropriate patient selection criteria and state-of-the-art surgical techniques(6). Surgical treatments include liver transplantation (LT) and liver resections, with a recurrence rate of 20% after LT and 70% after liver resection(7). Thus, LT is the best curative treatment in cirrhotic patients, but due to organ shortages and long waiting times associated with subsequent risk of drop-out due to tumor progression, it should be reserved for patients who are not candidates for liver resection or thermal ablations due to uncompensated cirrhosis, to patients with unfavorable prognostic factors on pathological examination after resection and those with recurrent HCC in transplantable patients(8). Consequently, liver resection is still considered the first-line treatment for HCC in patients with compensated cirrhosis. According to current guidelines, thermal ablation is considered effective only for lesions smaller than 3 cm, if technically feasible(9). On the other hand, for unresectable liver disease, trans-arterial chemoembolization (TACE) represents the treatment of choice, if the patient has an adequate performance status. Medical therapy is reserved for cases with disseminated disease or when other therapies are not feasible. To date, medical therapy mainly relies on the use of the kinase inhibitor sorafenib, but due to a better understanding of the molecular pathways of HCC carcinogenesis, other immunotherapy drugs are licensed in some countries or currently in late-stage clinical trials(10).

Liver resection is an extremely technically complex operation, also considering the fragile cirrhotic patients. Thus, the risk stratification and the correct case-by-case selection constitute a fundamental step in the management of the HCC patients, allowing to achieve a postoperative mortality lower than 1% in highly specialized centers(11).

Such pre-operative risk stratification is firstly based on patients' performance status and cirrhosis compensation, allowing for an early selection of patients and leading to mortality rates that are close to 0.5% in patients with a Model for End-stage Liver Disease (MELD) score <8, but with an increase of the same up to 29% in patients with a higher MELD(12). Currently, European guidelines for the treatment of hepatocellular carcinoma (HCC) are based on the Barcelona Clinic Liver Cancer (BCLC) staging system(9). In this staging system, patients are classified based on Child-Turcotte-Pugh (CTP) class, number and size of the lesion, and Performance Status (PS) of the patient(13). Furthermore, in the context of HCC patients, a new CTP class (CTP 0) has recently been proposed, as it correlates better with the survival and prognosis of these patients(14).

Given the same CTP class, a fundamental parameter in the decision-making process is the presence of Portal Hypertension (PHT), which alone contraindicates surgery because of disappointing results on long-term survival(15). However, the evolution of surgical techniques and patient management has led many centers to overcome the limits proposed by the BCLC for surgical resections, highlighting the need for new criteria(16). Ishizawa et al. from the University of Tokyo reported large case series of patients undergoing hepatic resection despite PHT, with more than satisfactory results(17). In this study, multivariable analysis showed that PHT did not to play a prognostic role on OS, while a CTP-B Class was significantly associated with unfavorable outcomes. Subsequent studies have then highlighted how the results can vary within the same CTP-B class, based on other characteristics, such as the use of minimally invasive access, as demonstrated by recent multicenter studies coordinated by our Department of Clinical Medicine and

Surgery(18). Indeed, international guidelines regarding HCC management have officially approved the use of laparoscopy in the treatment of early-stage disease(9). Several authors have proposed that MILS can reduce the risk of postoperative decompensation of patients with HCC and, in daily practice, high-volume centers routinely perform LLR even for difficult cases in frail cirrhotic patients(7, 16, 19, 20). However, there are still numerous limitations to the universal adoption of LLR for HCC.

Finally, there is the need to consider multiple additional factors in each patient in order to choose the most suitable treatment: the CTP class, the presence of clinically significant portal hypertension (CSPH), the type of surgery, the anesthetic risk, as well as PS or the disease extension.

Within the pre-operative assessment on the extent of liver resection, a key role is played by the volumetric calculation of the remaining liver parenchyma (Future Liver Remnant, FLR) and by the liver functional reserves estimated by the blood clearance of Indocyanine Green (ICG), and specifically by its retention rate after 15' from injection (ICG-R15)(21, 22). ICG has been used for decades to evaluate the excretory function of the liver. It is a water-soluble fluorescent dye excreted in the bile without being metabolized, whose blood clearance depends on hepatic blood flow and hepatocyte function. In particular, in Asia, ICG-R15 is routinely used in the evaluation of functional reserves in cirrhotic livers to evaluate the risk of morbidity and postoperative liver failure depending on the FLR and the extent of liver resections (the so-called Makuuchi's criteria, dating back to 1993)(23).

As aforementioned, after the volumetric and functional evaluation of the liver, the presence of PHT should be investigated. Almost all the studies in the literature analyzing the prognostic role of portal hypertension in patients undergoing liver surgery are based on retrospective data. Furthermore, almost all the previous studies use an indirect evaluation of the presence of PHT, and not on the direct measurement of hepatic venous portal gradients (HVPG). Indeed HVPG is the gold standard to measure portal pressure, but it is an invasive procedure: it is given by the difference between hepatic vein free pressure and hepatic vein wedge pressure, measured directly by selective catheterization(24). As indirect methods, the presence of splenomegaly associated with low platelets (< 100.000 /cm^3) or the presence of esophageal varices are the most commonly used(25). Before elective surgery, the patient should be up to date with variceal screening through esophagogastroduodenoscopy, with an eventual subsequent appropriate management in accordance with the American Association for the Study of Liver Diseases (i.e. band ligation or initiation of nonselective beta blocker medication if medium or large varices identified)(26). However, it is well known that indirect signs have low sensibility and specificity on the presence of CSPH(27, 28).

A correlation between serum ICG levels and HVPG has recently been proposed: Pind et al. reported a significant association between ICG-R15 and HVPG, but only in Child A patients(29). Moreover, ICG-R15 was assessed by measuring plasma levels from serial samples, while currently it is possible to obtain the ICGr15 through a pulse-spectrometric measurement with a dedicated device, the LiMON (Pulsion Medical System, Munich, Germany), non-invasively and at the patient's bedside.

Recently, among the indirect methods of evaluating PHT, the use of hepatic elastography using FibroScan® has been consolidated. The latest European guidelines recommend avoiding screening with EGDS in patients with liver stiffness (LSM) < 20kPa and platelet count > 150,000. Furthermore, given the splenic congestion secondary to PHT, sufficient to increase its stiffness, a new diagnostic algorithm for CSPH has recently been proposed, which takes into account the spleen stiffness (SSM)(24). However, such a method is not routinary available everywhere. Nonetheless, LSM has been shown to be associated with postoperative complications after liver resections(30).

1.1 *Aims of the study*

The aim of this study was to evaluate the accuracy of HVPG (direct method, measured invasively through venous catheterization), ICG-R15 (non-invasive method, measured through Limon device) and LSM (non-invasive method, measured through Fibroscan) in predicting the risk of post-operative liver failure and hepatic decompensation.

Furthermore, we tried to investigate the real burden of HVPG in a multivariate analysis that takes into account patient demographics, CHILD, MELD, tumor characteristics, extent of surgery, blood loss, invasiveness of the approach.

2- Methods

2.1.1 Study design

This is a multicenter prospective non-interventional study.

2.1.2 Inclusion criteria

Consecutive cirrhotic patients with indication to surgical resection for HCC were included.

Patients were selected for surgery based on standard criteria according to current guidelines, i.e. remaining liver volume (≥ 50% of total liver volume), PS 0 and Child class (0, A or B), after being discussed in the institutional multidisciplinary team (MDT).

2.1.3 Exclusion criteria

The exclusion criteria were the following: patients undergoing emergency surgery; patients unable to understand or to sign an informed consent.

2.2.1 Data

Clinical, instrumental, and laboratory data were collected at the beginning of the study (at the time of hospitalization and during the intervention) and during a 1-year follow-up after the intervention.

During pre-hospitalization, patients underwent a non-invasive measurement of ICG-R15, using a pulse spectrometer with a dedicated device (LiMON, Pulsion Medical Systems, Munich, Germany) and a non-invasive evaluation of the liver stiffness with the use of FibroScan®. Finally, HVPG was measured according to the methods described below, in the radiological unit or in the operating room.

Patients was monitored to record the clinical course, the development of post-surgical complications and mortality. Any complications that was developed during hospitalization, the values of the liver function and cholestasis, the duration of hospitalization, and any transfusion of blood products were recorded.

2.2.2 Ethical aspects

Patients eligible for enrollment were adequately informed and informed consent was obtained. The study was conducted according to Helsinki Declaration and ethical approval was obtained from the Institutional Review Board of each center (Prot. 368/20).

2.3.1 Patients' management

The patients followed the normal therapeutic management of any other patient undergoing liver surgery. After the surgery, patients were managed in sub-intensive care unit, for 24 hours in case of no postoperative complications, where they received a careful management of fluid therapy, pain therapy, monitoring of vital parameters and drainage. Upon return to the surgery department, a fast-track surgery protocols was applied where possible(31). Fluid management was carried out following an equal or slightly negative daily balance in order to have low central venous pressure(32). Antibiotic prophylaxis was carried out according to current recommendations, of a short-term nature(33). Pain therapy was conducted by limiting the use of opioids to a minimum. Upon returning to the ward, the oral feeding and the mobilization were early re-introduced.

Patients' clinical conditions and laboratory tests were evaluated daily, as well as the development of any complications.

2.3.2 Follow-up

After discharge, patients were followed as outpatient after 3 weeks, 3 months, 6 months and 12 months.

A clinical evaluation was carried out to investigate the presence of surgical complications, together with a biochemical evaluation of liver function. The state of liver function was then assessed according to the CTP score. Any clinical manifestations of cirrhotic decompensation were carefully investigated: hepatic encephalopathy, acute kidney injury, jaundice, ascites.

2.4 HVPG measurement

The HVPG is given by the difference between the wedge hepatic venous pressure (Wedged Hepatic Vein Pressure, WHVP) and the free hepatic venous pressure (FHVP). FHVP is the pressure measured with the free catheter in the hepatic vein. WHVP is therefore a measure of hepatic sinusoidal pressure, not portal pressure: in the normal liver, in fact, WHVP is slightly lower, due to the pressure balance through the interconnection given by the fenestrations of the sinusoids. In liver cirrhosis, however, the static column of blood created by occluding the hepatic vein cannot be decompressed to a sinusoidal level because the connections between the sinusoids are disrupted by the presence of fibrous septa and cirrhosis nodule formation, so WHVP provides an accurate estimate of portal pressure.

In practice, FHVP was measured by holding the catheter tip free in the hepatic vein lumen, 2-4 cm from its opening into the inferior vena cava; its value should be similar to that of the inferior vena cava. WHVP is measured by occluding the hepatic vein; the arrest of blood flow causes stasis of the blood column, thus equalizing the pressure with the vascular territory upstream - in this case, the hepatic sinusoids. WHVP was measured by occluding the hepatic vein, “stuck” the catheter in a small branch of the hepatic vein by inflating a balloon at the tip of the catheter. Adequate occlusion of the hepatic vein was confirmed by slowly injecting contrast medium into the vein without observing its reflux or its passage through communications with other hepatic veins(34).

Hepatic vein catheterization was performed under sedation, in combination with non-invasive monitoring of vital signs (electrocardiography, blood pressure, and pulse oximetry). Under local anesthesia, the right jugular vein (or femoral or antecubital vein) was catheterized, a venous introducer is inserted, and a balloon catheter is advanced under fluoroscopic guidance into the inferior vena cava and a hepatic vein to measure WHVP, FHVP, and blood pressure. inferior vena cava. This is a moderately invasive technique, but no more than other procedures that are routinely performed in patients with chronic liver disease.

2.5 Evaluation of ICG-R15

ICG clearance was measured using pulse spectrometry. Patients received 0.25 mg/kg of ICG intravenously injected the day before liver resection. Plasma disappearance rate (PDR) and ICG retention rate at 15 minutes (ICG-R15) were measured by pulse spectrometry with a LiMON device (Pulsion Medical Systems, Munich, Germany).

2.6 Evaluation of LSM

Liver stiffness (LSM) was assessed by Liver Elastography using FibroScan® instrumentation (Echosens, Paris, France) under ultrasound guidance after fasting for at least 4 hours. The exam was carried out by an expert operator who has performed more than 500 tests. LSM values were obtained according to the European recommendations of the Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB)(35). For each patient, LSM value was considered adequate if the success rate is > 60% and the interquartile range (IQR) is < 30% of the median value.

2.8 Definitions

Post-hepatectomy Liver Failure (PHLF) was defined and graded according to ISGLS as an acquired postoperative deterioration in the ability of the liver (in patients with normal and abnormal liver function) to maintain its synthetic, excretory, and detoxifying functions, characterized by an increase in INR (or need for clotting factors to maintain normal INR) and hyperbilirubinemia (according to normal cut-off levels defined by the local laboratory) on or after postoperative day 5(36).

Ascites in the postoperative period was defined as drainage production greater than 10/mL/kg/24h(37).

Hepatic encephalopathy was defined clinically based on two types of symptoms: impaired mental status and impaired neuromotor function, such as defined by the West Haven Criteria (WHC)(38).

AKI was defined according to the recent International Club of Ascites criteria(39).

Postoperative complications were defined according to the Clavien-Dindo classification(40).

2.9.1 Primary endpoints

The primary endpoint was the comparison of the predictive accuracy (evaluated as Area Under the Curve of the ROC curve -AUC - see statistics) of HVPG, ICG-R15 and LSM on a Composite Endpoint defined as the development of PHLF, severe postoperative ascites, in-hospital mortality, severe postoperative complications (defined as major than 3A according to Clavien-Dindo classification).

2.9.2 Secondary endpoints:

Secondary endpoints were postoperative results and 3-months survival outcomes.

2.9.3 Statistical analysis

Continuous data were expressed as mean and standard deviation (SD) or median and interquartile range (IQR) depending on whether they had a normal distribution, and comparisons between groups was performed using Student's T test or Wilcoxon test, depending on the distribution of the variable.

Categorical data was expressed as frequencies and associated percentages. Comparisons between groups was performed using Pearson's Chi Square test. The presence of a linear correlation between the variables was verified by linear regression.

The accuracy of a continuous variable in predicting a categorical outcome was assessed using Receiver Operating Characteristic (ROC) curves. In particular, the value of the area under the curve (AUC), reported together with the 95% confidence interval, was used as an index of predictive accuracy. Comparison between the AUCs of different variables was performed using the method described by Hanley et al(41). Sensitivity and specificity were calculated for different cut-off values of each continuous variable. Youden's *J* test was performed to evaluate the performance of a positive score on the POPF occurrence. P values ≤ 0.05 were considered statistically significant.

Furthermore, a univariate and multivariable analysis was carried out on the basis of the studies present in the literature regarding the risk factors for surgery in cirrhotic patients: preoperative Child and MELD values, as well as the extent of the resection (wedge resections, anatomical segmentectomies and non-anatomical, resections of more than two segments) and the type of approach (minimally invasive versus traditional). Covariates for multivariable analysis were chosen via backward selection, based on a p-value <0.05.

Statistical analysis was conducted using SPSS software (version 28.0).

2.9.4 *Sample size*

The sample size was calculated in order to have a null hypothesis to be tested with a Type II error of 0.20 (β=0.80) and a Type I error of 0.05 (α=0.05), with a predictive accuracy (AUC) of the HVPG significantly higher ($\Delta \geq 0.20$) than the predictive accuracy of the ICG-R15 (AUC 0.70)29. Considering a frequency of PHLF in the literature of 8-12%, an in-hospital mortality of 2-4% and a severe complications rate of 10-20% in high volume centers, the necessary sample size resulted in 68 patients(12, 42-45). The software MedCalc V.19 was used to calculate the sample size.

3 - Results

3.1 Patients ‘characteristics

Seventy-two cirrhotic patients undergoing liver resection were enrolled between December 2020 and September 2023. Median age of the cohort was 72.5 years (IQR= 12), of which 82% were males (n= 59). The median BMI was 26.6 (IQR= 5.2).

A metabolic etiology was the most frequent cause of liver cirrhosis (41.8%), followed by Hepatitis C Virus (34.8%). Median Child-Turcotte-Pugh score was 5 (IQR = 0), with 3 Child B patients undergoing surgery (4.1%). All patients ‘characteristics are shown in Table 1.

3.2 Tumors' characteristics

Median HCC diameter was 31.5 millimeters, with 70.8 % of patients presenting 1 nodule, 19.5% presenting 2 nodules, 8.4% presenting 3 nodules and 1.3% with 4 nodules.

Fifteen patients (20.8%) were staged as BCLC-0, 44 patients as BCLC-A (61.1%) and 13 (18.1%) as BCLC-B. All tumors ‘characteristics are shown in Table 1.

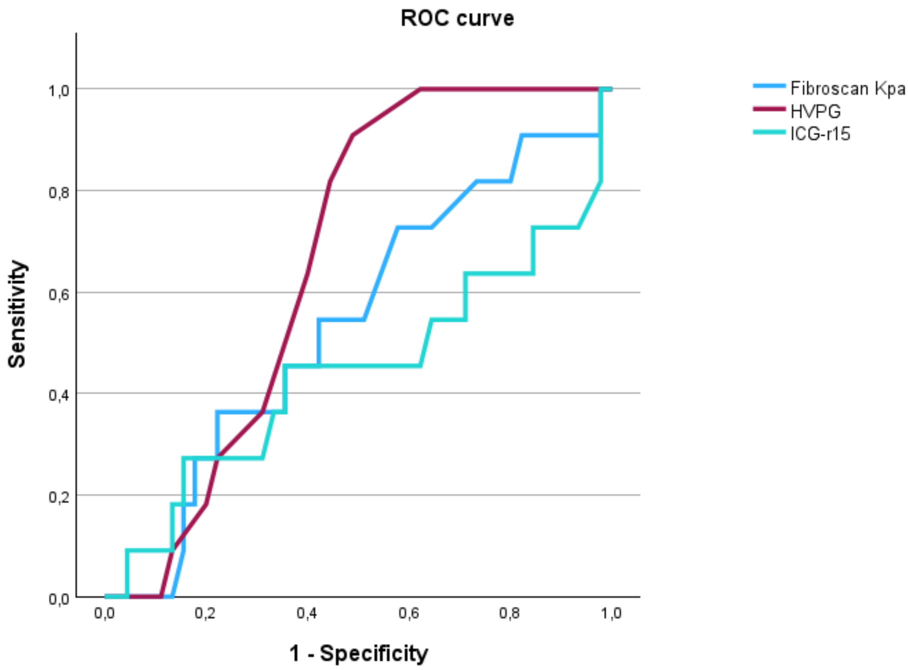
	Total (n=72)
Age, median (IQR)	72.5 (12)
Male gender, n (%)	59 (82)
BMI, median (IQR)	26.6 (5.2)
Etiology, n (%)	
HBV	13 (18.1)
HCV	25 (34.8)
Alcoholic	8 (11.3)
Metabolic	30 (41.8)
Child-Turgot-Pugh score median, (IQR)	5 (0)
Child A, n (%)	69 (95.8)
Child B, n (%)	3 (4.2)
Recurrent disease, n (%)	19 (26.4)
Previous treatments, n (%)	15 (20.8)
Previous TACE, n (%)	3 (4.2)
Previous liver surgery	8 (11.3)
ICG-R15, median (IQR)	8.7 (9.6
Liver stiffness, median in KPa (IQR)	12 (8.1)
Esophageal varices, n (%)	10 (13.9)
Splenomegaly, n (%)	15 (20.8)
Platelets < 100, n (%)	8 (11.1)
HCC Size, median (IQR)	31.5 (40)
HCC numbers, n (%)	
1	51 (70.8)
2	14 (19.5)
3	6 (8.4)
4	1 (1.3)
BCLC Stage	
0	15 (20.8)
A	44 (61.1)
B	13 (18.1)
Type of surgery, n (%)	
Atypical resection*	38 (52.8)
Segmentectomy*	25 (34.8)
Sectionectomy*	5 (6.9)
Hemi-epatectomy	4 (5.5)
Extent of surgery, n (%)	
Major resection	15 (20.8)
ASA score, n (%)	
2	26 (36.1)
3	46 (63.9)

Table 1: Patients' and tumors' characteristics. SD: standard deviation; IQR: inter-quartile range ; BMI : body mass index; HBV: Hepatitis B virus; HCV: Hepatitis C virus; TACE: trans-arterial chemo-embolization; ICG-R15: indocyanine green retention test at 15'; ASA: American Society of Anesthesiologists score. *alone or associated with additional thermal ablation or resection.

3.3 *Predictive performance analysis*

The predictive performance of the tests was examined on the ROC curves, showing an AUC (area under the curve) of 0.514 for ICG-R15 (p=0.61), 0.604 for LSM (p= 0.66), 0,716 for HVPG (p= 0.02) (Figure 1).

A Youden Index of 0.52 was associated with an HPVG threshold value of 6.5 mmHg, with a sensitivity calculated at 90.9% (95% CI: 79-95) and the specificity at 51.1% (95% CI: 41-72).



	AUC	-95% CI	+ 95% CI	p-value
ICG-r15	0,514	0,298	0,721	0,615
LSM	0,604	0,356	0,766	0,661
HVPG	**0,716**	0,566	0,861	**0,020**

Figure1: Receiving Operating Carachteristics curves for predictive ability of HVPG, ICG-R15 and LSM on the combined outcome.

3.4 *Postoperative outcomes analysis*

During the hospitalization period, 2 patients (2.8%) developed PHLF (graded A and C according to ISGLS), 6 patients (8.3%) developed large ascites, 5 patients (6.9%) developed severe postoperative complications, with 1 patient that died because of PHLF. Subsequently, a total of 13 patients developed the combined endpoint (18%). At univariate analysis for developing the combined endpoint the median HCC size, median intraoperative Estimated Blood Loss (EBL)(1000 ±1050 cc vs 200 ±353 cc; $p < 0.001$) and intraoperative transfusions (68.9% vs 0% ; $p < 0.001$) were significantly associated with the composite endpoint.

At multivariable analysis, only EBL was significantly associated (OR 1.03 [CI 95% 1.01-1.05]; $p < 0.001$) (Table2).

	Developing combined endpoint (n=13)	**Non – developing endpoint (n=59)**	**Univariate analysis p-value**	**Multivariate analysis p-value**
Age, mean (SD)	72.4 (6.5)	71.3 (8.2)	0.57	
BMI, mean (SD)	27.7 (5.2)	26.5 (4)	0.40	
Male gender, n (%)	10 (76.9)	49 (83)	0.90	
Etiology, n (%) HBV HCV Alcoholic Metabolic	 1 (7.6) 5 (38.5) 2 (15.4) 5 (38.5)	 13 (22) 20 (33.9) 6 (10.1) 24 (40.6)	 0.50 0.75 0.58 0.71	
Child-Turgot-Pugh, n (%) Child A Child B	 13 (100) 0	 56 (95) 3 (5)	0.40	
Recurrent disease, n (%)	2 (15.4)	13 (22)	0.59	
Previous treatments, n (%)	2 (15.4)	17 (28.8)	0.32	
Previous TACE, n (%)	0 (0)	3 (5)	0.41	
Previous liver surgery	0 (0)	8 (13.5)	0.35	
ICG-R15, median (IQR)	7.4 (14.2)	8.8 (9.3)	0.41	
HVPG, median (IQR)	8 (3)	5 (5)	0.07	
CSPH, n (%)	2 (15.4)	9 (15.2)	0.99	
ASA score, n (%) 2 3	 3 (23) 10 (77)	 23 (39) 36 (61)	0.47	
Esophageal varices, n (%)	3 (23)	7 (11.9)	0.29	
Splenomegaly, n (%)	4 (30.8)	11 (18.6)	0.33	
Platelets < 100, n (%)	2 (15.4)	6 (10.1)	0.58	
HCC Size, median (IQR)	45 (65)	30 (25)	**0.003**	0.40 (OR 1.002 [0.99-1.02])
HCC numbers, n (%) 1 2 3 4	 9 (68.9) 3 (23) 1 (7.1) 0 (0)	 42 (71.2) 11 (18.6) 5 (8.5) 1 (1.7)	0.91	
BCLC Stage, n (%) 0 A B	 0 (0) 7 (54.7) 6 (46.2)	 5 (8.5) 39 (65.9) 15 (25.6)	0.16	
Type of surgery, n (%) Atypical resection* Segmentectomy* Sectionectomy* Hemi-hepatectomy	 3 (23.1) 6 (46.2) 2 (15.4) 2 (15.4)	 35 (59.3) 19 (32.2) 3 (5.1)) 2 (3.4)	0.09	
Extent of surgery, n (%) Major resection	4 (30.8)	11 (18.6)	0.31	
Laparoscopy, n (%)	7 (54.7)	46 (78)	0.09	

EBL, median (IQR)	1000 (1050)	200 (353)	**<0.001**	**<0.001 (OR 1.03 [1.01-1.05])**
Transfusions, n (%)	9 (68.9)	0 (0)	**<0.001**	

Table 2: Univariate and multivariable analysis for the combined endpoint. SD: standard deviation; IQR: inter-quartile range ; BMI : body mass index; HBV: Hepatitis B virus; HCV: Hepatitis C virus; TACE: trans-arterial chemo-embolization; ICG-R15: indocyanine green retention test at 15'; ASA: American Society of Anesthesiologists score; EBL: intraoperative estimated blood loss. *alone or associated with additional thermal ablation or resection.

3.5 Portal hypertension analysis

Portal hypertension, defined as HVPG > than 6mmhg, was present in 32 patients (44.4%), while CSPH only in 11 patients (15.2%) (Table 3). Interestingly, only 36.3% of patients with CSPH had platelets lower than 100000 per cm^3, only 45.4% of CSPH patients showed esophageal varices and 63.6% of CSPH patients presented splenomegaly.

CSPH was associated with a higher rate of 90-day cirrhotic decompensation (36.4% vs 3.2%, p = 0.002), and the only death happening within the first 90 postoperative days was in the CSPH group (Table 3).

	CSPH (11)	No CSPH (61)	p-value
Age, median (IQR)	73 (15)	72 (11)	0.57
Male gender, n (%)	7 (63.6)	52 (85.2)	0.19
BMI, median (IQR)	26 (5)	27.3 (4.8)	0.19
Etiology, HBV HCV Alcoholic Metabolic	 2 (18.2) 3 (28.3) 1 (9.1) 6 (54.6)	 11 22 7 24	 0.99 0.82 1.00 0.52
Child-Turgot-Pugh score median, (IQR) Child A, n (%) Child B, n (%)	5 (1) 10 (90.9) 1 (9.1)	5 (0) 59 (96.7) 2 (3.3)	0.21 0.46
Recurrent disease, n (%)	4 (36.3)	15 (24.6)	0.45
Previous treatments, n (%)	3 (27.2)	12 (19.7)	0.86
Previous TACE, n (%)	0 (0)	3	0.46
Previous liver surgery	1 (9.1)	7	0.81
ICG-R15, median (IQR)	17 (27.9)	8.4 (8.2)	0.19
Liver stiffness, median in KPa (IQR)	20 (28)	9 (5)	**0.001**
Esophageal varices, n (%)	5 (45.4)	5 (8.2)	**0.005**
Splenomegaly, n (%)	7 (63.6)	8 (13.1)	**<0.001**
Platelets < 100, n (%)	4 (36.3)	4 (6.5)	**0.003**
HCC Size, median (IQR)	30 (15)	34 (43)	0.62
HCC numbers, n (%) 1 2 3 4	 6 (54.5) 3 (27.2) 2 (18.2) 0 (0)	 45 (73.9) 11 (18) 4 (6.5) 1 (1.6)	0.46
BCLC Stage 0 A B	 0 (0) 7 (63.7) 4 (36.3)	 5 (8.2) 39 (63.9) 17 (27.9)	0.39
Type of surgery, n (%) Wedge resection* Segmentectomy* Sectionectomy* Hemi-epatectomy	 7 (63.6) 3 (27.4) 1 (9.1) 0 (0)	 31 (50.8) 22 (36) 4 (6.6) 4 (6.6)	0.41
Extent of surgery, n (%) Major resection	 1 (9.1)	 15	 0.25
ASA score, n (%) 2 3	 2 (18.2) 9 (81.8)	 24 (39.3) 37 (60.7)	0.29
Operation time, mean (SD)	343.7 (156.5)	389.5 (160.5)	0.42
EBL, median (IQR)	300 (850)	300 (400)	0.96
Transfusions, n (%)	1 (9.1%)	8 (13.1)	0.71
Severe postoperative complications, n (%)	0 (0)	5 (8.2)	0.32
In-hospital mortality, n (%)	0 (0)	1 (1.7)	0.66
Length of stay, n (%)	7 (5)	5 (3)	0.15
90-days decompensation	4 (36.4)	2 (3.2)	**0.002**
90-days mortality	1 (9.1)	0 (0)	**0.04**

Table 3: Analysis of secondary outcomes according to HVPG measurement and Clinically Significant Portal Hypertension. SD: standard deviation; IQR: inter-quartile range; BMI: body mass index; HBV: Hepatitis B virus; HCV: Hepatitis C virus; TACE: trans-arterial chemoembolization; ICG-R15: indocyanine green retention test at 15'; ASA: American Society of Anesthesiologists score; EBL: intraoperative estimated blood loss. *alone or associated with additional thermal ablation or resection.

4- Discussion

This prospective study showed the predictive role of preoperative HVPG on short-term results of liver resection for HCC on liver cirrhosis. Preoperative HVPG showed to have a better predictive ability than both ICG-R15 and Fibroscan on a composite outcome including PHLF, large postoperative ascites, severe postoperative complications and in-hospital mortality.

Such results are coherent with previous literature. A retrospective study by Stremitzer et al. reported that HVPG exceeding 5 mmHg was associated with higher rates of postoperative liver dysfunction (5 of 13 *versus* 1 of 18; *P* = 0·022) and ascites (7 of 14 *versus* 3 of 21; *P* = 0·022), and a longer hospital stay (median (range) 11 (7–26) *versus* 8 (4–20) days; *P* = 0·034)(46). Similarly, a prospective study by Boleslawsky et al. showed how a raised HVPG was associated with postoperative liver dysfunction (median 11 and 7 mmHg in those with and without dysfunction respectively; *P* = 0·017) and 90-day mortality (12 and 8 mmHg in those who died and survivors respectively; *P* = 0·026)(47). Esophageal varices, splenomegaly and thrombocytopenia were not associated with any of the endpoints. Indeed, in our study all the aforementioned indirect signs were not associated with the composite endpoint, as well as they were not constantly present in case of CSPH.

All these results may suggest the implementation of the use of HVPG measurement before liver resection in cirrhotic patients to give an additional tool in the preoperative assessment and patients ‘selection. Indeed, according to current guidelines, the presence of CSPH should be ruled out, since it is a contraindication to surgery(9, 48). Most liver centers investigate the presence of esophageal varices, splenomegaly and thrombocytopenia. However, such indirect signs were present only in 45.4%, 63.6% and 36.3%, respectively, of patients with CSPH. Nonetheless, CSPH was associated with a higher rate of 90 days cirrhotic decompensation: 36.4% vs 3.2% (p = 0.002), coherently with previous studies from Bruix et colleagues(15).

To date, few studies tried to address this lack of consensus among HPB centers regarding how PHT should be evaluated in the decision-making process(47, 49-51). All these studies included various definitions of PHT, considering that HVPG was directly measured only by Bruix et al. and Boleslawsy et. al. The first, published almost 30 years ago, described a series of 29 patients with cirrhosis, in whom a preoperative HVPG value of at least 10mmHg proved to be the most powerful predictor of liver decompensation at 3months(15). In an updated series of 43 patients reported by Llovet et al. in1999, the same group demonstrated that an HVPG of 10mmHg or more correlated independently with poor long-term survival(52). In the second study, the French authors focused on postoperative outcomes, concluding that an increased HVPG was associated with postoperative liver dysfunction and mortality after liver resection in patients with HCC and liver cirrhosis, whereas indirect criteria of PHT were not(47). Then, it must be underlined that both studies date back to 30 and 10 years ago, respectively, included few patients and were focused on different outcomes.

In the other studies, PHT was not measured, but defined by various indirect criteria (esophageal varices, splenomegaly associated with platelet count below 100000/mm3 and/or hepatofugal portal flow). All but one of these studies failed to demonstrate an influence of PHT on surgical outcome(49). However, these studies were retrospective and based on a wide variety of endpoints.

As in previous literature, a statistically significant association was found between the presence of esophageal varices and HVPG values, as well as for splenomegaly(53). Despite these correlations, neither esophageal varices nor splenomegaly and thrombocytopenia, which are classically used as indirect criteria to identify patients with significant PHT, were associated with the composite outcome, a finding consistent with the previous retrospective studies that investigated the influence of indirect criteria of PHT on surgical outcomes(17, 50, 51, 54).

In previous studies, liver stiffness was proposed as a valid candidate as a non-invasive surrogate marker for HVPG(55, 56). Similarly, LSM measured by Fibroscan showed a linear correlation with HVPG in a subgroup of patients within the study by Boleslawsy et al(47). However, in this latter paper the subgroup of patients undergoing LSM measurement was too small to investigate whether preoperative LSM might predict postoperative morbidity and mortality, a hypothesis that had been proposed already by other authors(57). The authors concluded that there is still a need for a precise measure of liver function in early-stage cirrhosis before liver resection.

Subsequent prospective studies confirmed that LSM measured by Fibroscan was an independent predictor of PHLF(58), and values higher than 12kPa had significantly lower 5-year overall survival rate (75.1% vs 57.3%, $p < 0.001$) and disease free survival rate (45.8% vs. 26.7%, $p < 0.001$)(59). However, both studies focused on a heterogeneous cohort of patients, investigating different outcomes, with no correlation to HVPG or CSPH. In our study, the comparison of ROC Curves showed an AUC of 0.604 (95% CI: 0.356 – 0.766) for LSM on the developing of the primary outcome, significantly lower than HVPG in a cohort of only cirrhotic patients.

The Eastern approach has always been to measure ICG clearance. In a previous Japanese study, ICG clearance was the single best test for predicting in-hospital mortality after hepatectomy for HCC in 127 patients, of whom 75 had cirrhosis and 91underwent major hepatectomy(60). However, only a few centers in Western countries routinely measure ICG. As ICG evaluates the detoxification function of the liver, whereas HVPG evaluates PHT and probably severity of fibrosis, both measurements may be useful independently in predicting morbidity and mortality. Thus, it may be of interest to investigate whether combining these tools for liver function assessment before hepatectomy would be more accurate than using each parameter alone. Our study firstly compared ROC Curves to predict the prognostic role of ICG-R15, HVPG and LSM on developing PHLF, major postoperative complications, large ascites and in-hospital mortality, showing a lower AUC for ICG (0.514, CI 95%: 0.298 – 0.721). It is interesting to note that a previous study by Pind et al. reported that ICG-r15 can be used as an indirect assessment of CSPH in compensated cirrhotic patients, proposing it as a screening tool for the identification of patients for endoscopy and measurement of HVPG. However, such findings were not confirmed by our study, where median ICG-R15 was not significantly associated with CSPH (17 ±27.9 vs 8.4 ±8.2, $p = 0.19$). Further studies could further investigate in this direction.

Despite its prospective design, this observational study has some limitations. Firstly, it is limited by the small sample size, that should be taken into account, especially when interpreting the negative and positive predictive values because the prevalence of some clinical endpoints, including mortality, was low. This also precluded a multivariable analysis of mortality. Secondly, the limited number of the events precluded some statistical analysis and added a size effect on the results of secondary outcomes analysis. Finally, the enrollment and the follow-up are still ongoing: these ones are only the results of an advanced interim analysis. Thus, data and results about the 1-year follow-up will be updated accordingly.

Nonetheless, this was the first prospective study to compare the predictive role of HVPG on cirrhotic patients undergoing surgery.

5- Conclusion

The predictive ability of HVPG on developing PHLF, in-hospital mortality, large postoperative ascites and major postoperative complications in cirrhotic patients undergoing elective surgery for HCC was significantly higher than LSM and ICG-R15 (p= 0.02).

Excluding patients with CSPH from HCC resection remains questionable in the absence of direct measurement of HVPG because indirect criteria of PHT are not constantly present in such patients.

Further prospective studies with dedicated designs should investigate on the exact role of HVPG within the pre-operative assessment of cirrhotic HCC patients, to reach the best postoperative outcomes, building a reproducible model tailoring case by case the available preoperative evaluations.

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