Systematic Review

Hepatic venous pressure gradient in hepatic resection for hepatocellular carcinoma

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Abstract

Liver transplantation is considered the gold standard for curative treatment of hepatocellular carcinoma (HCC) in patients with cirrhosis, but limited organ availability and high costs necessitate alternative options. Hepatic resection (HR) is preferred for select patients, providing tumor removal and prognostic information. However, HR has been associated with life-threatening complications, especially in the presence of clinically significant portal hypertension (CSPH). Current guidelines recommend HR only for patients with well-preserved liver function, normal bilirubin levels, good performance status, and no CSPH. However, advancements in surgical techniques and portal hypertension management are challenging these guidelines, potentially allowing the consideration of hepatic resection for HCC in cirrhotic patients with CSPH. Indeed, minimally invasive approaches improve safety and outcomes for selected CSPH patients and accurate assessment of CSPH allows risk stratification according to liver function, tumor location, and extent of resection. Thus, despite the negative impact of CSPH on HR outcomes, careful patient selection and minimally invasive techniques expand the potential for HR in CSPH patients. This comprehensive review examines the evidence on HR in HCC treatment for cirrhotic patients with CSPH, highlighting challenges in surgical decision-making, the importance of direct measurement of hepatic venous pressure gradient, and exploring the benefits and risks associated with HR. Moreover, it underscores the need for refined prediction models and algorithms to optimize patient selection and enhance surgical outcomes.

Keywords: Hepatocellular carcinoma, hepatic resection, hepatic venous pressure gradient, clinically significant portal hypertension, unresolved postoperative hepatic decompensation

INTRODUCTION

Patients with cirrhosis face an elevated likelihood of developing hepatocellular carcinoma (HCC)[1], which is one of the major causes of death, particularly in patients with decompensated disease[2]. According to the European association for the study of the liver (EASL), American association for the study of liver diseases (AASLD) guidelines, which are mainly based on the barcelona clinic liver cancer (BCLC) staging system, liver transplantation remains undoubtedly the best curative option for HCC in cirrhotic patients[3-5]. Nevertheless, graft shortage and high costs are increasing the demand for alternative treatments. In this context, hepatic resection (HR) represents the first choice, which has been historically regarded as a primary option for managing one to three unilobar HCC nodules of any size and, in particular, for tumors > 2 cm in the absence of extrahepatic disease or macrovascular invasion[6-9]. Indeed, HR allows radical removal of the tumors, and provides prognostic information on the basis of histology examination of the specimen. However, HR remains hampered with possibly life-threatening consequences, the most severe and difficult to treat of which is liver decompensation. As for now, there is consensus between European and American guidelines to perform HR in patients with well-preserved liver function, normal bilirubin levels, good performance status, and absence of clinically significant portal hypertension (CSPH), given that sufficient liver remnant is maintained[3-5]. The presence of preoperative CSPH is still widely considered a contraindication for HR, due to the reported higher risk of unresolved postoperative hepatic decompensation (UPHD), defined as the occurrence of jaundice, ascites, or encephalopathy after surgery persisting for > 3 months or variceal bleeding within 3 months after surgery) and mortality[6-8,10]. Nevertheless, the current advancements in the surgical scenario and management of portal hypertension are creating a "grey zone", challenging the exclusivity of traditional international recommendations. Indeed, updated EASL guidelines recently endorsed a risk algorithm for the prediction of UPHD and mortality, which loosens the inclusion criteria for minor resections[11], opening the door to HR for HCC in cirrhotic patients with CSPH. The aim of this review is to discuss the available published evidence regarding HR for treating HCC in cirrhotic patients with clinically significant portal hypertension.

Definition of clinically significant portal hypertension

A correct definition of the presence of CSPH, according to the most updated definitions, is paramount to avoid bias in patient selection and conclusions. Portal hypertension is defined as the presence of increased pressure in the portal venous system, and the gold standard for its detection in cirrhotic patients is still represented by the measurement of the hepatic venous pressure gradient (HVPG). HVPG is determined by the difference between the "wedged" (occluded) and "free" hepatic venous pressures, obtained through catheterization of a hepatic vein via transjugular access, and is considered normal when it is ≤ 5 mmHg. HVPG values > 5 mmHg and < 10 mmHg identify mild or subclinical portal hypertension, whereas in patients with viral or alcoholic cirrhosis, an HVPG ≥ 10 mmHg identifies CSPH[12]. HVPG measurement is safe, objective, reproducible, accurate and provides prognostic information independent of liver function[7,13]. Patients presenting CSPH are more likely to develop gastroesophageal varices, overt clinical decompensation (ascites, variceal bleeding, and hepatic encephalopathy), and postsurgical decompensation. The gradient threshold of 12 mmHg has been identified as the threshold above which cirrhotic patients are at high risk of developing ascites, presenting a first variceal bleeding event, or rebleeding[14-17], whereas HVPG values > 16 mmHg, especially ≥ 20 mmHg, have been associated with a high risk of postsurgical mortality in elective extrahepatic surgery[18]. In the context of HR, EASL and AASLD practice recommendations indicate that in HCC patients with a single tumor, an evaluation of portal hypertension should be performed prior to treatment choice[3,4]. HVPG measurement is considered the gold-standard methodology for this purpose and should be regarded as the standard of care. However, it is not widely available, and its routine use has not yet been integrated into non-specialized centers. Thus, non-invasive methods, sufficient to rule in CSPH, have been individuated over the last decades. The currently recognized ones are[12]:

● the presence of abdominal portosystemic collaterals visualized by upper endoscopy or imaging studies;

● in patients with virus-related "compensated advanced chronic liver disease" (cACLD) and non-obese (BMI ≤ 30 kg/m²) metabolic dysfunction-associated steatohepatitis (MASH)-related cACLD, liver stiffness measured by transient elastography value ≥ 25 kPa in at least two measurements on different days under fasting conditions.

These methods show high specificity for the diagnosis of CSPH, but rather low sensitivity in ruling it out. Moreover, LS is still limited by: (1) the presence of ongoing liver damage, ascites, and non-viral and non-alcoholic etiologies of liver disease; (2) tumor location, which might interfere with LS measurements; (3) obesity, with or without associated steatotic liver disease. Moreover, its correlation with values of portal pressure and, thus, thresholds of different risks is obviously suboptimal.

According to the Baveno III expert consensus, the presence of ascites could also define CSPH; however, this criterion has been excluded in the updated definition during Baveno VI and VII consensus[12,19] and is now classified as a non-specific sign of CSPH due to its low specificity.

Another non-specific sign is represented by the combination of splenomegaly (longitudinal diameter exceeding 12 cm) and thrombocytopenia (platelet count < 100,000/µL). Even though the current EASL guidelines accept this association as a surrogate method for diagnosing CSPH[7,20], their sole presence is not sufficient, as it also includes a variety of other pathological conditions, mainly hematological, which do not necessarily involve portal hypertension[6,21-23].

Moreover, approximately 50%-60% of compensated patients, without any evident indirect signs of portal hypertension, already exhibit CSPH upon hemodynamic assessment, so HVPG still represents the gold standard with the highest positive and negative predictive value for the assessment of portal hypertension[6,7,13].

Clinically significant portal hypertension and HCC
Portal hypertension predicts the development of HCC regardless of the degree of liver impairment or the length of liver illness. Interestingly, the presence of esophageal varices in patients with cirrhosis has been associated with the risk of HCC occurrence[24,25], and Ripoll *et al.* demonstrated that patients with an HVPG > 10 mmHg have an HCC incidence of 2.1% per year, while those with an HVPG < 10 mmHg only 0.35% per year[26]. One possible explanation for this association might be that portal hypertension may cause an upregulation of vascular endothelial growth factor (VEGF) expression, leading to a higher risk of developing HCC and its progression[27]. Conversely, HCC can aggravate portal hypertension due to arteriovenous shunts within the tumor, as well as macroscopic or even microscopic invasion of the portal vein and/or its branches or the development of portal vein thrombosis[28,29].

Patients with CSPH and HCC are also at an increased risk of developing UPHD after HR. Previous studies conducted in the late 1990s reported that the presence of preoperative CSPH was independently associated with UPHD and with poor long-term survival in Child-Pugh A patients, compared to those with an HVPG < 10 mmHg[8,10]. Although no differences were individuated according to the extent of liver resection or location of the tumor, all patients included in these studies underwent laparotomic HR. Furthermore, the group of non-decompensated patients still included some with a pre-surgical HVPG ≥ 10 mmHg, up to 15 mmHg in one study[10], and the odds ratio for decompensation of patients with HVPG ≥ 10 mmHg had a very wide confidence interval in the other one[8]. Moreover, the main cause of death was tumor

progression (68%), whereas hepatic failure only in 16% of patients. Even though subsequent studies[23,30] and meta-analyses[6,31,32] confirmed the negative prognostic impact of CSPH on postoperative outcomes, in each study, it was possible to appreciate a subgroup of patients with CSPH who did not face UPHD. Moreover, the heterogeneity in the different methods used for diagnosing CSPH in these studies, which included non-specific ones as well, coupled with the differences between surgical approaches and the extent of liver resections, do not allow for a correct assessment of the role of CSPH in the selection process of surgical candidates for HR using this data[33]. Nonetheless, the existing evidence, while influential in forming international recommendations[3,4], is now beginning to falter due to the significant change in the surgical scenario in cirrhotic patients.

The technical refinements, the implementation of laparoscopy as the standard of care for HR, the possibility to perform minimally invasive surgery, and improvements in postoperative management have increased the overall safety of HR during recent years, achieving a parallel reduction of resection-related mortality in "ideal patients" without CSPH from 10%-20% to a near-zero rate in hub centers[1,8,34-40]. Moreover, much evidence confirms the superiority of HR in terms of oncological response over locoregional treatments for a similar number of nodules[41-44]. In this light, HR has become competitive with liver transplantation in terms of survival benefits[45]. In addition, HR can also be considered as a bridge to liver transplantation to avoid dropout and tumor progression, allowing at the same time for pathological characterization of the tumor to better predict the risk of post-transplant recurrence and subsequent graft allocation[34,46-49]. Thus, the interest in exploring its outcomes in patients with CSPH previously labeled as "non-ideal" has been renewed.

In 2011, Truant *et al.* demonstrated that the laparoscopic approach strongly impacted postsurgical morbidity and mortality in a small cohort of cirrhotic patients, allowing HR despite the presence of CSPH [death rate was 33.3% (4/12) in the open surgery group and 0% (0/5) in the laparoscopy group ($P = 0.2$)][50]. Similarly, Boleslawski *et al.* showed a significant decrease in overall morbidity in patients who underwent laparoscopic HR and that the highest negative impact of CSPH on mortality was observed after major hepatectomy (≥ 3 segments)[21]. Although there are no randomized controlled trials comparing laparoscopic *vs.* open liver resection for HCC, the available data coming from tertiary referral centers indicate that minimally invasive HR of up to two segments is safe and feasible in patients with CSPH[51-55]. Recent systematic reviews and meta-analyses are also confirming that minimally invasive surgery allows a reduction in both postoperative liver failure and postoperative ascites development over an open approach for same-sized tumors[36,55-58]. The most relevant difference between the two approaches is that the laparoscopy minimizes the HR-induced parenchymal damage and loss of the liver's collateral blood/lymphatic flow, without compromising the oncological outcome[36]. In this light, several other centers explored the option of HR in patients with CSPH, and it has been estimated that the strict exclusion of patients with CSPH from surgery precludes successful resections to approximately one-quarter of the patients who do not exhibit any short to mid-term postoperative sequelae[21,46,50,51,53,59-63]. Among these studies, those assessing the presence of CSPH by means of HVPG measurement are reported in Table 1[10,21,23,46,50,51,53,59-61]. Comparing the results obtained in different studies is difficult, since the surgical techniques, the extent of resections, the characteristics of the selected patients, and the definitions of the outcomes differ significantly. However, it is worth noting that in each study, there are subpopulations of patients with CSPH who are not presenting significant complications following surgery. Indeed, the selection criteria applied by Azoulay *et al.* (no previous history of ascites, variceal rupture, or spontaneous encephalopathy; no prohibitive comorbidities; Child-Pugh class A or B)[59] increased the number of HR for HCC by 21% compared to standard BCLC criteria, including also patients with severe portal hypertension (HVPG up to 26 mmHg) and Child-Pugh class B patients (provided that this was because of biliary obstruction). Thus, these data suggest that CSPH should not be considered an absolute contraindication to

Table 1. Studies assessing outcomes of hepatic resection in cirrhotic patients with clinically significant portal hypertension (only studies defining CSPH by means of HVPG measurement and considering patients with HVPG ≥ 10 mmHg have been included)[10,21,23,45,49,50,52,58-60]

Study	Number of patients	Surgical approach	Number of patients with HVPG ≥ 10 mmHg	HVPG ranges according to study outcome: postoperative liver decompensation	HVPG ranges according to study outcome: Mortality	Relevant conclusions
Bruix *et al.*[10] 1996	29 (100% Child A)	NA	NA Total mean ± SD: 9.9 ± 4.4 mmHg	Postoperative liver decompensation defined as: jaundice, ascites, or encephalopathy Yes: HVPG 7.4 ± 3.4 mmHg No: HVPG 13.9 ± 2.4 mmHg	NA	Preoperative HVPG value of at least 10 mmHg proved to be the most powerful predictor of liver decompensation at 3 months
Truant *et al.*[50] 2011	37 (90% Child A)	Laparoscopy group (n = 19) Open surgery group (n = 18)	16 patients (HVPG up to 19 mmHg) Laparoscopic group: 10 (52.6%) Open surgery group: 6 (33.3%)	Postoperative liver decompensation defined as: ascites, encephalopathy, variceal bleeding Yes: -Laparoscopic group: HVPG range 4-14 mmHg -Open surgery group: HVPG range 2-19 mmHg No: NA	NA	Laparoscopic approach strongly impacts postsurgical morbidity and mortality, despite similar portal hypertension severity
Boleslawski *et al.*[21] 2012	40 (97.5% Child A)	Laparoscopy group (n = 17), 4 were converted to open surgery Open surgery group (n = 23)	18 patients (HVPG 3rd quartile: 11 mmHg)	Postoperative liver decompensation (defined as: serum bilirubin > 5 mg/dl on or after port-operative day 5, INR > 2 associated with bleeding complications requiring transfusion, ascites, and/or encephalopathy): Yes: HVPG 11 mmHg (IQR 8-13) No: HVPG 7 mmHg (IQR 5-10)	Yes: HVPG 12 mmHg (IQR 10-14) No: HVPG 8 mmHg (IQR 6-11)	HVPG ≥ 10 mmHg was associated with postoperative liver dysfunction, severe complications, and mortality However, a significant decrease in overall morbidity was observed in patients who underwent laparoscopic HR, and the highest negative impact of CSPH on mortality was observed after major hepatectomy
Llop *et al.*[23] 2012	97 (100% Child A) potentially candidate - 46 underwent HR	NA	10 patients (HVPG up to 12.5 mmHg)	Postoperative liver dysfunction (defined as: ascites): Yes: 3 patients with HVPG > 10 mmHg (within 8 months from HR) No: up to 12.5 mmHg Mortality: NA		Patients with HVPG < 10 mmHg treated with hepatic surgery have a very good outcome (no deaths or clinical decompensation)
Cucchetti *et al.*[45] 2016	70 (100% Child A)	Laparotomic: 96.9% Laparoscopic 3.1% (2 patients with HVPG < 10 mmHg, and none of those	34 patients (HVPG up to 18 mmHg)	Postoperative liver decompensation (defined as: at least one grade B/C complication according to ISGLS proposal*) Yes: -4 patients (11.1%) with HVPG < 10 mmHg (1	NA	Postoperative and 90 days mortality rates were null HVPG ≥ 10 mmHg was correlated to a higher risk of ascitic decompensation in the short term after surgery An HVPG ≥ 10 mmHg but a MELD score still below 10 was correlated with safety surgery if a limited resection can be

	with HVPG ≥ 10 mmHg)		needed salvage transplantation), -17 patients (50%) of those with HVPG ≥ 10 mmHg (none needed salvage transplantation)		performed
	Minor resection group (18 patients with HVPG < 10 mmHg, and 27 of those with HVPG ≥ 10 mmHg)				
	Major resection group (18 patients with HVPG < 10 mmHg, and 7 of those with HVPG ≥ 10 mmHg)				
Molina *et al.*[61] 2018	45 (100% Child A)	Laparoscopic, 3 were converted to open	15 patients (HVPG up to 14 mmHg)	NA	NA	Three patients (6%) developed ascites, and only one of them was in the CSPH group Postoperative hospital stay was similar in both groups No significant difference between the groups in terms of survival. None of the patients in the CSPH group died within the first year after surgery
Lim *et al.*[60] 2018	45 (98% Child A)	Laparoscopic and robot-assisted, 4 were converted to open	27 patients (HVPG up to 26 mmHg)	NA	NA	Severe morbidity and the 90-day mortality were nil, whereas overall moderate morbidity was significantly higher in the CSPH group; however, the two groups did not differ in the rate of unresolved liver decompensation (jaundice, ascites or encephalopathy 3 months after surgery).
		Minor resection group (*n* = 43)	Minor resection group: 25 (58%)			
		Major resection group (*n* = 2)	Major resection group: 2 (100%)			Expanding laparoscopic liver resection for HCC to selected patients with HVPG ≥ 10 mmHg can increase the feasibility of surgery by 40% at the cost of significant increases in the moderate morbidity rate and the duration of stay compared to patients without CSPH
Lim *et al.*[60] 2019	65 (95% Child A)	Laparoscopic and robot-assisted laparoscopic group (*n* = 25)	14 (HVPG 3rd quartile: 11 mmHg)	Postoperative liver decompensation defined as: jaundice, ascites, or encephalopathy within 3 months after surgery	NA	Unresolved liver decompensation rates did not differ in patients with HVPG ≥ or < 10 mmHg.
		Open surgery group (*n* = 40)		Yes: HVPG 8 mmHg (IQR 4-9)		Intensive care unit and hospital stays were significantly longer in the CSPH group.
		Minor resection group (*n* = 19)		No: HVPG 7 mmHg (IQR 5-10)		No difference in the 1 and 2 years overall survival and recurrence-free survival.
		Major resection group (*n* = 46)				
Azoulay *et al.*[59] 2020	79 (99% Child A)	Laparoscopy group (*n* = 27), 1 was converted to open surgery	79 patients (HVPG up to 26 mmHg)	Postoperative liver decompensation **:	NA	The 90-day mortality was 6%, the morbidity rate 67%, and severe morbidity rate 27 %.
				Yes: HVPG 4 mmHg (IQR 12-20)		
		Open surgery group (*n* = 52)		No: HVPG 11 mmHg (IQR 10-13)		An HVPG ≥ 10 mmHg, an elevated preoperative serum total bilirubin, and an open approach were independent predictors of postoperative liver decompensation

			Textbook outcome**:		Patients with cirrhosis, HCC, and HVPG ≥ 10 mmHg can undergo HR with acceptable mortality, morbidity, and liver decompensation rates.
		Minor resection group (*n* = 57)			
			Yes: HVPG 11 mmHg (IQR 10-14)		
		Major resection group (*n* = 22)	No: HVPG 12 mmHg (IQR 11-16)		The laparoscopic approach was the sole predictor of a textbook outcome.
Casellas-Robert *et al.*[51] 2020	96 (100% Child A)	Laparoscopy	NA	NA	Patients with HVPG ≥ 10 mmHg had higher rates of postoperative ascites, liver failure, encephalopathy, and length of stay.
		Minor resection group (*n* = 91)	31 patients (HVPG 3rd quartile: 10 mmHg)		
		Major resection group (*n* = 5)	Minor resection group: 30 (33%)		The postoperative mortality rate was nil.
			Major resection group: 1 (20%)		

* Definition according to ISGLS proposal: grade A corresponds to a substantial regular postoperative course, whereas grade B results in a deviation from the regular clinical management but is manageable without invasive treatment, and grade C results in a deviation from the regular clinical management requiring invasive treatment; ** Postoperative liver decompensation was defined as present when at least 1 of the following complications occurred within 3 months after resection: liver failure, ascites, or encephalopathy. Persistent liver decompensation was defined as present when at least 1 of the following three liver complications occurred at 3 months after resection: jaundice and/or ascites and/or encephalopathy. A textbook outcome was achieved when all 6 of the following criteria were met: no perioperative transfusion; no major postoperative complications (CCI < 26.2); no mortality within 90 days or during the hospital stay; hospital stay < 50th percentile of the total cohort ≥ 1 mm), and no readmission.

HR on its own[62-65], and justify an update of current guidelines. Moreover, in all these studies, the threshold of 10 mmHg was still used as the only discriminant concerning the presence of CSPH, whereas stratification of post-HR risk of decompensation or mortality according to HVPG values should be investigated in this area.

How to predict the postoperative risk of liver decompensation in patients with CSPH?
The current challenge lies in determining the optimal treatment for patients who do not meet the criteria of being Child-Pugh A with no CSPH, having normal liver function tests, and possessing early-stage tumors, all of which may safely qualify them for HR. To address this, the best strategy would involve combining the predictive value of HVPG with other patient- and tumor-related variables[9,44,62,66,67], such as liver function, comorbidities, performance status, body mass index, the feasibility of minimally invasive approaches, and the extent of liver resection, as well as localization, volume, and number of HCC nodules. Moreover, the availability of surgical innovations, the expertise of medical centers, and the number of procedures performed per year should also be considered in the decision-making process, as they could also impact the morbidity and mortality rates associated with HR in patients with CSPH[44,60,65,68]. For instance, referral centers may offer complex procedures such as major hepatectomy via portal vein embolization to obtain a sufficient future remnant liver, enabling subsequent HR of larger areas[60].

Unlike American guidelines, which are still not recommending HR in patients with Child other than A and/ or in CSPH, EASL endorsed a simple ready-to-use algorithm allowing preoperative risk stratification according to a hierarchic order of factors represented by the presence of CSPH, extension of the hepatectomy, and model for end-stage liver disease (MELD) score[11]. A study of 543 HCC resections revealed that in the presence of CSPH, the probability of decompensation is mostly determined by the volume of the liver resection, with minor hepatectomy showing acceptable outcomes for patients with CSPH (a postoperative decompensation rate of 28,6%, a median hospital stay of 8 days, and a liver-related mortality of 9%). After the extension of liver resection, the evaluation MELD score represents the next step of the algorithm, for which a cutoff of 9 has been individuated to discriminate low and intermediate risk. For patients lacking all risk factors (no CSPH, minor hepatectomy, MELD ≤ 9), the risk for postsurgical liver decompensation and liver-related mortality was < 5%. Despite the fact that this algorithm was developed from a series of HR performed with an open approach and CSPH was defined by the presence of indirect signs of portal hypertension (presence of esophageal varices or the coexistence of a low platelet count and splenomegaly), some authors reported reasonable surgical and acceptable long-term oncological outcomes by following this protocol in this subset of well-selected patients with HVPG ≥ 10 mmHg, showing postoperative liver decompensation rates ranging between 6%-33% and 3-year survival ranging between 72%-79%[60,69]. Accordingly, minor resections can be safely operated in patients with HVPG ≥ 10 mmHg but with a MELD score lower than 10[46].

Moreover, recent studies[70,71] have proposed online calculators predicting the risk of UPHD in patients with HCC using pre-surgery variables. However, due to current recommendations, the small number of patients with portal hypertension included in this cohort lowers the robustness of these predictions on patients with CSPH. Berardi *et al.* evaluated the outcomes of Child B patients undergoing HR (56.9% showed signs of CSPH)[72]. They were able to demonstrate that a strict selection of candidates and minimization of surgical stress could lower the rate of adverse events, offering good long-term outcomes, and proposed an online model for the prediction of surgical morbidity risk (mainly predicting the risk of ascites), long-term survival and disease-free survival for these patients. There is evidence that laparoscopic and robotic-assisted resections of HCC might lower the risk of UPHD in Child B patients[73,74]. Furthermore, the China liver cancer staging (CNLC) system already enables HR in BCLC B patients, including those with multinodular and locally advanced HCC with neoplastic portal vein thrombus[75]. As a matter of fact, the Child B class includes a wide variety of patients with significantly different degrees of portal hypertension and liver function, so it should not be seen as an absolute contraindication per se, but should instead be included in the global evaluation of the patient together with the other available variables. Although the previously cited prediction models[70,72] have suggested that minor hepatectomies using a minimally invasive approach can be safely performed in well-selected patients by considering various factors, such as the presence of comorbidities and CSPH, they primarily assess CSPH indirectly in their design. Consequently, their prognostic power might not be optimal in this context. Further studies focusing on the presence of CSPH rather than the Child-Pugh class could aim at the implementation of direct measurement of HVPG, obtaining a more precise allocation of some of these patients to potentially radical surgery, especially when they are not eligible for liver transplantation. On the other hand, considering the limits posed by HVPG availability, these algorithms highlight a crucial distinction: CSPH has a limited impact on postsurgical complications in cases of minimally invasive surgery for superficially located tumors, whereas the need for direct measurement of HVPG becomes apparent when planning a major staged hepatectomy. Therefore, the role of indirect signs of CSPH should be explored in the first subgroup of patients.

Is HVPG measurement replaceable with indirect surrogates in the prediction of clinical outcomes after HR in patients with HCC?

The role of non-invasive surrogates in estimating the presence of CSPH has been explored in the many contexts in which HVPG has demonstrated its significance, including for the stratification of postoperative outcomes after HR. However, there is no agreement on how CSPH should be assessed in this decision-making process. A recent meta-analysis[6] revealed that direct measures of evaluating CSPH have a stronger correlation with clinical outcomes after HR compared to indirect methods (presence of gastroesophageal varices or thrombocytopenia associated with splenomegaly), particularly for the assessment of UPHD. Boleslawski *et al.* conducted a study involving 40 patients with HCC and cirrhosis[21]. They found that a preoperatively elevated HVPG [median 11 mmHg (IQR 8-13)] was independently linked to a higher risk of postoperative liver dysfunction and 90-day mortality following hepatic resection (HR). In contrast, indirect markers of CSPH, such as the presence of esophageal varices and/or splenomegaly coupled with thrombocytopenia, did not exhibit such an association. The albumin-bilirubin score (ALBI score) has also been investigated for the stratification of patients for HR, showing more granularity than the Child-Pugh score[76,77]. However, data are insufficient to determine if these indirect criteria are reliable enough to substitute direct HVPG measurement in the prediction of postsurgical outcomes.

Liver stiffness (LS), as assessed by transient elastography, has been demonstrated to have a stronger correlation with HVPG[78,79], and also seems to perform well as a predictor of postoperative liver failure in HCC patients undergoing HR[23,67,80,81]. Approximately 50% of patients with potentially resectable HCC can be categorized based on the presence of CSPH using a LS measurement of 25 kPa or higher[12,23,82]. Moreover, it has been demonstrated that patients with an LS value < 13.6-14.2 kPa (depending on the different characteristics of the studied cohorts) do not develop postoperative liver failure and can be safely allocated to HR, excluding CSPH, whereas about 55% of patients with LS ≥ 21 kPa developed it, suggesting that these patients should be instead evaluated for liver transplantation[23,80]. Nevertheless, patients with LS values between 13.6-21 kPa had an intermediate risk; thus, LS is not useful by itself to correctly predict the postsurgical prognosis of patients included in this "grey zone"[80,81]. Moreover, the aforementioned limits of LS must be kept in mind in this context as well. Spleen stiffness, which demonstrates a stronger correlation with HVPG, could overcome LS limitations[83,84]. However, there remains insufficient data to confidently advocate for its immediate adoption as a reliable tool to predict the outcome of HR in patients with cirrhosis.

These results suggest that indirect methods for HVPG estimation still need further validation and cannot yet be recommended for precise risk stratification in the hepatic surgery context. One strategy to improve their reliability could be the combination of different measures by integrating complementary information[82]. For example, it has been reported that the combination of LS with platelet count, body mass index, and spleen diameter has the potential to reduce the number of patients included in the "grey zone", allowing for correctly ruling in CSPH in a share of patients as high as 85%[22]. Several other studies are now succeeding in demonstrating the high potential of various combinations of indirect methods in predicting CSPH[12,85,86], but their reliability in the prediction of postoperative liver failure needs to be established.

In the attempt to use current evidence, even if still limited, we propose an algorithm to help decide when to perform HVPG measurement prior to HR [Figure 1]. Research should continue towards the further refinement of preoperative algorithms, including direct measurement of HVPG, until reliable indirect markers are defined. One strategy to allow higher inclusion in future studies of patients with CSPH for HR could involve considering HR and liver transplantation together rather than individually, presenting transplantation as a "salvage" option in the event of recurrence or for significant decompensation following surgery.
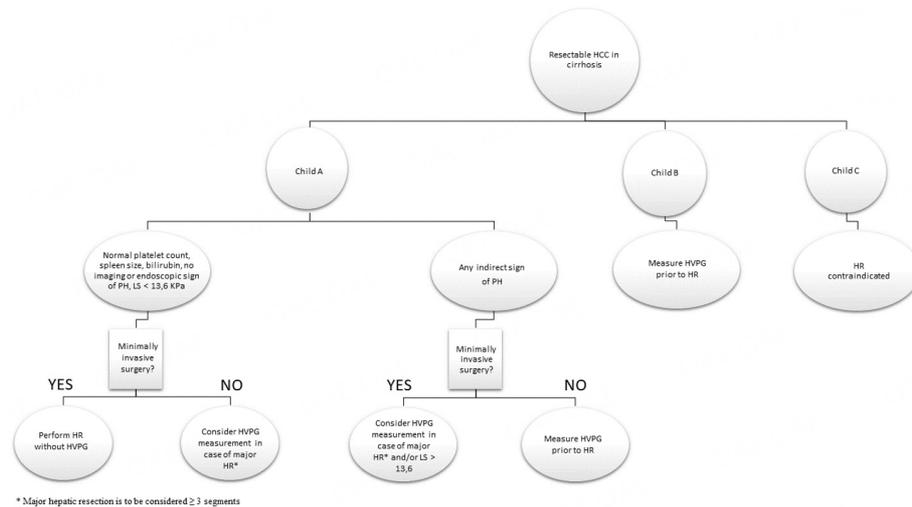
Figure 1. A decision-supporting algorithm to determine when to measure HVPG before HR. HCC: hepatocellular carcinoma; PH: portal hypertension; LS: liver stiffness; HR: hepatic resection; HVPG: hepatic venous pressure gradient.

CONCLUSIONS

In conclusion, CSPH adversely impacts the prognosis of patients with HCC and cirrhosis undergoing HR. However, CSPH alone should not be considered an absolute contraindication to proceeding with the surgery. By considering the feasibility of minimally invasive surgery, the location of nodules, liver remnant volume, preoperative care management, center expertise, and patient comorbidities, access to HR can be safely expanded to a significant share of patients. Through this evaluation process, selected patients with a MELD score < 10 and CSPH, including some selected Child-Pugh B patients, can benefit from HR, showing improved morbidity rate and survival compared to previous reports, without jeopardizing the possibility of a "salvage transplant" in case of histological indicators of a high risk of early recurrence. Research should focus on the individuation of multi-parametric algorithms for an individualized prediction of the prognosis of HR for patients with HCC and cirrhosis, simultaneously considering multiple easy-to-access preoperative variables and HVPG. HVPG direct measurement remains the most useful tool for preoperative assessment. A further sub-stratification of HVPG levels might highlight different thresholds to properly assess the risks and advantages of surgery *vs.* locoregional treatments or liver transplantation. Meanwhile, the role of non-invasive estimators of HVPG should also be validated in this context, which can be achieved by combining several different methodologies to improve their reliability. Until then, direct measurement of HVPG should still retain the "gold standard" label and be considered the only method for a correct definition of CSPH in future studies aiming to predict postsurgical clinical outcomes.

DECLARATIONS

Authors' contributions

Conception and design of the study, selection and interpretation of data, drafting the article and revising it critically for important intellectual content, final approval of the version to be published: Shalaby S, Senzolo M

Revising it critically for important intellectual content, final approval of the version to be published: Burra P

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Ethical approval and consent to participate

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