HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

Portal Hypertension and the Outcome of Surgery for Hepatocellular Carcinoma in Compensated Cirrhosis: A Systematic Review and Meta-analysis

Annalisa Berzigotti,[1,2]* Maria Reig,[1,3]* Juan G. Abraldes,[1,2] Jaime Bosch,[1,2]** and Jordi Bruix[1,3]**

Whether preoperative clinically significant portal hypertension (CSPH) has or not an impact on the outcome of surgery for hepatocellular carcinoma (HCC) in patients with compensated cirrhosis is debated. This systematic review assesses the impact of CSPH on the outcome of HCC in patients with compensated cirrhosis treated with surgery. We performed a systematic search of the MEDLINE database (articles published in full in English language from 1996 to October 2013) and related bibliography for studies reporting on the postoperative outcomes (3- and 5-year mortality and/or early clinical decompensation) of patients with HCC and compensated cirrhosis treated with surgery according to the presence or absence of CSPH. Independent extraction of articles by two authors using predefined data fields, including study quality indicators, was used; pooled analyses were based on random-effects models. Eleven studies in total met our inclusion criteria (eight studies for 3- and 5-year postoperative mortality and eight for postoperative clinical decompensation). Moderate heterogeneity among studies for both outcomes was observed, which disappeared after pooling studies using similar methods to assess CSPH. The presence of CSPH increased the risk of 3- and 5-year mortality versus absence of CSPH (pooled odds ratio [OR] for 3-year mortality: 2.09; 95% confidence interval [CI]: 1.52-2.88; for 5-year mortality: 2.07; 95% CI: 1.51-2.84). CSPH also increased the risk of postoperative clinical decompensation (pooled OR: 3.04; 95% CI: 2.02-4.59). *Conclusions:* CSPH (evaluated by any method) significantly increases the risk of 3- and 5-year mortality and of clinical decompensation after surgery for HCC. (HEPATOLOGY 2015;61:526-536)

The current guidelines for the management of hepatocellular carcinoma (HCC)[1,2] suggest that surgical resection should be considered the first treatment option for patients with normal bilirubin and without clinically significant portal hypertension (CSPH) in the very early stage (Barcelona Clinic Liver Cancer [BCLC] stage 0) with a single nodule of HCC (nodule $\leq$2 cm) and for patients in the early stage (BCLC stage A) with a single nodule of HCC *of any size*.[3] For patients at a very early stage, the analysis of the resected HCC informs about risk of recurrence and potential consideration for liver transplantation.[4] If this option is not feasible, ablation will offer the same survival expectancy and may be considered the first-line approach.[4]

These recommendations arise from studies of the BCLC group,[5,6] which reported that presence of

Abbreviations: AASLD, American Association for the Study of Liver Diseases; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CSPH, clinically significant portal hypertension; EASL, European Association for the Study of the Liver; GEV, gastroesophageal varices; HCC, hepatocellular carcinoma; HVPG, hepatic venous pressure gradient; OR, odds ratio; PH, portal hypertension; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QUIPS, Quality In Prognosis Studies tool; PVP, portal vein pressure.

From the [1]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Barcelona, Spain; [2]Hepatic Hemodynamic Laboratory, Liver Unit, Hospital Clinic, Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; and [3]BCLC group, Liver Unit; Hospital Clinic, Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS), Barcelona, Spain.

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.27431/suppinfo.

Received April 24, 2014; accepted September 8, 2014.

This study has been supported by grants from the Instituto de Salud Carlos III (PI11/01830 to Jordi Bruix and FIS 13/00341 to Jaime Bosch), FEDER. CIBERehd is funded by the Instituto de Salud Carlos III.

**Joint first authors. Both equally contributed to this work.*

***Joint senior authors.*

CSPH and total bilirubin >1 mg/dL are independent predictors of a higher risk of clinical decompensation and mortality after surgical resection of HCC in patients with compensated cirrhosis.

Given this evidence, European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) guidelines[1,7,8] recommend to assess CSPH in patients with compensated cirrhosis, preserved liver function, and HCC to better define the first treatment option, as well as to consider the presence of CSPH as a predictor of worse survival in candidates for surgery. Nonetheless, these recommendations have been matter of debate. Groups from various countries,[9,10] using different criteria to diagnose CSPH, have suggested that according to their experience CSPH has small, if any, impact on postoperative outcomes of patients with compensated cirrhosis and continue to advocate surgical resection as the first treatment option for HCC regardless of the presence of portal hypertension (PH). Because this debate is still open,[11] robust data are required to provide evidence for guiding clinical decision making in this field.

The aim of the present systematic review and meta-analysis is to explore in detail the impact of CSPH on the postoperative outcomes (survival and clinical decompensation) in published series of compensated patients with cirrhosis with preserved liver function and HCC without extrahepatic spread and/or macrovascular invasion.

Materials and Methods

Literature Search. This systematic review was conducted following an *a priori* established protocol and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12]

Search Strategy. A systematic search of MEDLINE was performed with different combinations of the following keywords: "hepatocellular carcinoma" AND ["surgery" OR "hepatectomy", OR "resection"] AND "portal hypertension" limiting the dates from January 1996 (year of publication of the first article in this area reporting that hepatic venous pressure gradient [HVPG] ≥10 mmHg is an independent negative prognostic factor on postoperative outcome in this setting[5]) to October 10, 2013. In addition, bibliographies of review articles and all included studies were handsearched to identify other relevant studies. The title and abstract of studies identified in the search were reviewed by two authors independently (M.R. and A.B.) to exclude studies that did not address the research question of interest, based on prespecified inclusion and exclusion criteria (see below). After this initial screening, the database of selected studies was cross-checked to identify discrepancies. If multiple publications from the same cohort were found, data from the most recent comprehensive report were included. Thereafter, review of full-text articles and quality assessment was carried out by the same independent reviewers, and a third reviewer was available to adjudicate on any conflicts arising between the two reviewers. Figure 1 summarizes the process of study identification, inclusion, and exclusion according to PRISMA guidelines.[12]

Studies Selection. Taking into account that this systematic review researched data regarding prognosis, both retrospective and prospective studies were considered eligible. In order to ensure the quality of this research, only fully published reports were considered and abstracts were not looked for.

Studies were included in the qualitative analysis if they met all the following criteria: (1) were original complete publications in English language with full-text accessible; (2) included patients with cirrhosis and HCC eligible for surgery with clearly defined criteria; (3) assessed PH in these patients clearly stating how this was defined; (4) reported postoperative outcome of surgical therapy of HCC (survival and/or clinical decompensation); and (5) reported the postoperative outcome according to the presence or absence of CSPH.

CSPH was defined according to the following definitions: HVPG ≥10 mmHg or portal vein pressure

Address reprint requests to: Jordi Bruix, M.D., Barcelona Clinic Liver Cancer (BCLC) Group, Liver Unit, Hospital Clinic Barcelona, IDIBAPS, University of Barcelona, c/Villarroel 170, 08036 Barcelona, Spain. E-mail: jbruix@clinic.ub.es; fax: (34) 3-4515522 or Prof. Jaume Bosch, M.D., Barcelona Clinic Liver Cancer (BCLC) Group, Liver Unit, Hospital Clinic Barcelona, IDIBAPS, University of Barcelona, c/Villarroel 170, 08036 Barcelona, Spain. E-mail: jbosch@clinic.ub.es; fax: +34 3-4515522.

View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep.27431

Potential conflict of interest: Dr. Bruix consults, advises, and received grants from Bayer. He consults and advises BioCompatibles and Novartis. He consults and received grants from Daichi and Arqule. He consults for Abbott, Bristol-Myers Squibb, GlaxoSmithKline, Kowa, Lilly, and Roche.

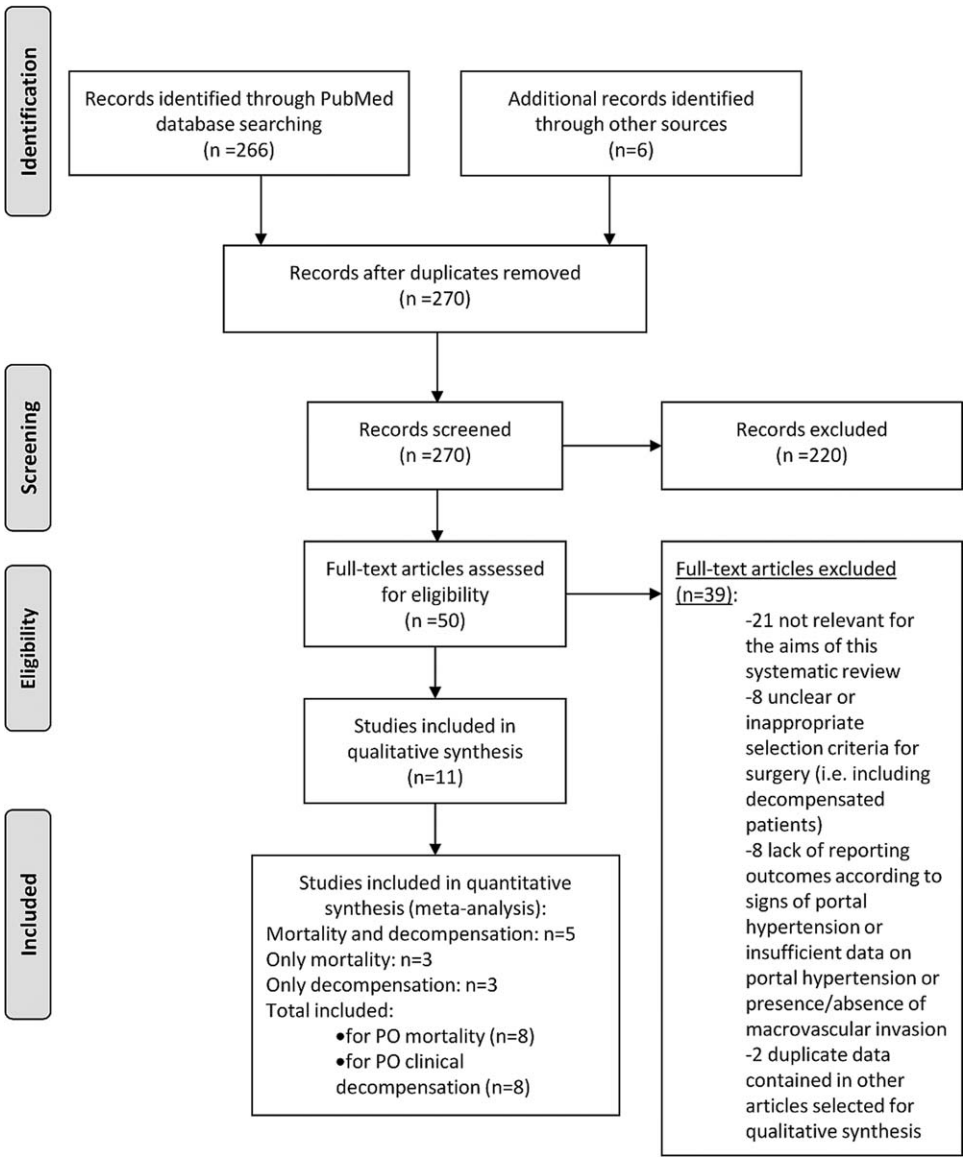

Fig. 1. PRISMA flowchart showing study identification and selection process. Abbreviation: PO, postoperative.

(PVP) ≥20 cmH2O or standard surrogate criteria, including presence of gastroesophageal varices (GEV) or platelet count <100,000/mL and spleen diameter >12 cm.

Studies were excluded if they did not meet the above-mentioned criteria; in addition, case reports, reviews, corresponding letters, or editorials were excluded.

Data Extraction. Data regarding the following aspects were abstracted in a standardized data abstraction form Microsoft Excel 2007 (Microsoft Corp, Redmond, WA): (1) study characteristics: reference; inclusion period of study; countries where the study was carried out; retrospective or prospective design; and duration of follow-up (mean or median); (2) patient characteristics: Child-Pugh class and proportion of patients belonging to Child-Pugh A class; proportion of patients with PH and with esophageal varices; proportion of patients with a single HCC nodule; (3) methods used to assess PH; (4) type of resection; (5) outcomes according to the presence or absence of PH: 3- and 5-year overall survival after surgery (primary outcomes); postoperative clinical decompensation (30-90 days); (6) intraoperative transfusion (as a marker of quality of surgery); (7) potential sources of heterogeneity; and (8) study design and quality analysis.

The corresponding authors of included studies were contacted by e-mail for missing data regarding the primary outcomes. Conflicts in data extraction were resolved by consensus after discussion and referral back to the original publication.

Quality Assessment. The quality assessment was performed independently by two study investigators (M.R. and A.B.), using the Quality In Prognosis

Studies (QUIPS) tool,[13,14] which evaluates validity and bias in studies of prognostic factors across six domains: participation; attrition; prognostic factor measurement; confounding measurement and account; outcome measurement; and analysis and reporting.

Outcomes. The primary analysis focused on mortality (at 3 and 5 years) after surgery, while postoperative clinical decompensation of liver disease (defined as the onset of complications related to cirrhosis, such as ascites, variceal bleeding, hepatic encephalopathy, progressive jaundice, spontaneous bacterial peritonitis, and hepatorenal syndrome) served as secondary outcome.

Statistical Analysis. We used Review Manager (RevMan; computer program; Version 5.2; The Nordic Cochrane Center, The Cochrane Collaboration, 2012 Copenhagen, Denmark) to pool data. The odds ratio (OR) and 95% confidence interval (CI) were calculated for each study, and results were compared through the use of a random-effects model (DerSimonian and Laird's method).[15] Statistical heterogeneity was evaluated with X^2 and I^2 statistics, which assess the appropriateness of pooling the individual study results[16]; specifically, the I^2 value provides an estimate of the amount of variance across studies resulting from heterogeneity, rather than chance. A value of >50% was considered suggestive of considerable heterogeneity.[16]

Additionally, according to QUIPS recommendations, we used sensitivity analyses to assess the robustness of the primary results. Anticipating potential heterogeneity in the direction and magnitude of effect among the studies, we performed preplanned stratified meta-analysis on study-related variables to assess sources of heterogeneity. The following were used as grouping variables for stratified meta-analysis: (1) quality of the studies (low or moderate vs. high risk of bias); (2) method used to estimate the presence of PH (invasive vs. noninvasive assessment); (3) proportion of patients with fully preserved hepatic function (Child class A vs. others); (4) tumor burden (solitary HCC vs. more than one nodule); and (5) type of surgery used in patients with and without CSPH (studies reporting similar prevalence of anatomic resection in patients with and without CSPH vs. studies reporting statistically significant differences in this regard).

An additional sensitivity analysis was carried out by evaluating the impact of CSPH on the subgroup of patients with Child A cirrhosis, which is specifically reported in some studies.

To quantify the quality of the included studies, a score based on QUIPS domains was used: 1 point was given to each "low-risk" category, 2 points to each "moderate-risk" category, and 3 points to "high-risk" category. After summing the points of all six domains, studies achieving a score of 6-7 were considered at low risk of bias; studies achieving 8-9 points were considered at medium risk of bias, and studies scoring ≥10 were considered at high risk of bias.

Agreement between authors selecting the articles was assessed by calculating the kappa concordance coefficient (k); agreement was graded by the scale proposed by Landis and Koch.[17]

Results

Literature Search. The search performed in October 2013 identified 272 citations. Figure 1 shows the process of studies selection according to PRISMA guidelines.[12]

After excluding two duplicates, 181 articles unrelated to the surgical outcome of patients with cirrhosis and HCC, 23 reviews, 7 case reports, 2 editorials, and 3 articles reporting the surgical outcome of patients with advanced HCC, 54 potentially relevant articles were selected. For four articles, the full-text article was not accessible online (no purchase option) and was asked by e-mail to the authors without success.

After retrieving the full text of the remaining 50 articles, 21 were excluded because they were not relevant to the aim of the present systematic review. Twenty-nine full-text articles were then reviewed independently. Of them, 18 (listed in the Methods section of the Supporting Information) were further excluded because they had poorly identifiable inclusion criteria for surgery and/or included both patients with and without cirrhosis (n = 8), or because they did not report outcomes according to PH or gave insufficient data on PH (n = 8), or because they duplicated the information contained in other articles by the same group selected for the analysis (n = 2). The agreement between the two reviewers for article selection among those independently reviewed was almost perfect (k = 0.859; 95% CI: 0.671-1.000).

Eleven studies were eventually included in the analysis.

Characteristics of Included Studies. Eleven studies[5,6,9,10,18-24] including a total of 1,737 patients with cirrhosis finally met eligibility criteria (Table 1). Four of them were prospective,[5,6,18,22] and the remaining were retrospective. All studies were unicentric except two that included patients from two hospitals in Europe (n = 1)[24] or from different hospitals within a single country (n = 1; Italian Liver Cancer Group [ITA.LI.CA]).[20] Nine studies were performed in European countries and two in Japan.[10,21]

Table 1. Main Characteristics of Studies Included in This Systematic Review, in Alphabetical Order

Reference	Included Population (Cirrhosis)	Proportion of Child A Cirrhosis (%)	Proportion of Single Nodule (%)	Study Design	Geographical Area	Period of Inclusion	Assessment of PH	Proportion of Patients With PH and GEV
Boleslawski, 2012[18*‡	40	97.5	90	Prospective	Europe (France)	January 2007-December 2009	HVPG	45%; 62.5% varices
Bruix, 1996[4*	29	100	100	Prospective	Europe (Spain)	May 1991-June 1994	HVPG	51.7%; 0% varices
Capussotti, 2006[19	217	82	76	Retrospective	Europe (Italy)	January 1985-December 2003	Standard surrogate criteria	45.6%; 37.8% varices
Cucchetti, 2009[8	241	94.6	83.8	Retrospective	Europe (Italy)	January 1997-March 2007	Standard surrogate criteria	36.9%; 28.2% varices
Giannini, 2013[20†‡	152	100	79.7	Retrospective	Europe (Italy)	January 1987-December 2008	Standard surrogate criteria	44.7%; 29.6% varices
Hidaka, 2012[21	177	90.3	73.4	Retrospective	Asia (Japan)	January 1997-December 2009	PVP	27.1%; varices N/R
Ishizawa, 2008[9†	434	81.8	74	Retrospective	Asia (Japan)	November 1994-December 2004	Standard surrogate criteria	41.1%;14.5% varices
Llop, 2012[22*‡	46	100	100	Prospective	Europe (Spain)	June 2007-April 2011	HVPG	21.7%; 0% varices
Llovet, 1999[5†	43	100	100	Prospective	Europe (Spain)	1989-1997	HVPG	48.8%; 0% varices
Ruzzenente, 2011[23	135	81.4	71.9	Retrospective	Europe (Italy)	1995-2008	Standard surrogate criteria	32.6%; 12.6% varices
Santambrogio, 2013[24	223	100	100	Retrospective	Europe (Italy and France)	February 1997-May 2012	Standard surrogate criteria	28.3%; 21.5% varices

CSPH was defined according to the following definitions: HVPG $\geq$10 mmHg; PVP $\geq$20 cmH2O; standard surrogate criteria: presence of GEV or platelet count $<$100,000/mL and spleen diameter $>$12 cm.

*Included only among studies addressing postoperative decompensation; the authors provided additional data that were used for this systematic review.

†Included only among studies addressing postoperative survival.

‡The authors provided additional data that were used for this systematic review.

Five studies reported data of postoperative survival and of postoperative clinical decompensation,[9,19,21,23,24] while three only showed data of postoperative survival[6,10,20] and three only showed data of postoperative decompensation.[5,18,22]

Six authors were contacted in order to have additional data on their articles; three of six kindly provided the requested additional information.[18,20,22]

Overall, 1,572 patients (574 with and 998 without PH) enrolled in eight studies[6,9,10,19-21,23,24] were included in the analysis of postoperative survival and 1,108 (386 with and 722 without PH) enrolled in eight studies were included in the analysis of postoperative clinical decompensation. The definition of clinical decompensation, usually assessed in a 90-day frame, was variable across studies (Supporting Table 1), but in all cases included jaundice and ascites.

PH was evaluated by the gold-standard method (HVPG measurement[25]) in four studies, by direct measurement of PVP in one,[21] and by standard surrogate criteria (namely, presence of GEV or platelet count $<$100,000/mL and spleen diameter $>$12 cm) in all the remaining studies (Table 1).

Table 2 summarizes the characteristics of surgical operations (type of resection and rate of blood transfusion) and of postoperative liver-related complications and mortality in the included studies.

Quality of the Included Studies. Supporting Table 2 shows the overall quality assessment of the included studies using the QUIPS tool. The agreement between the two reviewers for quality assessment (90%) was very good.

According to the QUIPS tool results, four studies[5,6,18,22] scored 6-7 points and were considered at low risk of bias, three studies[10,20,24] scored 8-9 points and were considered at medium risk of bias, and four studies[9,19,21,23] scored $\geq$10 points and were considered at high risk of bias.

Primary Outcome: Risk of 3- and 5-Year Mortality After Surgery According to the Presence of CSPH. Table 3 summarizes overall survival according to the presence or absence of CSPH in the studies included in the analysis of the primary outcome. All but one[20] of the eight studies reported a statistically significant association between CSPH and higher risk of death at 3 and 5 years after surgery on univariate analysis; only two of them[6,21] reported an independent value of CSPH on multivariate analysis (Supporting Table 3).

On meta-analysis (491 deaths at 3 years and 694 deaths at 5 years), the presence of CSPH was associated with a higher risk of death on both time points.

Table 2. Characteristics of Surgical Intervention, Operative, and Perioperative Outcomes in the Included Studies

		Type of Resection				Blood Transfusion (%)			Liver-Related Complications (%)			Operative Mortality (%)		
		Anatomical (≥2 Segments)												
Author/Year	No. of Patients	N (%)	CSPH (%)	No CSPH (%)	*P* Value	CSPH (%)	No CSPH (%)	*P* Value	CSPH (%)	No CSPH (%)	*P* Value	CSPH (%)	No CSPH (%)	*P* Value
Boleslawski, 2012	40	9 (22.5)	22.2	22.7	ns	22.2	4.4	0.115	33.3	4.5	**0.033**		15	NA
Bruix, 1996	29	23 (79.3)		NR		0.7 ± 1.8*	0.2 ± 0.6	ns	73.3	0	**0.0002**			NA
Capussotti, 2006	217	51 (23.5)	12.1	33.1	**0.0003**	51	38	**0.004**	27.3	15.3	**0.030**	11.1	5.1	ns
Cucchetti, 2009	241	12 (5.0)	2.2	6.6	NR	16	34	ns	11.9	3.9	**0.035**	5		NA
Giannini, 2013	152						NR							
Hidaka, 2012	177	130 (73.5)	15.0	31.1	**0.001**		NR		31.3	15.5	**ns**	2.8		
Ishizawa, 2008	386	223 (58.0)	39.0	68.0	**<0.001**	6	10	ns	13	30	ns†		NR	
Llop, 2012	46	15 (32.6)	40.0	30.5	ns		NR		3	0	**0.0039**		0	
Llovet,1999	77	51 (66.2)		NR			NR			NR		3.9		NA
Ruzzenente, 2011	135	20 (15.0)	18.0	25.0	ns		NR		32	13	**0.030**	4.6	1.1	ns
Santambrogio, 2012	223	61 (27.4)	17.0	31.0	**0.038**	11	5.6	ns	29	14	**0.009**	0.5	0	ns

*Median of transfusion requirements (unit of packed red blood cells).
†Liver-related complications and no related complications.
Abbreviations: PTH, portal hypertension; no-PTH, no portal hypertension; NR, data no reported; ns, not statistically significant; NA, not applicable.

The pooled OR was, respectively, 2.09 (95% CI: 1.52-2.88; $P < 0.00001$) for 3-year mortality and 2.07 (95% CI: 1.51-2.84; $P < 0.00001$) for 5-year mortality (Fig. 2A,B). There was moderate, borderline significant heterogeneity for this analysis both for 3- ($P = 0.07$; $I^2 = 47\%$) and 5-year mortality ($P = 0.05$; $I^2 = 49\%$); this was primarily noted in the magnitude of effect, but not in the direction of effect. Only one study[20] showed no effects of CSPH on 3- and 5-year mortality.

Stratified meta-analysis showed that heterogeneity was largely attributable to the diagnostic method used to assess CSPH (test for difference between subgroups: $P = 0.008$ for 3-year mortality; $P = 0.02$ for 5-year mortality; Fig. 3A,B); when only studies using standard surrogate markers of CSPH (presence of GEV or platelet count <100,000/mL and spleen diameter >12 cm) were analyzed,[9,10,19,20,23,24] CSPH was still associated with an increased risk of death at 3 and 5 years after surgery, being pooled OR, respectively, of 1.76 (95% CI: 1.38-2.25; $P < 0.00001$) and 1.75 (95% CI: 1.36-2.26; $P < 0.0001$). However, these studies provided a lower estimate of the postoperative risk associated with preoperative PH, as compared to studies using invasive measurement of portal pressure. Of note, the OR was maximal in studies using the gold-standard measurement of HVPG to estimate presence of PH (OR, 8.00; 95% CI: 2.59-24.69; $P = 0.0003$), followed by measurements of PVP (OR, 3.61; 95% CI: 1.78-7.29; $P = 0.0004$). No heterogeneity was observed within subgroups of studies.

Stratified meta-analysis according to QUIPS studies quality showed stable results and no heterogeneity among studies rated at low-moderate versus high risk of bias (Supporting Fig. 1A,B). Similar results were obtained when studies rated at low risk of bias were compared to those at moderate-high risk (data not shown).

Similarly, stable results were observed among studies reporting similar prevalence of anatomic resection in patients with and without CSPH and studies reporting statistically significant differences in this regard (data not shown).

Stratified meta-analysis according to the proportion of patients with a single nodule included in the studies (≥80% vs. <80%) also showed stable results and no heterogeneity among subgroups (Supporting Fig. 2A, B).

Finally, the results were stable after restricting the analysis to patients with Child A cirrhosis (Supporting Fig. 3A,B).

Table 3. 3- and 5-Year Overall Survival (OS) in the Studies Included in the Analysis of the Primary Endpoint (n = 8)

Study	No. of Patients (n)	Child A(%)	Single Nodule (%)	3-Year OS		5-Year OS	
				Without CSPH	WithCSPH	Without CSPH	With CSPH
Capussotti, 2006	217	82.0	76.0	62.1; Child A 64.8	44.8; Child A 59.9	39.8; Child A 41.5	28.9; Child A 40.8
Cucchetti, 2009	241	94.6	83.8	75.3	46.4	63.9	37.3
Giannini, 2013	152	100	79.7	69.8	71.7	45.1	47.7
Hidaka, 2012	177	90.4	73.5	72.0	49.0	63.7	31.0
Ishizawa, 2008	434 (386 with cirrhosis)	83.8	29.1	Child A 81.0 Child B 62.0	Child A 71.0 Child B 59.0	Child A 71.0 Child B 31.0	Child A 56.0 Child B 41.0
Llovet, 1999	77	96.1	100	87.0	TotBil <=1 mg/dL 59; TotBil >1 mg/dL 39	74.0	TotBil <=1 mg/dL 50; TotBil >1 mg/dL 25
Ruzzenente, 2011	135	81.5	71.9	68.4	48.7	61.2	44.9
Santambrogio, 2013	223	96.0	NR	80.0	66.0	65.0	48.0

Abbreviations: NR, data not reported; TotBil, total bilirubin.

Secondary Outcome: Risk of Clinical Decompensation According to the Presence of CSPH. On meta-analysis of eight studies (197 cases of clinical decompensation),[5,9,18,19,21-24] the presence of CSPH was associated with an increased risk of developing decompensation of cirrhosis (pooled OR: 3.04; 95% CI: 2.02-4.59; $P < 0.00001$; Fig. 2C). There was moderate, nonsignificant heterogeneity in this analysis ($P = 0.23$; $I^2 = 25\%$); this was primarily noted in the magnitude of effect, but not in the direction of effect.

Stratified meta-analysis according to the method used to diagnose CSPH did not show significant heterogeneity across groups. Estimates of risk of clinical decompensation associated with CSPH were much higher in studies using HVPG[5,18,22] (pooled OR: 14.59; 95% CI: 2.81-80.06; $P = 0.002$), as compared to those using surrogate markers of PH[9,19,23,24] (pooled OR: 2.56; 95% CI: 1.73-3.80; $P = 0.04$; Fig. 3C).

Stratified meta-analysis according to QUIPS studies quality showed stable results and no heterogeneity among studies rated at low-moderate versus high risk of bias (Supporting Fig. 1C). Similar results were obtained when studies rated at low risk were compared to those at moderate-high risk (data not shown).

Stratified meta-analysis according to the proportion of patients with a single nodule included in the studies ($\geq$80% vs. <80%) also showed stable results and no heterogeneity among subgroups (Supporting Fig. 2C).

Finally, the results were stable after restricting the analysis to patients with Child A cirrhosis (Supporting Fig. 3C).

Discussion

The results of this systematic review and meta-analysis indicate that the presence of CSPH negatively impacts on the postoperative outcomes of patients with compensated cirrhosis undergoing surgery for HCC, thus validating the recommendations contained in current international guidelines.[1,2]

The presence of CSPH was a clear negative prognostic marker in patients undergoing surgery for HCC in this meta-analysis: the odds of 3- and 5-year mortality was roughly double in patients with CSPH, as compared to patients without CSPH, and the odds of clinical decompensation was increased by approximately three times in patients with CSPH. Of note, this result was stable across all the subanalyses that were performed, showing consistency in studies of different quality and design (namely, rated differently according to QUIPS, using different methods to assess PH and with different proportions of single HCC nodule). Moreover, the same was confirmed in the subgroup of patients with Child A cirrhosis for whom data were available in the included studies.

Interestingly, we did not observe a very large heterogeneity among studies; furthermore, the major source of heterogeneity was easily identifiable by stratified meta-analysis and was a result of the different methods used for diagnosing CSPH. The strength of the association between the presence of CSPH and clinical outcomes was greater when the gold-standard method (HVPG measurement) was used to assess CSPH. This was particularly evident in the assessment of postoperative clinical decompensation, where three independent studies using HVPG were available for the meta-analysis. HVPG allows diagnosing more precisely even small increases of portal pressure above the threshold allowing the complications of cirrhosis to appear (10 mmHg, CSPH).[25,26] PH is the pathophysiological basis of the formation of GEV in patients with cirrhosis, and it has been demonstrated that varices only form in patients with HVPG $\geq$10 mmHg[27]; hence,

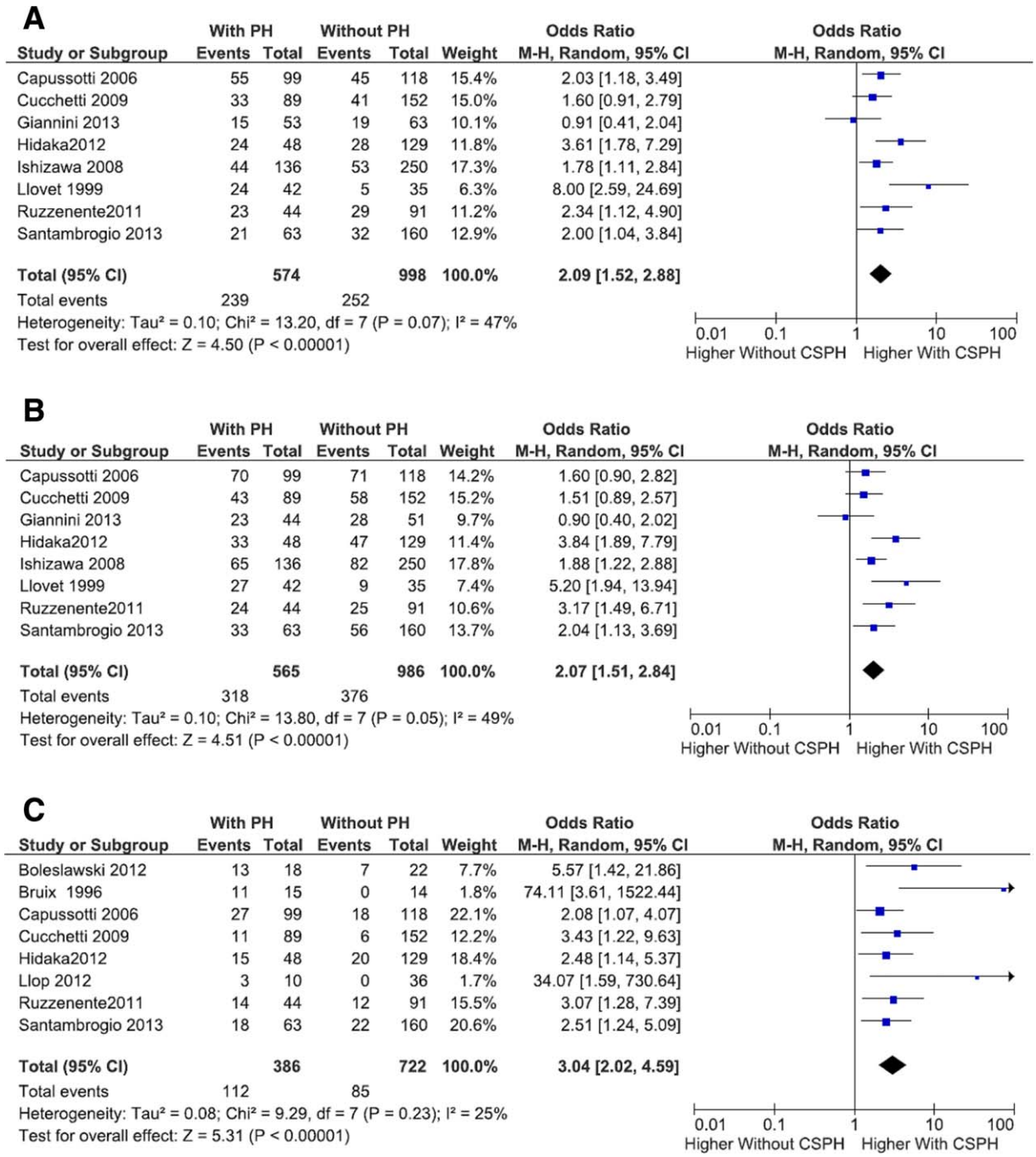

Fig. 2. Impact of CSPH on postoperative outcomes of patients with HCC and compensated cirrhosis in all the included studies. (A) Three-year mortality. (B) Five-year mortality. (C) Clinical decompensation.

the finding of varices is sufficient to confirm the presence of CSPH.[27] On the other hand, in patients who have no varices, platelet count and spleen size are not accurate enough to rule out CSPH, which is present in up to 40% of cases.[22,28-30] In addition, one study comparing HVPG to standard noninvasive surrogate criteria of CSPH (platelet count <100,000/mL and splenomegaly) in patients undergoing surgery for HCC showed that surrogate criteria of CSPH were not able to predict postoperative prognosis, whereas CSPH measured by HVPG confirmed its value. These data, together with the results of the present meta-analysis, strongly suggest that CSPH cannot be confidently excluded relying upon the standard noninvasive surrogate markers, and that the measurement of HVPG should be used instead, until new more-

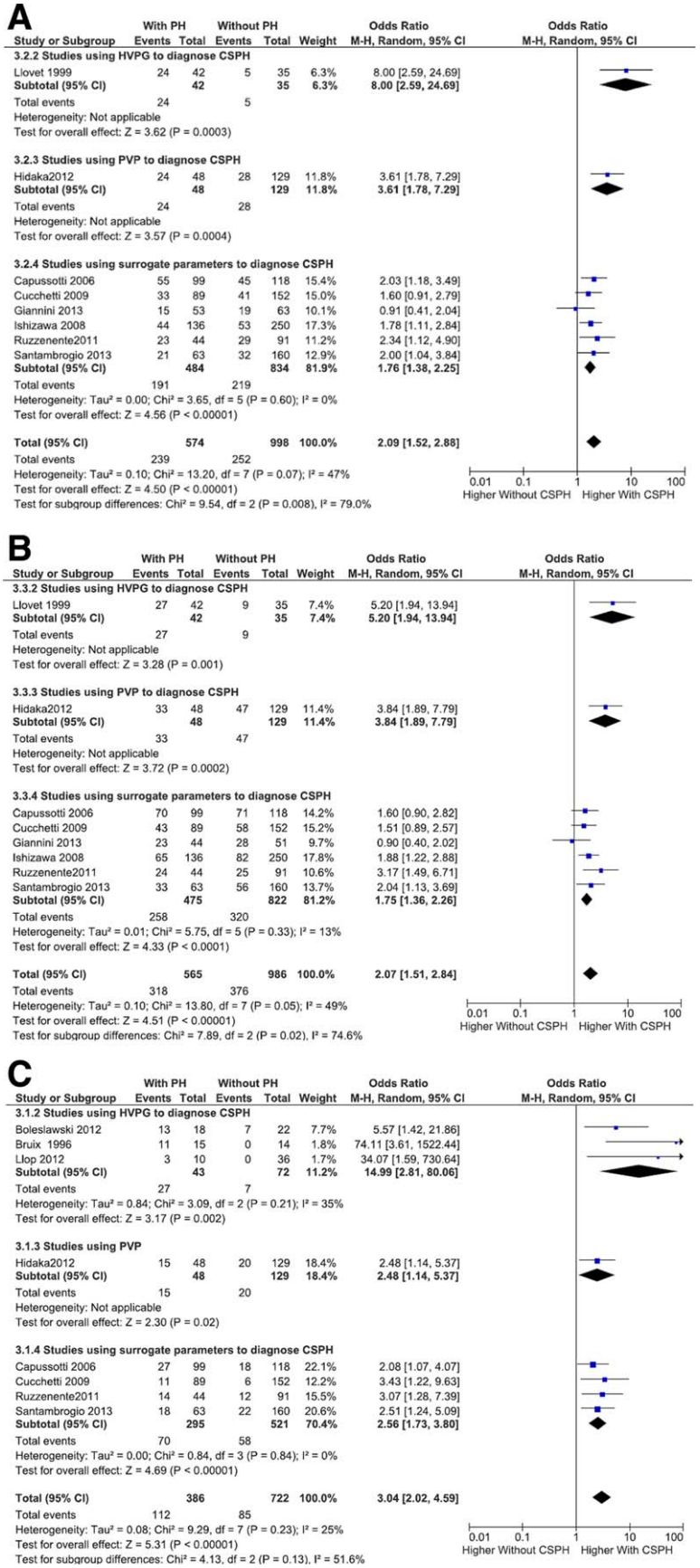

Fig. 3. Stratified meta-analysis according to the diagnostic method used to assess the presence of CSPH. (A) Three-year mortality. (B) Five-year mortality. (C) Clinical decompensation.

accurate noninvasive surrogates become available. According to recent data, liver stiffness assessed by transient elastography appears to be a promising tool to safely reduce the number of patients requiring invasive hemodynamic assessment in this scenario,[22,31-33] but further prospective data should confirm these preliminary experiences.

As for any meta-analysis, the validity of the present results depends upon the strength of association between presence of CSPH and postoperative outcomes shown in individual studies. This is especially relevant when considering observational studies, in which the reliability of the methodology is difficult to evaluate from an abstract report. This is the reason why we decided to use only published articles in order to avoid the impact of scarce quality studies, such as those often found in the so-called "gray literature" on the final results.

We acknowledge that a limitation of our meta-analysis is that it is based on pooled data from observational studies, mostly retrospective. This limits the ability to control for confounding variables. Given that most studies did not adjust the estimates of the association between CSPH and postoperative events for all known confounders, we could not control for the potential influence of prognostic factors other than CSPH and we were forced to use crude measures of association.

It could be argued that less-invasive surgical procedures, such as laparoscopic resection,[34] less use of clamping maneuvers to prevent intraoperative bleeding, and specific interventions to preserve liver function during surgery[35] should result in better tolerance of the patients and less postoperative morbidity and mortality. The same expectation can be awaited from the refinement of selection criteria using liver volume assessment and/or use of portal vein embolization to increase the liver remnant volume. However, it should be retained that HCC surgery will not result in reduction in portal pressure with amelioration of the existing degree of PH. Given that this is a marker of a more advanced evolutionary stage of cirrhosis,[25,27] and this more advanced stage is linked to worse prognosis, presence of PH should not be seen as an unexpected survival predictor and should be incorporated in treatment decision making for those patients with a technically resectable HCC. In patients with CSPH, treatments that may be considered alternative to surgery are transplantation and ablation, given that all provide potential long-term cure. Cohort studies and modeling approaches show that survival of HCC <2 cm is the same for resection and ablation both for patients with and without CSPH. Transplant offers better survival in patients with CSPH. This analysis is the backbone of the BCLC staging and treatment strategy that has been extensively reviewed elsewhere.[3,4] If patients have CSPH and large tumors that may not be ablated, recent studies have suggested that chemoembolization may represent a good option.[36,37]

In conclusion, our systematic review and meta-analysis confirms that the presence of CSPH negatively impacts on the postoperative outcome of patients with compensated cirrhosis undergoing surgery for HCC. These results reinforce that (1) the existence of CSPH should be investigated before indicating surgery to correctly stratify postoperative risk of liver-related events and (2) HVPG should be used in this population to diagnose CSPH, the only exception being those patients known to have GEV, because this represents a specific indicator of the presence CSPH. Even if the presence of CSPH should not be regarded as an absolute contraindication to surgery, our results demonstrate that it has to be considered a major negative prognostic factor.

Acknowledgment: The authors thank Drs. Emmanuel Boleslawski and Edoardo Giannini (who answered on behalf of the Italian Liver Cancer Group [ITA.LI.CA]) for providing additional data from their studies that were used in the present systematic review and meta-analysis. The authors also express their gratitude to Ms. Clara Esteva for her secretarial support and to Ms. M.A. Baringo, L. Rocabert, and R. Saez for their expert nursing hemodynamic assistance.

References

1. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908-943.
2. Verslype C, Rosmorduc O, Rougier P. Hepatocellular carcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23(Suppl 7):vii41-vii48.
3. Bruix J, Gores GJ, Mazzaferro V. Hepatocellular carcinoma: clinical frontiers and perspectives. Gut 2014;63:844-855.
4. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet 2012 31;379:1245-1255.
5. Bruix J, Castells A, Bosch J, Feu F, Fuster J, Garcia-Pagan JC, et al. Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. Gastroenterology 1996;111:1018-1022.
6. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology 1999;30:1434-1440.
7. Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology 2005;42:1208-1236.
8. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020-1022.
9. Cucchetti A, Ercolani G, Vivarelli M, Cescon M, Ravaioli M, Ramacciato G, et al. Is portal hypertension a contraindication to hepatic resection? Ann Surg 2009;250:922-928.
10. Ishizawa T, Hasegawa K, Aoki T, Takahashi M, Inoue Y, Sano K, et al. Neither multiple tumors nor portal hypertension are surgical

contraindications for hepatocellular carcinoma. Gastroenterology 2008; 134:1908-1916.
11. Forner A, Bruix J. East meets the West—portal pressure predicts outcome of surgical resection for hepatocellular carcinoma. Nat Clin Pract Gastroenterol Hepatol 2009;6:14-15.
12. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264-9.
13. Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med 2006;144:427-437.
14. Hayden JA, van der Windt DA, Cartwright JL, Cote P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med 2013; 158:280-286.
15. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. Contemp Clin Trials 2007;28:105-114.
16. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-560.
17. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159-174.
18. Boleslawski E, Petrovai G, Truant S, Dharancy S, Duhamel A, Salleron J, et al. Hepatic venous pressure gradient in the assessment of portal hypertension before liver resection in patients with cirrhosis. Br J Surg 2012;99:855-863.
19. Capussotti L, Ferrero A, Vigano L, Muratore A, Polastri R, Bouzari H. Portal hypertension: contraindication to liver surgery? World J Surg 2006;30:992-999.
20. Giannini EG, Savarino V, Farinati F, Ciccarese F, Rapaccini G, Marco MD, et al. Influence of clinically significant portal hypertension on survival after hepatic resection for hepatocellular carcinoma in cirrhotic patients. Liver Int 2013;33:1594-1600.
21. Hidaka M, Takatsuki M, Soyama A, Tanaka T, Muraoka I, Hara T, et al. Intraoperative portal venous pressure and long-term outcome after curative resection for hepatocellular carcinoma. Br J Surg 2012;99:1284-1289.
22. Llop E, Berzigotti A, Reig M, Erice E, Reverter E, Seijo S, et al. Assessment of portal hypertension by transient elastography in patients with compensated cirrhosis and potentially resectable liver tumors. J Hepatol 2012;56:103-108.
23. Ruzzenente A, Valdegamberi A, Campagnaro T, Conci S, Pachera S, Iacono C, et al. Hepatocellular carcinoma in cirrhotic patients with portal hypertension: is liver resection always contraindicated? World J Gastroenterol 2011;17:5083-5088.
24. Santambrogio R, Kluger MD, Costa M, Belli A, Barabino M, Laurent A, et al. Hepatic resection for hepatocellular carcinoma in patients with Child-Pugh's A cirrhosis: is clinical evidence of portal hypertension a contraindication? HPB (Oxford) 2013;15:78-84.
25. Bosch J, Abraldes JG, Berzigotti A, Garcia-Pagan JC. The clinical use of HVPG measurements in chronic liver disease. Nat Rev Gastroenterol Hepatol 2009;6:573-582.
26. Ripoll C, Groszmann R, Garcia-Tsao G, Grace N, Burroughs A, Planas R, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology 2007; 133:481-488.
27. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet 2014; 383:1749-61.
28. Qamar AA, Grace ND, Groszmann RJ, Garcia-Tsao G, Bosch J, Burroughs AK, et al. Platelet count is not a predictor of the presence or development of gastroesophageal varices in cirrhosis. HEPATOLOGY 2008;47:153-159.
29. Berzigotti A, Gilabert R, Abraldes JG, Nicolau C, Bru C, Bosch J, et al. Noninvasive prediction of clinically significant portal hypertension and esophageal varices in patients with compensated liver cirrhosis. Am J Gastroenterol 2008;103:1159-1167.
30. Berzigotti A, Seijo S, Arena U, Abraldes JG, Vizzutti F, Garcia-Pagan JC, et al. Elastography, spleen size, and platelet count identify portal hypertension in patients with compensated cirrhosis. Gastroenterology 2013;144:102-111.
31. Berzigotti A, Reig M, Abraldes JG, Bruix J, Bosch J, García-Pagán JC. Letter to the editor: "Value of transient elastography measured with FibroScan in predicting the outcome of hepatic resection for hepatocellular carcinoma". Ann Surg 2013 Nov 20. doi: 10.1097/SLA.0000000000000394. [Epub ahead of print].
32. Cescon M, Colecchia A, Cucchetti A, Peri E, Montrone L, Ercolani G, et al. Value of transient elastography measured with FibroScan in predicting the outcome of hepatic resection for hepatocellular carcinoma. Ann Surg 2012;256:706-712; discussion, 712-713.
33. Cescon M, Cucchetti A, Colecchia A, Ercolani G, Festi D, Pinna AD. Reply to letter: "Value of transient elastography measured with FibroScan in predicting the outcome of hepatic resection for hepatocellular carcinoma". Ann Surg 2013 Nov 20. doi: 10.1097/SLA.0000000000000393. [Epub ahead of print].
34. Cherqui D, Laurent A, Tayar C, Chang S, Van Nhieu JT, Loriau J, et al. Laparoscopic liver resection for peripheral hepatocellular carcinoma in patients with chronic liver disease: midterm results and perspectives. Ann Surg 2006;243:499-506.
35. Taura P, Fuster J, Mercadal J, Martinez-Palli G, Fondevila C, Blasi A, et al. The use of beta-adrenergic drugs improves hepatic oxygen metabolism in cirrhotic patients undergoing liver resection. J Hepatol 2010;52:340-347.
36. Burrel M, Reig M, Forner A, Barrufet M, de Lope CR, Tremosini S, et al. Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using Drug Eluting Beads. Implications for clinical practice and trial design. J Hepatol 2012;56: 1330-1335.
37. Malagari K, Pomoni M, Moschouris H, Bouma E, Koskinas J, Stefaniotou A, et al. Chemoembolization with doxorubicin-eluting beads for unresectable hepatocellular carcinoma: five-year survival analysis. Cardiovasc Intervent Radiol 2012;35:1119-1128.

Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.27431/suppinfo.