REVIEW ARTICLE

Impact of clinically significant portal hypertension on outcomes after partial hepatectomy for hepatocellular carcinoma: a systematic review and meta-analysis

Jianwei Liu*, Han Zhang*, Yong Xia*, Tian Yang, Yuzhen Gao, Jun Li, Yeye Wu & Feng Shen

Department of Hepatic Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China

Abstract

Background: Whether clinically significant portal hypertension (CSPH) is a contraindication of partial hepatectomy for patients with hepatocellular carcinoma (HCC) remains controversial. The aim was to assess the impact of CSPH on surgical morbidity, mortality and long-term survival of HCC patients who underwent partial hepatectomy.

Methods: A systematic review and meta-analysis was conducted through analyzing the data published before October 2016 on outcomes following partial hepatectomy for HCC patients with CSPH from the Medline, Embase and CENTRAL databases and related literature.

Results: A total of 16 studies involving 4029 patients met the inclusion criteria. HCC patients with CSPH had increased incidences of severe postoperative complications (pooled odds ratio [OR]: 1.66; 95% CI: 1.31–2.10), surgical mortality (2.56, 1.77–3.70) and 5-year mortality (1.29, 1.11–1.50) compared with patients without CSPH. Subgroup analysis suggested that CSPH had no impact on peri-operative mortality and long-term survival for European HCC patients whose CSPH was diagnosed by the standard surrogate criteria (1.95, 0.96–3.96; 1.24, 0.98–1.55).

Conclusions: CSPH had a negative impact on short- and long-term prognoses for HCC patients undergoing partial hepatectomy. However, CSPH did not affect the prognoses in a subgroup of European HCC patients whose CSPH was diagnosed by the standard surrogate criteria.

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Correspondence

Feng Shen, Department of Hepatic Surgery, The Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, 20438, China. E-mail: shenfengehbh@sina.com

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the second leading cause of cancer-related mortality worldwide.[1,2] More than half of the global incidence and mortality of HCC occurs in China.[3,4] Partial hepatectomy is the first-line therapy with curative potential for patients with HCC.[5] Unfortunately, advanced tumor stage and underlying cirrhosis significantly limit the use of curative resection in patients with HCC. According to the Barcelona Clinic Liver Cancer (BCLC) staging system, HCC patients with clinically significant portal hypertension (CSPH) are not recommended for surgical resection,[6] which has also been adopted by the guidelines of the European Association for Study of Liver (EASL) and American Associations for Study of Liver Diseases (AASLD).[7–10] For patients with tumors within Milan criteria, liver transplantation is recommended as an appropriate treatment to achieve possible long-term survival.[6,11,12] However, the use of liver transplantation is greatly limited by the shortage of liver donors, particularly in regions with high incidence of HCC.[12–14]

Whether HCC patients with CSPH could be treated with partial hepatectomy is still under debate.[15] Currently, surgeons from different countries or regions are performing surgical resections adopting distinct indications based on their own experiences, and satisfactory postoperative outcomes have frequently been reported.[11,16–30] Some authors advocate partial hepatectomy as an effective treatment option for patients with relatively more advanced HCC, even for those with CSPH.[6,20–28] Berzigotti *et al.* conducted a meta-analysis to evaluate the impact of CSPH on postoperative complication and long-term outcomes in patients undergoing partial hepatectomy and demonstrated a negative prognostic impact of CSPH presence.[31] However, only

* These authors contributed equally to this work.

11 original studies were included in the study and the impact of CSPH on peri-operative mortality was not reported, which was a critical factor that might influence the surgical decision-making. In addition, the study did not specifically investigate the difference in clinical data among different geographical areas which might have distinct racial descent, CSPH definition and indication of partial hepatectomy.

In this study, we included a larger number of articles to analyze the effect of CSPH presence on short- and long-term outcomes after partial hepatectomy in patients with HCC. In addition, stratified meta-analyses based on different diagnostic methods of CSPH and distinct geographical areas were conducted.

Methods

Search strategy

A search of relevant studies was performed using the Medline, Embase and CENTRAL databases for original studies that were published before October 2016. Search terms included "portal hypertension", "hepatocellular carcinoma", "liver cancer", "liver neoplasm", "hepatic neoplasm", "hepatocellular cancer", "hepatectomy", "liver resection" and "hepatic resection". The titles, abstracts and conference proceedings of these studies were evaluated independently by two investigators (Liu and Zhang) according to pre-specified inclusion and exclusion criteria to determine whether they were consistent with the objectives and requirements of our study. After the initial screening, these articles were re-examined to eliminate those with repeated or overlapping data. The full-text of the remaining articles were carefully reviewed and subjected to independent quality assessment by two investigators (Liu and Zhang). In case of disagreement, a third scholar would make the decision. Fig. 1 is the flow diagram in line with the PRISMA guideline summarizing the process of identification, inclusion and exclusion of the published primary studies.[32]

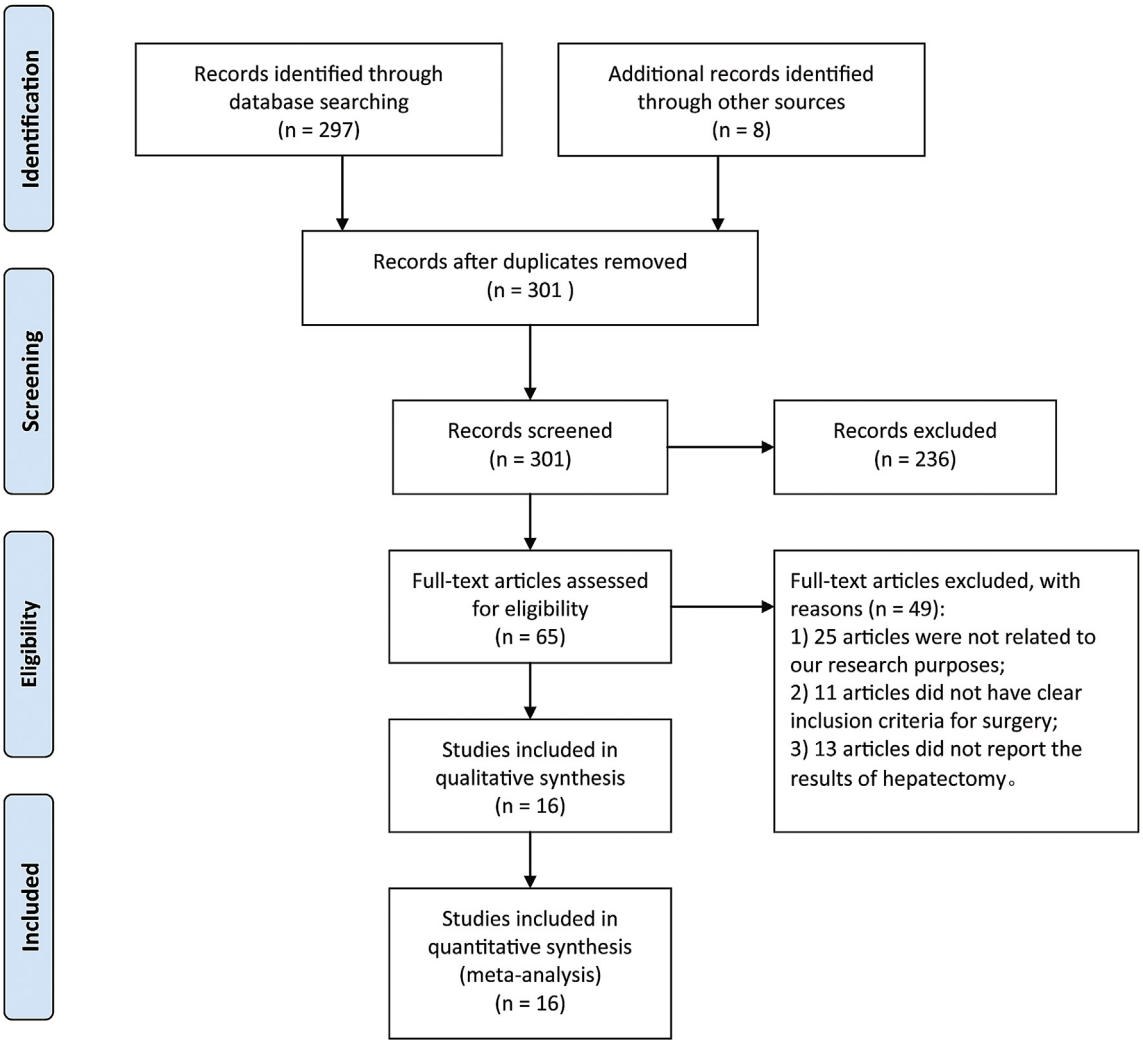

Figure 1 Flow chart of the study

Study selection

Original studies of both prospective and retrospective nature were included into our analysis. To ensure the quality of our study, only studies with complete documentation were included while abstracts, case reports and reviews were excluded.

Studies were included in the qualitative analysis if they met all the following criteria: (1) drafted in English; (2) involving HCC patients with or without CSPH who underwent partial hepatectomy; (3) the diagnostic criteria for CSPH were clearly stated; (4) the postoperative outcomes, including postoperative 5-year overall survival (OS) or postoperative 5-year mortality, and postoperative complications and mortality were clearly reported. Studies that did not meet the above criteria were excluded.

CSPH was defined as patients with hepatic venous pressure gradient (HVPG) $\geq$ 10 mm Hg or portal vein pressure (PVP) $\geq$ 20 cm H_2O, or met the standard surrogate criteria including the presence of gastroesophageal varices (GEV) or platelet count < 100,000/mL and spleen diameter > 12 cm.[33–35]

Data extraction

Data regarding the following aspects were extracted from the included articles: (1) characteristics of the study: including authors, publication time, beginning and end time of the study, countries or regions where the study was carried out, study population, and the type of study (prospective or retrospective); (2) characteristics of patients: Child-Pugh class of liver function with number and proportion of patients with different class and proportion of patients with or without CSPH, proportion of patients with solitary or multiple tumors, diagnostic methods of portal hypertension (PH), proportions of patients with different types of partial hepatectomies, the 5-year OS of patients with or without CSPH and the corresponding mortality, postoperative complications and mortality, duration of operation and intraoperative blood transfusion as an indicator of quality of surgery, potential sources of heterogeneity, as well as study design and quality analysis.

Quality assessment

Using the Quality In Prognosis Studies (QUIPS) tool,[36,37] the qualities of included studies were independently assessed by 2 investigators (Liu and Zhang) to evaluate the 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. Each of the 6 potential bias domains was rated as high, moderate or low risk of bias. The overall quality of each study was judged as follows: a study would be rated as low risk of bias if all of the 6 bias domains were rated as low risk of bias, and study would be rated as high or moderate risk of bias if one or more domains of the 6 bias domains are rated as high or moderate risk of bias.

Outcomes

The primary focus of this study was the postoperative long-term survival while the postoperative complications and surgical mortality were regarded as secondary outcomes. The impact of CSPH on postoperative long-term survival was assessed by postoperative 5-year mortality. The 5-year mortality was obtained from the 13 studies that reported on postoperative long-term survival.[11,14,15,18–27] Postoperative complications were defined as the adverse events that occurred within 90 days after surgery that required clinical treatments, including ascites, rupture and hemorrhage of esophageal varices, jaundice, spontaneous bacterial peritonitis, and hepatic encephalopathy. Surgical mortality was defined as death within 90 days after surgery. Stratified-meta analyses were carried out in this study. Firstly, stratified-meta analyses were performed according to different diagnostic methods of CSPH (CSPH was diagnosed by HVPG or PVP, CSPH was diagnosed by standard surrogate criteria). Secondly, in different geographical areas (European and Asian), the relationship between CSPH and surgical outcomes was reanalyzed according to different diagnostic methods of CSPH. A total of 6 subgroups were established for postoperative 5-year mortality, postoperative complications and mortality, including subgroup of patients whose CSPH was diagnosed by HVPG or PVP, subgroup of patients whose CSPH was diagnosed by standard surrogate criteria, subgroup of Asia where CSPH was diagnosed by HVPG or PVP, subgroup of Europe where CSPH was diagnosed by HVPG or PVP, subgroup of Asia where CSPH was diagnosed by standard surrogate criteria, subgroup of Europe where CSPH was diagnosed by standard surrogate criteria.

Statistical analysis

Data extracted from the 16 included studies were statistically analyzed using Stata 12.0 software (Corp. STATA, Station college, TX). A random-effects model was used to derive pooled estimates of odds ratio (OR) with 95% confidence interval (CI) for the explored outcomes. A Chi-squared test was used to analyze the heterogeneity of the data and I^2 was used to analyze the degree of data inconsistency. Specifically, the I^2 value provided an estimate of the amount of variance across the studies resulting from heterogeneity rather than chance. A value of $p < 0.05$ or $I^2 >$ 50% was suggestive of considerable heterogeneity.[38] In addition, sensitivity analyses and funnel plot were performed to investigate the potential sources of bias in the results of the included studies.

Results

Literature search

The last search time for literature was October 2016. Fig. 1 shows the complete selection process of primary studies. A total of 301 studies were obtained after the preliminary search of the Medline, Embase and CENTRAL databases using the above-mentioned keywords. After initial screening and review of the

Table 1 Characteristics of the Studies included in the study

Author & Time	Number of patients	CSPH/No CSPH	Proportion of Child-Pugh A cirrhosis (n, %)	Proportion of single nodule (n, %)
Llovet JM 1999	77	42/35	96.1	83.1
Giannini EG 2013	152	68/84	100	79.7
Hidaka M 2012	177	48/129	97.5	73.4
Boleslawski E 2012	40	18/22	100	90
Llop E 2012	46	10/36	100	100
Kawano Y 2008	134	31/103	82.1	NR
Choi GH 2011	100	47/53	100	83.0
Capussotti L 2006	217	99/118	82.0	76.0
Ruzzenente A 2011	135	44/91	81.5	71.9
Santambrogio R 2013	223	63/160	100	100
Cucchetti A 2009	241	89/152	94.6	83.8
Ishizawa T 2008	386	136/250	83.4	70.5
He W 2015	209	102/107	97.6	70.8
Zhong JH 2014	1738	386/1352	100	NR
Xiao H 2015	125	58/67	96.8	81.6
Bruix J 1996	29	15/14	100	100

CSPH, clinically significant portal hypertension; NR, not reported; HVPG, HVPG, hepatic venous pressure gradient; PVP, portal vein pressure.

study titles and abstracts, 236 articles were excluded. Full-text of the remaining 65 articles were downloaded and re-evaluated. Among which, 49 studies were excluded due to irrelevance to the research purposes (n = 25), failure to clarify inclusion criteria for partial hepatectomy (n = 11), and failure to report the results of surgery including postoperative OS, postoperative complications and surgical mortality (n = 13). The remaining 16 studies including a total of 4029 patients with HCC were included and further analyzed.

Characteristics of the included studies

Among the 16 included studies, 4 were prospective[11,18,19,30] and 12 were retrospective[16,17,20–29] in nature. The geographical distribution of the included studies was Italy (n = 4), Spain (n = 3), Japan (n = 3), France (n = 1), Korea (n = 1), China (n = 3), and both Italy and France (n = 1).

Of the 16 studies, 13 reported the postoperative 5-year mortality of HCC patients with or without CSPH,[11,16,17,20–29] 14 reported postoperative complications,[17–30] and 13 reported the surgical mortality.[11,16,18–24,27–30] Among 4029 HCC patients included in the study, 1256 (31.2%) had CSPH and 2773 (68.8%) had no CSPH. Among those with CSPH, 344 (27.4%) experienced postoperative complications and 68 (5.4%) had peri-operative death. Among those without CSPH, 529 (19.1%) had postoperative complications and 59 (2.1%) had peri-operative death.

CSPH was evaluated by HVPG measurement, the gold-standard method of CSPH,[39] in 5 studies,[11,18,19,21,30] by direct measurement of PVP in 1 study;[17] by standard surrogate criteria (presence of GEV or platelet count <100,000/mL and spleen diameter >12 cm) in 9 studies[16,22–29]; and by esophageal varices in 1 study.[20] (Table 1).

The number of patients enrolled in our study, as well as the type of resection, transfusion status, postoperative complications, peri-operative mortality, 5-years OS and 5-years mortality in patients with or without CSPH were listed in Table 2.

Quality of the included studies

Supplemental Table 1 presents the quality assessment results of included studies. Three studies were recognized as having low risk of bias, 6 as having medium risk of bias, and 7 as having high risk of bias.

Primary outcome: impact of CSPH on long-term survival in HCC patients after partial hepatectomy

Table 2 shows the 5-year survival and mortality of patients with or without CSPH. Four articles considered that CSPH was a contraindication for surgery,[11,17,18,30] 11 articles did not consider this or showed that at least some of HCC patients with CSPH could be treated by partial hepatectomy,[16,20–29] and 1 article only reported that the incidence of postoperative complications of patients with CSPH was higher than that of patients without it.[19]

All 16 articles were included in the meta-analysis, among which the 5-year OS ranged from 25% to 70.1% in patients with CSPH, and from 31% to 78.7% in patients without CSPH,

Study design	Study areas	Study period	Assessment of PH	Ref
prospective	Spain	1989–1997	HVPG	Llovet et al.[11]
retrospective	Italian	1987–2008	standard surrogate criteria	Giannini et al.[16]
tetrospective	Japan	1997–2009	PVP	Hidaka et al.[17]
prospective	France	2007–2009	HVPG	Boleslawski et al.[18]
prospective	Spain	2007–2011	HVPG	Llop et al.[19]
retrospective	Japan	1982–2003	esophageal varices	Kawano et al.[20]
retrospective	Korea	1996–2006	HVPG	Choi et al.[21]
retrospective	Italy	1985–2003	standard surrogate criteria	Capussotti et al.[22]
retrospective	Italy	1995–2008	standard surrogate criteria	Ruzzenente et al.[23]
retrospective	Italy, France	1997–2012	standard surrogate criteria	Santambrogio et al.[24]
retrospective	Italy	1997–2007	standard surrogate criteria	Cucchetti et al.[25]
retrospective	Japan	1994–2004	standard surrogate criteria	Ishizawa et al.[26]
retrospective	China	2003–2008	standard surrogate criteria	He et al.[27]
retrospective	China	2007–2010	standard surrogate criteria	Zhong et al.[28]
retrospective	China	2001–2008	standard surrogate criteria	Xiao et al.[29]
prospective	Spain	1991–1994	HVPG	Bruix et al.[30]

respectively. The corresponding 5-year mortality was 29.0%–72.4% and 20.8%–60.2% in patients with or without CSPH, respectively.

At 5 years after surgery, a total of 668/1213 (55.1%) patients with CSPH and 1174/2701 (43.5%) patients without CSPH died, respectively. The results of meta-analysis showed that CSPH was an independent risk factor for postoperative long-term survival for HCC patients who were treated with partial hepatectomy. The pooled OR was 1.29 (95% CI: 1.11–1.50; P = 0.001). There was mild or no significant heterogeneity in the analysis of long-term survival (P = 0.233; I^2 = 20.8%) (Fig. 2A). Sensitivity analysis revealed that result of each individual study had little effect on the total effect estimate (Supplement Figure 1A).

The stratified meta-analysis based on the different areas and diagnostic methods of CSPH showed that CSPH presence did not increase the 5-year mortality in patients from European countries in which CSPH was diagnosed based on the standard surrogate criteria. The pooled OR was 1.24 (95% CI: 0.98–1.55; P = 0.071), and no heterogeneity was found in this analysis (P = 0.906; I^2 = 0.0%) (Fig. 3F).

However, the stratified meta-analysis showed that patients with CSPH had significantly higher 5-year mortality than other subgroups, including the subgroup of CSPH that was diagnosed by HVPG or PVP, the subgroup from Asia or Europe in whom CSPH was diagnosed by HVPG or PVP, the subgroup of patients whose CSPH was diagnosed by the standard surrogate criteria and the subgroup from Asia where CSPH was diagnosed by the standard surrogate criteria (Fig. 3A, B, 3C, 3D, and 3E).

Secondary outcome: risks of surgical complications and peri-operative mortality of HCC patients with CSPH after partial hepatectomy

Table 2 summarizes the characteristics of surgical procedures (types of resection and rate of blood transfusion), postoperative complications and peri-operative mortality in the included studies.

The meta-analysis was performed for postoperative complications in 873 patients from 14 articles.[17–30] The complication rate was 344/1146 (30.0%) in patients with CSPH and 529/2654 (19.9%) in patients without CSPH. CSPH was significantly associated with higher postoperative complication rates (pooled OR: 1.66; 95%CI: 1.31–2.10; P < 0.0001; Fig. 2B). There was moderate, but nonsignificant heterogeneity in this analysis (P = 0.121; I^2 = 31.8%). Sensitivity analysis showed little effect from each individual study on the total effect (Supplement Figure 1B).

Subgroup meta-analysis showed that CSPH did not increase the postoperative complications in patients from Asia among those patients where CSPH was diagnosed by the standard surrogate criteria, as the pooled OR was 1.27 (95% CI: 0.94–1.70; P = 0.229). There was moderate, but nonsignificant heterogeneity in this subgroup analysis (Fig. 4E). In other subgroups (subgroup of patients whose CSPH was diagnosed by HVPG or PVP, subgroup from Asia or Europe where CSPH was diagnosed by HVPG or PVP, subgroup of patients whose CSPH was diagnosed by the standard surrogate criteria and subgroup from Europe where CSPH was diagnosed by the standard surrogate

Table 2 Hepatectomy, transfusion, and postoperative complications, peri-operative mortality and long-term survival in patients with or without CSPH

Author & Time	Number of patients	Type of resection (≥2 segments, n)			Blood transfusion (n)		Liver-Related Complications (n)	
		Total	CSPH	No CSPH	CSPH	No CSPH	CSPH	No CSPH
Llovet JM 1999	77	51	NR	NR	NR	NR	NR	NR
Giannini EG 2013	152	NR	NR	NR	NR	NR	NR	NR
Hidaka M 2012	177	60	7	53	NR	NR	15	20
Boleslawski E 2012	40	9	4	5	4	1	13	7
Llop E 2012	46	15	4	11	NR	NR	3	0
Kawano Y 2008	134	46	6	40	16	58	19	47
Choi GH 2011	100	38	21	17	29	23	17	8
Capussotti L 2006	217	51	12	39	51	38	27	18
Ruzzenente A 2011	135	31	8	23	NR	NR	14	12
Santambrogio R 2013	223	61	11	50	7	4	18	22
Cucchetti A 2009	241	12	2	10	16	34	11	6
Ishizawa T 2008	386	67	3	64	6	10	13	30
He W 2015	209	72	36	36	24	20	44	25
Zhong JH 2014	1738	134	62	72	NR	NR	120	311
Xiao H 2015	125	8	2	6	19	12	19	23
Bruix J 1996	29	NR	NR	NR	NR	NR	11	0

CSPH, clinically significant portal hypertension; NR, not reported.

criteria), the presence of CSPH was associated with high incidence of postoperative complications. There was mild-to-moderate heterogeneity in these subgroup meta-analyses (Fig. 4A, B, 4C, 4D, 4F).

Similarly, the meta-analysis of peri-operative mortality was performed in a total of 127 patients from 13 articles.[11,16,18–24,27–30] Peri-operative mortality occurred in 68/983 (6.9%) in patients with CSPH and 59/2242 (2.6%) in patients without CSPH, respectively.

The meta-analysis showed that the presence of CSPH significantly increased the risk of peri-operative mortality (pooled OR: 2.56; 95% CI: 1.77–3.70; $P < 0.001$; Fig. 2C) and there was no heterogeneity in this analysis ($P = 0.857$; $I^2 = 0$). Sensitivity analysis of peri-operative mortality was also performed and the results showed that each article had little effect on the total effect (Supplement Figure 1C).

The subgroup analysis showed that CSPH did not increase the risk of peri-operative mortality for patients from Europe where CSPH was diagnosed by standard surrogate criteria (pooled OR: 1.95; 95% CI: 0.96–3.96; $P = 0.067$). There was mild heterogeneity in this analysis ($P = 0.360$; $I^2 = 6.7$) (Fig. 5F). Besides, other subgroups (subgroup of patients whose CSPH was diagnosed by HVPG or PVP, subgroup of Asia or Europe where CSPH was diagnosed by HVPG or PVP) showed that CSPH did not increase the risk of peri-operative mortality (Fig. 5A, C, 5D). In the other subgroups (subgroup of patients whose CSPH was diagnosed by standard surrogate criteria, subgroup of Asia where CSPH was diagnosed by standard surrogate criteria), CSPH was associated with high peri-operative mortality (Fig. 5B and E).

Discussion

This systematical review and meta-analysis including 16 articles assessed the outcomes after partial hepatectomy in HCC patients with CSPH, showing that these patients had increased incidences of surgical complication and mortality, and decreased 5-year survival rate compared with patients without CSPH. However, the subgroup meta-analysis suggested that CSPH presence did not significantly reduce the short- and long-term outcomes in European patients with HCC in whom CSPH was diagnosed by the standard surrogate criteria.

Currently, three diagnostic modalities, i.e. HVPG ≥10 mm Hg, PVP ≥20 cm H_2O, or the standard surrogate criteria, have been frequently used for the clinical diagnosis of CSPH. Among which, HVPG measurement is regarded as the gold-standard diagnostic method.[39] However, because of its comparatively high cost, invasiveness and the potential presence other medical conditions, the direct monitoring of HVPG has not been widely used.[40] The standard surrogate criteria, which include the presence of GEV, or platelet count <100,000/mL and spleen diameter >12 cm, or platelet count <100,000/mL and spleen diameter >12 cm, were first proposed in 1999 and recognized by the Barcelona Clinic of Liver Cancer.[6] Moreover, due to its non-

peri-operative Mortality (n)		5-years OS (%)		5-years mortality (n)		Ref
CSPH	No CSPH	CSPH	No CSPH	CSPH	No CSPH	
2	1	TBIL <1 mg/dL 50; TBIL >1 mg/dL 25	74	27	9	Llovet et al.[11]
0	1	58.5	58.5	28	35	Giannini et al.[16]
NR	NR	31.0	63.7	33	47	Hidaka et al.[17]
5	1	NR	NR	NR	NR	Boleslawski et al.[18]
0	0	NR	NR	NR	NR	Llop et al.[19]
4	9	70.1	47.5	9	54	Kawano et al.[20]
3	1	37.9	78.7	29	11	Choi et al.[21]
11	10	28.9	39.8	70	71	Capussotti et al.[22]
6	3	44.9	61.2	24	35	Ruzzenente et al.[23]
4	3	48	65	31	56	Santambrogio et al.[24]
NR	NR	51.5	61.8	43	58	Cucchetti et al.[25]
NR	NR	Child-Pugh A:56Child-Pugh B:41	A:71B; 31	65	82	Ishizawa et al.[26]
5	2	46	50	55	54	He et al.[27]
26	28	45	54	212	622	Zhong et al.[28]
1	0	28.1	39.8	42	40	Xiao et al.[29]
1	0	NR	NR	NR	NR	Bruix et al.[30]

invasiveness, good feasibility and low cost, CSPH diagnosis through standard surrogate criteria has been widely accepted and adopted in clinical practice.[6,7,31] Furthermore, the EASL-EORTC Clinical Practice Guidelines have recommended that both HVPG and the standard surrogate criteria can be used in the assessment of the surgical safety and resectability of HCC.[9] Specifically, this Guidelines have indicated that the platelet count, a variable included in the criteria, remains the most accessible parameter of portal hypertension available. Our data also showed there were more studies using the standard surrogate criteria to diagnose CSPH when compared with HVPG alone (9 vs. 5 articles). However, the available diagnostic methods of CSPH might have varied diagnostic accuracy that might lead to different clinical outcomes. Generally, HVPG measurement could provide a more precise diagnosis, even if the portal pressure was slightly increased above the threshold.[39] On the other hand, CSPH presence diagnosed by using the standard surrogate criteria that is incorporated with only three clinical variables might less accurate than HVPG. Berzigotti *et al.* reported that CSPH diagnosed by HVPG predicted poorer short- and long-term outcomes compared with that by the standard surrogate criteria.[31] However, the advantage of this criteria is its noninvasive, cost-effective and easy-to-use nature. Considering the possible difference in the distinguishing ability between these two methods, we hereby carried out a stratified meta-analysis to observe the surgical prognoses in HCC patients with CSPH that was diagnosed by the two methods (CSPH diagnosed by HVPG or PVP, CSPH diagnosed by the standard surrogate criteria). In addition, as HCC developed from different areas might have different clinicopathological characteristics and different racial descent,[41] different geographical area was also used as an additional factor in the stratified meta-analysis.[42–44]

Our meta-analysis showed that presence of CSPH significantly decreased the short- and long-term outcomes when compared with patients without CSPH. According to the BCLC staging system,[6] surgical resection is contraindicated in HCC patients with CSPH and elevated bilirubin level, which has also been adopted by the AASLD and the EASL guidelines and consistent with the current international guidelines.[7–9,45] Our result was consistent with the above guidelines in general. However, our stratified meta-analysis showed that CSPH presence which was diagnosed by the standard surrogate criteria did not significantly impact the short- and long-term survival after liver resection in European HCC patients (pooled OR: 1.95, 95% CI: 0.96–3.96; pooled OR: 1.24, 95%CI: 0.98–1.55 for peri-operative mortality and postoperative long-term survival). In addition, there was no heterogeneity in this analysis. This result might support the theory that CSPH should not always be considered as an contraindication of partial hepatectomy in all patients with HCC, and at least some of certain subgroup of patients could benefit from the procedure.[16,20–29] Specifically, Child-Pugh A patients with portal hypertension could have similar short- and long-term outcomes, including morbidity and survival,[23] as patients without portal hypertension.[22] Cucchetti *et al.* reported that when other prognostic variables were balanced between the patients with versus without portal hypertension, portal hypertension had no significant impact

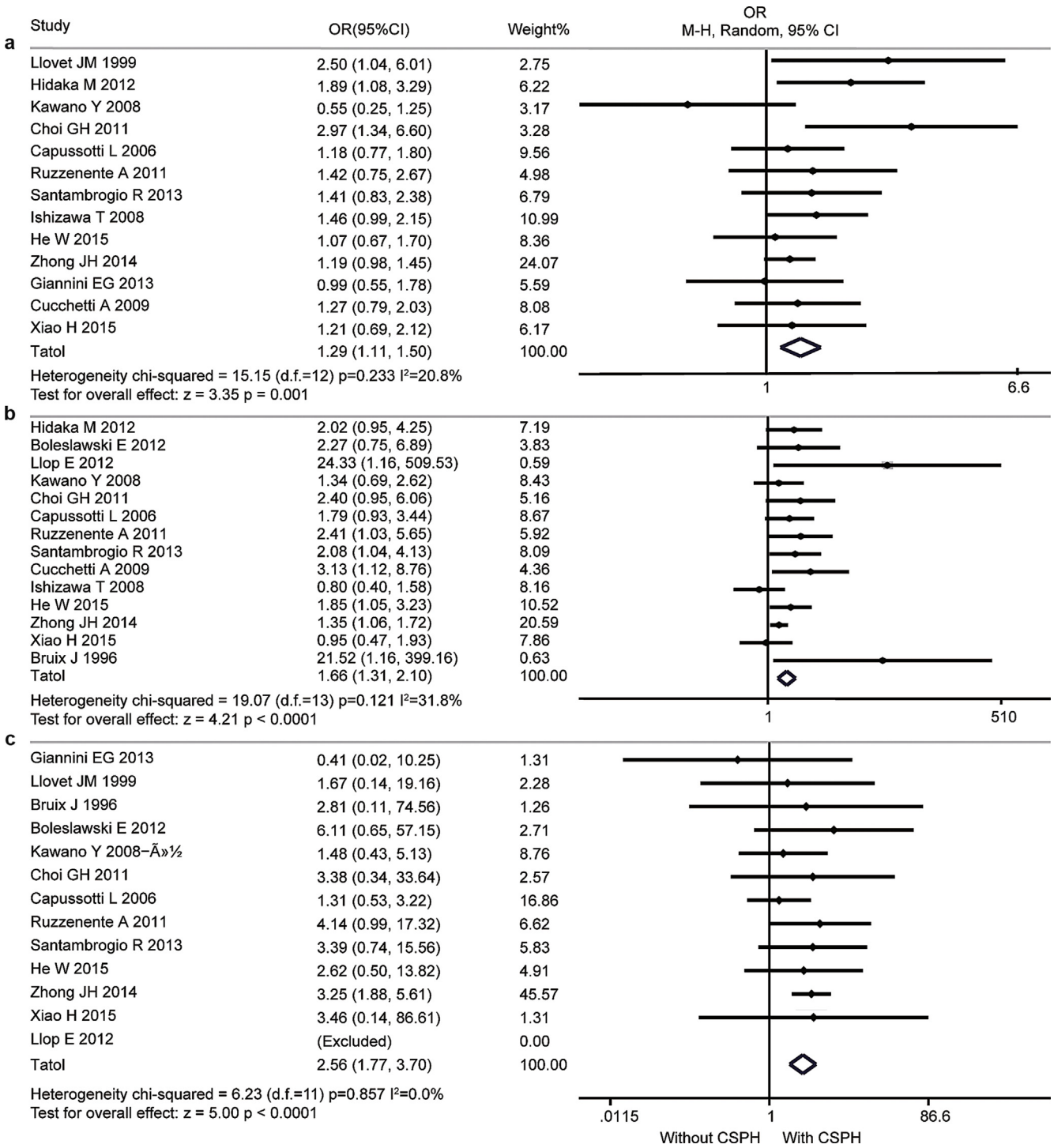

Figure 2 **A.** The impact of CSPH on postoperative 5-year mortality of patients with HCC underwent hepatectomy in all articles which reported postoperative 5-year mortality included studies. **B.** The impact of CSPH on postoperative complications of patients with HCC underwent hepatectomy in all articles which reported postoperative complications included studies. **C.** The impact of CSPH on perioperative mortality of patients with HCC underwent hepatectomy in all articles which reported perioperative mortality included studies

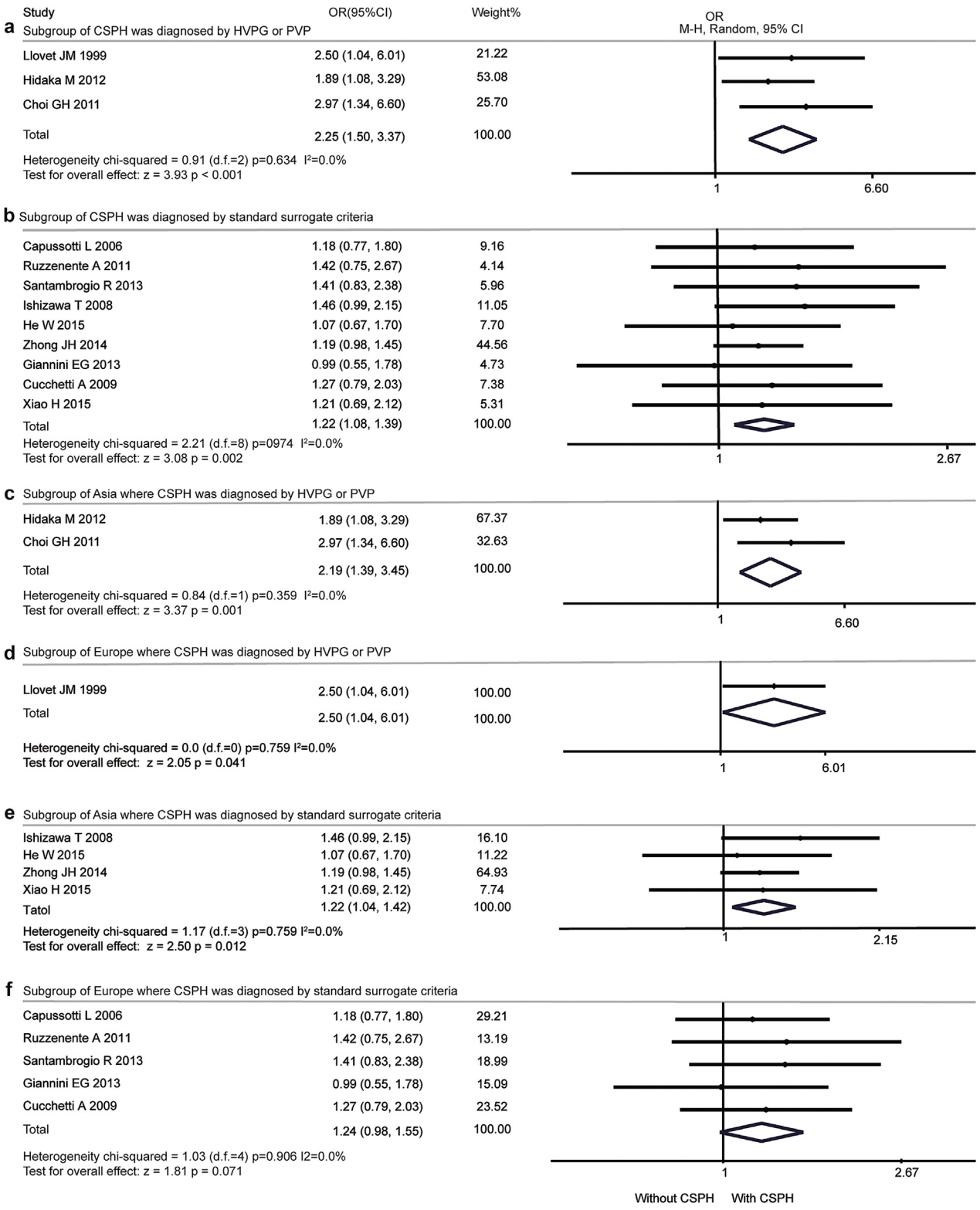

Figure 3 Stratified meta-analysis according to different diagnostic methods of CSPH and different areas to assess the impact of CSPH on postoperative 5-year mortality of patients with HCC underwent hepatectomy. (A) subgroup of patients whose CSPH was diagnosed by HVPG or PVP. (B) subgroup of patients whose CSPH was diagnosed by standard surrogate criteria. (C) subgroup of Asia where CSPH was diagnosed by HVPG or PVP. (D) subgroup of Europe where CSPH was diagnosed by HVPG or PVP. (E) subgroup of Asia where CSPH was diagnosed by standard surrogate criteria. (F) subgroup of Europe where CSPH was diagnosed by standard surrogate criteria

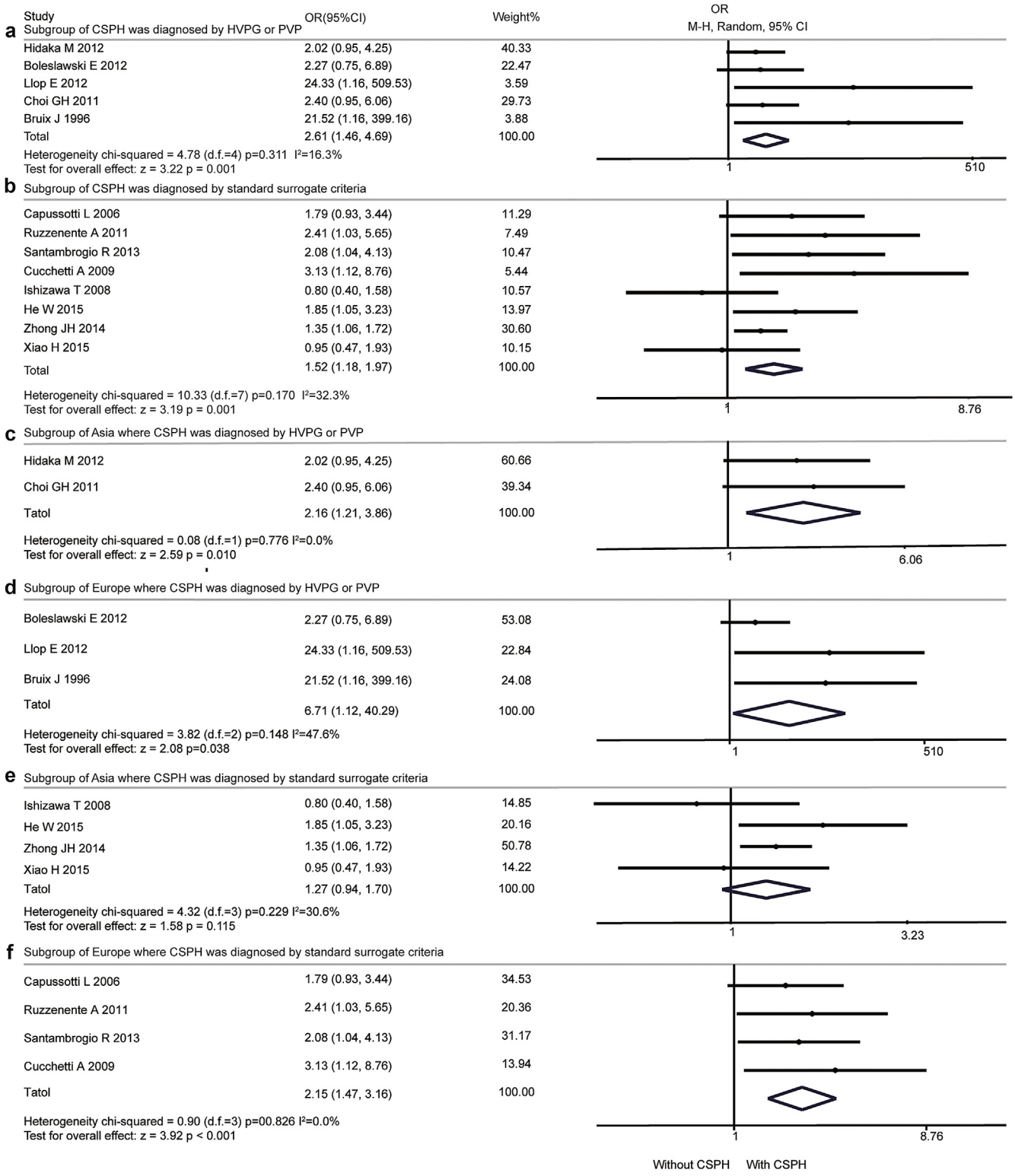

Figure 4 Stratified meta-analysis according to different areas and different diagnostic methods of CSPH to assess the impact of CSPH on postoperative complications of patients with HCC underwent hepatectomy. (A) subgroup of patients whose CSPH was diagnosed by HVPG or PVP. (B) subgroup of patients whose CSPH was diagnosed by standard surrogate criteria. (C) subgroup of Asia where CSPH was diagnosed by HVPG or PVP. (D) subgroup of Europe where CSPH was diagnosed by HVPG or PVP. (E) subgroup of Asia where CSPH was diagnosed by standard surrogate criteria. (F) subgroup of Europe where CSPH was diagnosed by standard surrogate criteria

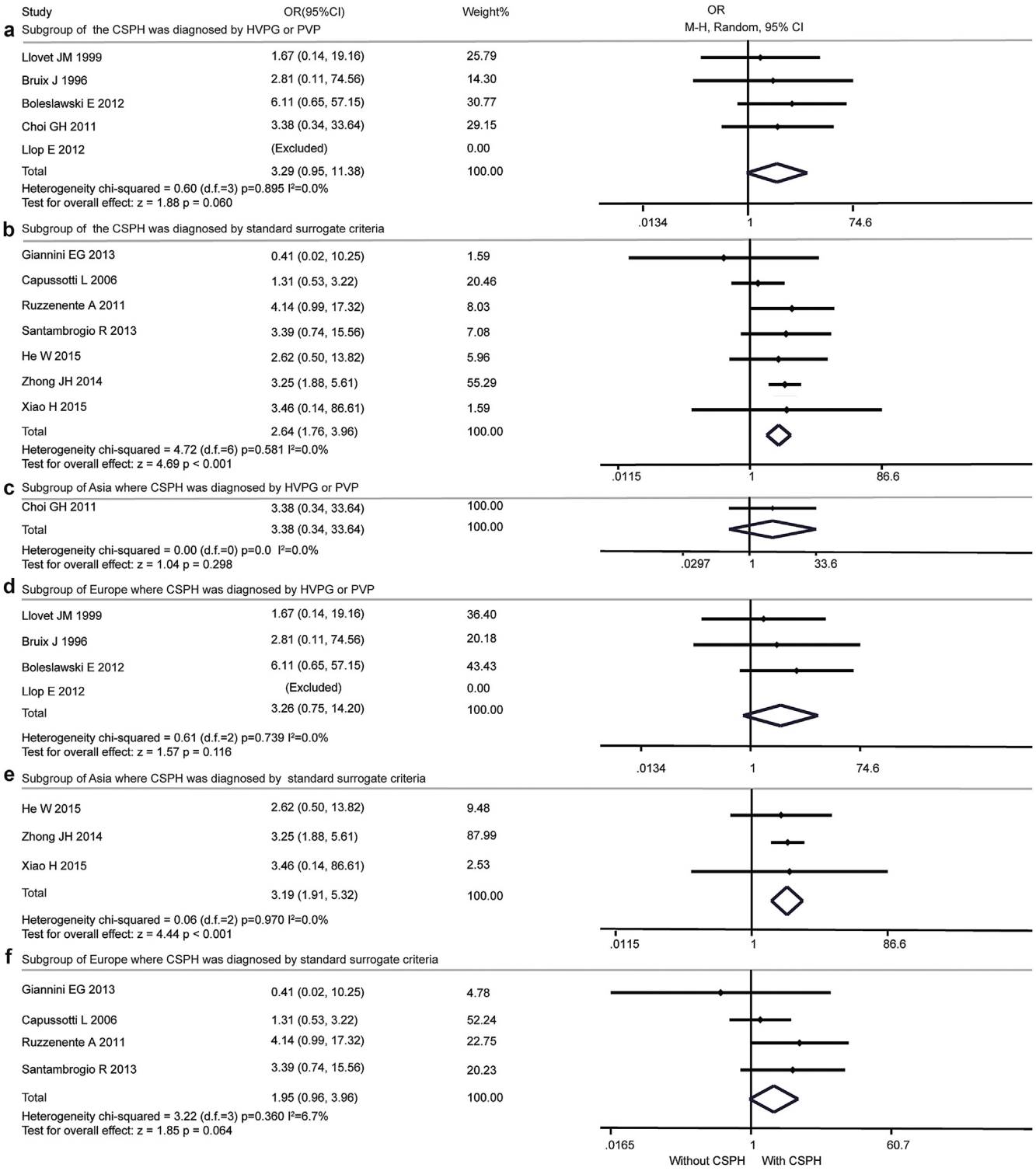

Figure 5 Stratified meta-analysis according to different areas and different diagnostic methods of CSPH to assess the impact of CSPH on perioperative mortality of patients with HCC underwent hepatectomy. (A) subgroup of patients whose CSPH was diagnosed by HVPG or PVP. (B) subgroup of patients whose CSPH was diagnosed by standard surrogate criteria. (C) subgroup of Asia where CSPH was diagnosed by HVPG or PVP. (D) subgroup of Europe where CSPH was diagnosed by HVPG or PVP. (E) subgroup of Asia where CSPH was diagnosed by standard surrogate criteria. (F) subgroup of Europe where CSPH was diagnosed by standard surrogate criteria

on postoperative survival outcomes.[25] A further study also demonstrated that resection for HCC could be used in patients who had portal hypertension, and the presence of CSPH was not significantly associated with a worse overall survival compared with the absence of CSPH in these patients.[26] These results indicated that liver resection for HCC was safe and effective in patients with CSPH who had an optimal liver functional reserve. CSPH seems not to be a definite contraindication in European HCC patients whose CSPH was diagnosed by the standard surrogate criteria. This can be attributed to the following facts: in Europe, the number of patients with HCC is significantly less than that in Asia, and the selection criterion for patients undergoing surgery is stricter. Besides, as a result of a better screening examination in Europe, many patients are in the early or middle stage when HCC was diagnosed. Contrarily, there are more HCC patients in the Asian region and many patients are found to be in the middle or late stage of HCC. Due to the current situation in Asia, many HCC patients who are not indicated for surgery in the European countries are still candidates for surgery in Asia. In other words, the overall baseline characteristic of European patients was significantly better than that of Asian patients. However, the specific reasons that CSPH did not have negative impact on perioperative and long-term outcome of European HCC patients whose CSPH was diagnosed by the standard surrogate criteria were not clear and this is an important topic for our future research.

To our best knowledge, the included studies contain all the current published evidences on portal hypertension in HCC, extending the evidence-base from the previously published study by Berzigotti *et al.*[31] This is the first meta-analysis showing that CSPH was not a negative prognostic factor for certain HCC patients (European HCC patients with CSPH diagnosed by standard surrogate criteria). Moreover, our study also systematically analyzed the influence of CSPH on postoperative complications and perioperative mortality, which are two factors affecting the decision-making of hepatectomy.

Our study had several limitations. Firstly, the most included studies were retrospective in nature, with only 25.0% (n = 4) of which were prospective studies. Second, heterogeneity among these articles in diagnostic methods existed. Finally, the presence of CSPH is not the only factor in making the decision of liver resection for HCC. Other factors such as tumor stage and tumor location, which would also affect the decision-making of surgery, were not considered in this study.

Conclusion

This systematic review and meta-analysis confirmed the negative effects of CSPH on surgical morbidity, mortality, and postoperative long-term survival in most HCC patients with CSPH. However, CSPH should not be seen as an absolute contraindication for hepatectomy in patients with HCC, especially in European HCC patients whose CSPH was diagnosed by the standard surrogate criteria.

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Authorship

Guarantor of the article: Feng Shen

Author contributions: J. Liu, H. Zhang, Y. Xia and T. Yang contributed in study concept, data collection, extraction and analysis and drafting of the manuscript; J. Liu, H. Zhang, Y. Gao, J. Li and Y. Wu contributed in data search and extraction; F. Shen contributed in study concept, design, drafting of the manuscript and study supervision.

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Declaration of personal and funding interests

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.hpb.2018.07.005.