RESEARCH ARTICLE

Influence of Clinically Significant Portal Hypertension on Hepatectomy for Hepatocellular Carcinoma: a Meta-analysis

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Abstract

Background: Clinically significant portal hypertension (PHT) is considered as a contraindication for hepatectomy according to the guidelines of the European Association for Study of Liver and the American Association for Study of Liver Diseases. However, this issue remains controversial. Here we performed a meta-analysis to evaluate the impact of PHT on the results of hepatectomy for hepatocellular carcinoma (HCC). Methods: Cohort studies evaluating the impact of clinically significant PHT, defined as oesophageal varices and/or splenomegaly associated with thrombocytopenia, on the results of hepatectomy for HCC were identified using a predefined search strategy. Summary risk ratios (RRs) and 95% confidence intervals (95% CIs) for PHT and outcomes after hepatectomy for HCC were calculated. Results: Seven cohort studies which including 574 cases with PHT and 1,354 cases without PHT were considered eligible for inclusion. The meta-analysis showed that, in all patients, pooled RRs of post-operative liver failure, post-operative ascites, peri-operative blood transfusion, operative mortality, 3- and 5-year overall survival associated with PHT were 2.23 (95% CI: 1.48-3.34, *P*=0.0001), 1.77 (95% CI: 1.19-2.64, *P*=0.005), 1.23 (95% CI: 1.03-1.49, *P*=0.03), 2.58 (95% CI: 1.12-5.96, *P*=0.03), 0.82 (95% CI: 0.75-0.88, *P*<0.00001) and 0.76 (95% CI: 0.69-0.85, *P*<0.00001), respectively. In subgroup analysis, similar results were found in Child-Pugh class A patients. Conclusion: This meta-analysis suggests that presence of oesophageal varices and/or splenomegaly associated with thrombocytopenia is associated with higher rates of post-operative complications and poor long-term survival after hepatectomy for HCC.

Keywords: Portal hypertension - hepatectomy - hepatocellular carcinoma - meta-analysis

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Introduction

Hepatocellular carcinoma (HCC), which is the fifth most common malignancy and the third leading cause of cancer death worldwide, is a global health burden (Parkin et al., 2005; Parkin, 2006). Hepatectomy is considered as a curative and safe treatment among all of the therapeutic approaches for HCC. It plays an important role, especially under the circumstance of lack of donor for transplantation.

However, according to the guidelines by the European Association for Study of Liver (EASL) and American Associations for Study of Liver Diseases (AASLD), clinically significant portal hypertension (PHT) is considered as a contraindication for hepatectomy (Bruix et al., 2001; Bruix et al., 2005). This recommendation is based on two studies, both from the Barcelona group (Bruix et al., 1996; Llovet et al., 1999). These studies demonstrated that the presence of clinically significant PHT, which was defined as hepatic venous pressure gradient (HVPG) ≥ 10 mmHg, was the most powerful predictor for post-operative liver failure or poor long-term survival in patients with Child-Pugh A liver function. Due to preoperative HVPG measurement is invasive and not performed routinely in most liver centers, indirect clinical parameters (oesophageal varices and/or splenomegaly associated with thrombocytopenia) are considered surrogate markers of clinically significant PHT. But in recent years, some Italian and Japanese studies have failed to confirm the association between indirect criteria of PHT and short- or long-term outcomes after hepatectomy for HCC (Imamura et al., 2003; Capussotti et al., 2006; Ishizawa et al., 2008; Cucchetti et al., 2009).

Up to now, there is no remarkable evidence have been presented to demonstrate that whether the outcomes after hepatectomy for HCC are similar or different between patients with and without clinically significant PHT. In order to clarify this issue, we conducted a meta-analysis by reviewing the existing literature to assess the impact of clinically significant PHT on the results of hepatectomy for HCC.

Materials and Methods

Search strategy

We searched PUBMED, EMBASE and CNKI (China National Knowledge Infrastructure Whole Article Database) by using the following search term: (liver or

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Table 1. Characteristics of Included Trials

Authors	Journal	Year	Country	All patients		Child-Pugh A patients	
				PHT	No PHT	PHT	No PHT
Capussotti et al	World J Surg	2006	Italy	99	118	66	112
Cucchetti et al	Ann Surg	2009	Italy	89	152	-	-
Ishizawa et al	Gastroenterology	2008	Japan	136	250	98	224
Choi et al	Liver Int	2011	Korea	47	53	47	53
Ruzzenente et al	World J Gastroenterol	2011	Italy	44	91	29	81
Santambrogio et al	HPB	2013	Italy	63	160	63	160
Yang et al	Chinese Hepatology	2012	China	96	530	96	530

hepatocellular) and (cancer or carcinoma or malignancy) and (hepatectomy or resection or surgery) and portal hypertension. All cohort studies evaluating the impact of clinically significant PHT on the results of hepatectomy for HCC published in English or Chinese prior to December 2013 were identified. If samples of two studies overlap, only the newest one was included. Additional articles were obtained from references within the articles identified by the electronic search. We did not consider abstracts or unpublished reports.

Inclusion and exclusion criteria

We reviewed abstracts of all citations and retrieved studies. The following criteria were used to include published studies: (1) cohort design; (2) patients were divided into groups according to presence of clinically significant PHT (defined as oesophageal varices and/or splenomegaly associated with thrombocytopenia); (3) evaluation of the association between clinically significant PHT and short- or long-term outcomes after curative hepatectomy for HCC; (4) sufficient sample data were presented to calculate the risk ratio (RR) and confidence interval (CI). Patients could be of any age, gender, and race. Studies were excluded if one of the following existed: (1) case-control design; (2) duplicate data; (3) no sufficient data were reported.

Data collection and analysis

Selection of trials and data extraction: The titles and abstracts of publications identified according to the above search strategy were assessed independently for inclusion by two authors (Tang Yun-Hao and Zhu Wen-Jiang), the full text was selected for further assessment if the abstract suggests relevance. Disagreement was resolved by discussion. Data was extracted by two independent authors (Tang Yun-Hao and Zhu Wen-Jiang). The following recorded data were extracted: author, publication data, country of the first or corresponding author, the number of patients. Outcome measures presented in at least 3 studies were extracted for combined analysis.

Data synthesis: We assessed statistical heterogeneity by using a Chi-squared test where $P<0.1$ indicates significant heterogeneity. If heterogeneity was found, we synthesized data using a random-effects model. If heterogeneity was not found, we synthesized data using a fixed-effects model. For meta-analysis, the results were reported with risk ratios (RR) for dichotomous data and weighted mean difference (WMD) for continuous data, and 95% confidence intervals (CI) were calculated for individual studies. *P*-value less than 0.05 was considered

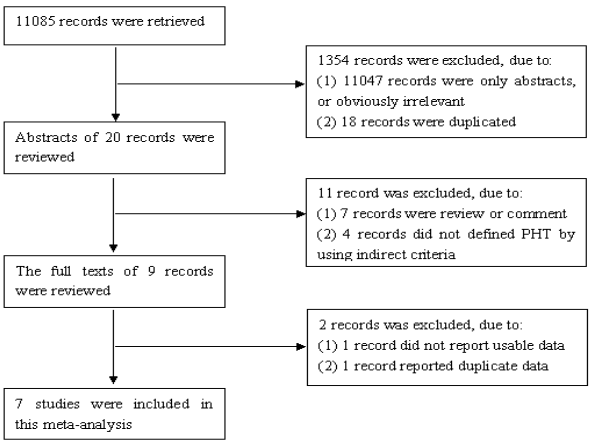

Figure 1. Flow Chart of Selection of Studies

to be statistically significant. Potential publication bias and other possible biases were examined by using the funnel plots. Trials with continuous data recorded as the form of median and range were excluded from meta-analysis. The results of the studies were analyzed using the statistical package RevMan 5.0.24 provided by the Cochrane Collaboration [http://www.cc-ims.net/RevMan/current.htm].

Results

Description of included trials

There were 11085 papers relevant to the search words. Via steps of screening the title and reading the abstract, 9 studies were identified (Imamura et al., 2003; Capussotti et al., 2006; Ishizawa et al., 2008; Cucchetti et al., 2009; Choi et al., 2011; Ruzzenente et al., 2011; Yang et al., 2012; Santambrogio et al., 2013; Giannini et al., 2013). Of these, two studies were excluded (one did not present usable data (Giannini et al., 2013); samples of two studies were partially overlapped (Imamura et al., 2003; Ishizawa et al., 2008), so only the newest one was included (Ishizawa et al., 2008). As a result, a total of 7 cohort studies (Capussotti et al., 2006; Ishizawa et al., 2008; Cucchetti et al., 2009; Choi et al., 2011; Ruzzenente et al., 2011; Yang et al., 2012; Santambrogio et al., 2013) which including 574 cases with PHT and 1354 cases without PHT were considered eligible for inclusion based on MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines (Stroup et al., 2000). The flow chart of selection of studies and reasons for exclusion is presented in Figure 1. Studies had been carried out in China, Japan, Korea and Italy. The following outcomes were presented in

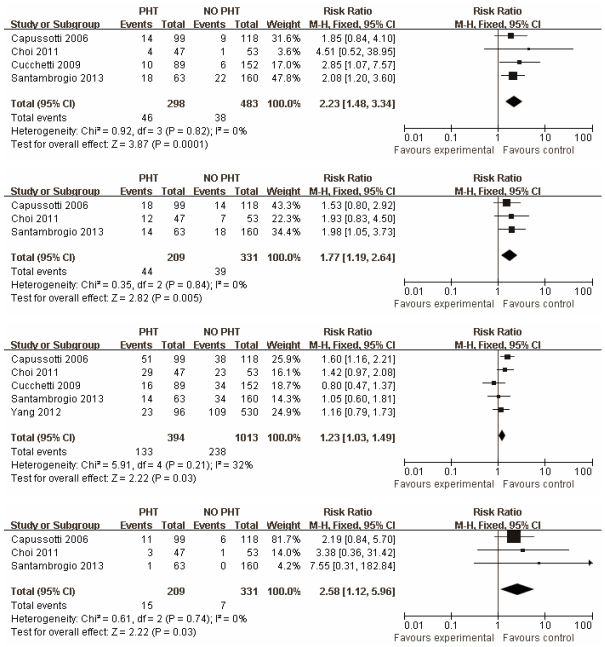

Figure 2. Risk Ratios and 95% CI of Individual Studies and Pooled Data of Short-term Outcomes Associated with PHT in All Patients (From top to bottom: post-operative liver failure, post-operative ascites, peri-operative blood transfusion, and operative mortality)

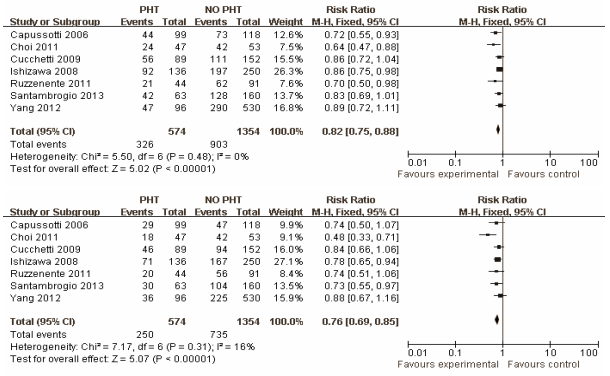

Figure 3. Risk Ratios and 95% CI of Individual Studies and Pooled Data of Survival Associated with PHT in All Patients (From top to bottom: 3-year survival and 5-year survival)

at least 3 studies and extracted for combined analysis: post-operative liver failure, post-operative ascites, peri-operative blood transfusion, operative mortality, 3- and 5-year survival. Six included studies divided patients according to Child-Pugh classification and did subgroup analysis of Child-Pugh class A patients (Capussotti et al., 2006; Ishizawa et al., 2008; Choi et al., 2011; Ruzzenente et al., 2011; Yang et al., 2012; Santambrogio et al., 2013). Therefore, we conduct a subgroup meta-analysis to evaluate the impact of clinically significant PHT on the results of hepatectomy for HCC in Child-Pugh class A patients separately. Characteristics of studies included in the meta-analysis are presented in Table 1.

Impact of clinically significant PHT on outcomes after hepatectomy for HCC (in all patients)

Short-term outcomes: Four included studies (Capussotti et al., 2006; Cucchetti et al., 2009; Choi et al., 2011;

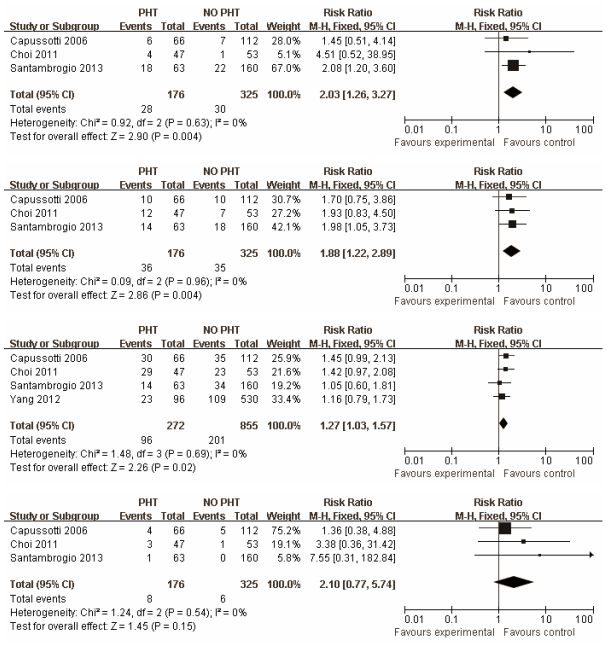

Figure 4. Risk Ratios and 95% CI of Individual Studies and Pooled Data of Short-term Outcomes Associated with PHT in Child-Pugh class A Patients (From top to bottom: post-operative liver failure, post-operative ascites, peri-operative blood transfusion,and operative mortality)

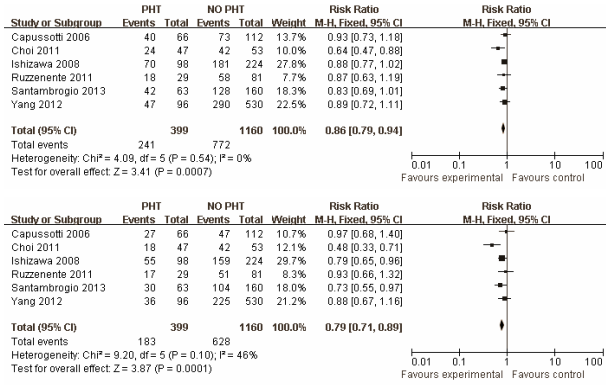

Figure 5. Risk Ratios and 95% CI of Individual Studies and Pooled Data of Survival Associated with PHT in Child-Pugh Class A Patients (From top to bottom: 3-year survival and 5-year survival)

Santambrogio et al., 2013) reported post-operative liver failure, three (Capussotti et al., 2006; Choi et al., 2011; Santambrogio et al., 2013) reported post-operative ascites, five (Capussotti et al., 2006; Cucchetti et al., 2009; Choi et al., 2011; Yang et al., 2012; Santambrogio et al., 2013) reported peri-operative blood transfusion, and three (Capussotti et al., 2006; Choi et al., 2011; Santambrogio et al., 2013) reported operative mortality. The *P* values of heterogeneity tests were 0.82, 0.84, 0.21, and 0.74, respectively. Thus, fixed-effect model was used in all combined analyses. The pooled RRs of post-operative liver failure, post-operative ascites, peri-operative blood transfusion, and operative mortality associated with PHT were 2.23 (95% CI: 1.48-3.34, *P*=0.0001), 1.77 (95% CI: 1.19-2.64, *P*=0.005), 1.23 (95% CI: 1.03-1.49, *P*=0.03), and 2.58 (95% CI: 1.12-5.96, *P*=0.03), respectively. Compared with patients without PHT, the rates of post-operative liver failure, post-operative ascites, peri-

operative blood transfusion, and operative mortality were significantly higher in patients with PHT (Figure 2).

Long-term outcomes: Only one included study reported 1-year overall survival rate (Choi et al., 2011). Choi et al. demonstrated that 1-year overall survival rate in patients with PHT was significantly lower (76.5% versus 92.4%, $P<0.001$) . All included studies reported 3- and 5-year overall survival. The *P* values of heterogeneity tests were 0.48 and 0.31, respectively. Thus, fixed-effect model was used in combined analyses. The pooled RRs of 3- and 5-year overall survival associated with PHT were 0.82 (95% CI: 0.75-0.88, $P<0.00001$) and 0.76 (95% CI: 0.69-0.85, $P<0.00001$), respectively. Compared with patients without PHT, 3- and 5-year overall survival rates were significantly lower in patients with PHT (Figure 3).
Impact of clinically significant PHT on outcomes after hepatectomy for HCC (in Child-Pugh class A patients)
Short-term outcomes: Of the 6 studies separated and analyzed Child-Pugh A patients, three (Capussotti et al., 2006; Choi et al., 2011; Santambrogio et al., 2013) reported post-operative liver failure, three (Capussotti et al., 2006; Choi et al., 2011; Santambrogio et al., 2013) reported post-operative ascites, four (Capussotti et al., 2006; Choi et al., 2011; Yang et al., 2012; Santambrogio et al., 2013) reported peri-operative blood transfusion, and three (Capussotti et al., 2006; Choi et al., 2011; Santambrogio et al., 2013) reported operative mortality. The *P* values of heterogeneity tests were 0.63, 0.96, 0.69, and 0.54, respectively. Thus, fixed-effect model was used in all combined analyses. The pooled RRs of post-operative liver failure, post-operative ascites, peri-operative blood transfusion, and operative mortality associated with PHT were 2.03 (95% CI: 1.26-3.27, $P=0.004$), 1.88 (95% CI: 1.22-2.89, $P=0.004$), 1.27 (95% CI: 1.03-1.57, $P=0.02$), and 2.10 (95% CI: 0.77-5.74, $P=0.15$), respectively. In Child-Pugh class A patients, the rates of post-operative liver failure, post-operative ascites, and peri-operative blood transfusion were significantly higher in patients with PHT versus without PHT (Figure 8-10); however, there was no significant difference in operative mortality (Figure 4).

Long-term outcomes: All of the 6 studies reported 3- and 5-year overall survival. The *P* values of heterogeneity tests were 0.54 and 0.1, respectively. Thus, fixed-effect model was used in combined analyses. The pooled RRs of 3- and 5-year overall survival associated with PHT were 0.86 (95% CI: 0.79-0.94, $P=0.0007$) and 0.79 (95% CI: 0.71-0.89, $P=0.0001$), respectively. In Child-Pugh class A patients, 3- and 5-year overall survival rates were significantly lower in patients with PHT versus without PHT (Figure 5).

Publication bias

Publication bias may exist when no significant findings remain unpublished, thus artificially inflating the apparent magnitude of an effect. Funnel plots were drawn to examine the potential publication bias in this meta-analysis, which showed basic symmetry in all of outcome measures. It suggested that publication bias was not evident in this meta-analysis.

Discussion

Since clinically significant PHT was recommended as a contraindication to hepatectomy for HCC according to the recent EASL/AASLD guidelines (Bruix et al., 2001; 2005), this issue has become a highly debated topic. In the earlier one of the two studies which were used to constitute the guidelines, Bruix et al. investigated the outcome after hepatectomy in 29 Child-Pugh class A patients. They defined clinically significant PHT as HVPG≥10 mmHg and found that was the most powerful independent risk factor for post-operative liver failure in multivariate analysis (Bruix et al., 1996). In the later one, Llovet et al. defined clinically significant PHT as indirect criteria (oesophageal varices and/or splenomegaly associated with thrombocytopenia) or HVPG≥10 mmHg. They analyzed 77 patients and showed that clinical significant PHT was a predictor for poor long-term survival (Llovet et al., 1999). After that, although preoperative HVPG measurement is not performed routinely in most liver centers, there were still some studies designed to evaluate the impact of direct HVPG measurement on the results of hepatectomy for HCC.

Boleslawski et al. (2012) conducted a study of 40 patients underwent HVPG measurement and found that severe complications were significantly more common in patients with HVPG≥10mmHg. In another study including 39 patients had preoperative HVPG assessment, Stremitzer et al. reported that patients with HVPG>5 mmHg had a higher rate of post-operative liver failure and ascites (Stremitzer et al., 2011). It seems that there was no doubt of clinically significant PHT being a predictor for outcomes after hepatectomy. However, these results were challenged by some other studies.

In a study including 217 patients (99 with PHT versus 118 without PHT), Capussotti et al. reported that patients without PHT have better 3- and 5-year survival compared with patients with PHT. But in Child-Pugh class A patients, short- and long-term outcomes were similar between patients with and without PHT (Capussotti et al., 2006). Similarly, Imamura et al. reported their experience in a series of 1056 consecutive hepatectomies without mortality and showed that presence of PHT was not a predictor for post-operative complications (Imamura et al., 2003). Kawano et al. also found that patients with oesophageal varices had similar outcomes compared with those without oesophageal varices in a study of 131 patients including (Kawano et al., 2008). It is noteworthy that, instead of measuring HVPG directly, indirect criteria were used to define PHT in these studies failed to replicate those Barcelona group's findings. Therefore, it is doubtful whether using indirect criteria of PHT to select patients for hepatectomy is adequate or not.

We conduct a meta-analysis to clarify this issue by using all the available published data to increase the statistical power. The data from this meta-analysis suggest that patients with clinically significant PHT had significantly higher rates of post-operative liver failure. Other short-term outcomes such as post-operative ascites, peri-operative blood transfusion and operative mortality

are found to be worse in patients with clinically significant PHT too. Presence of clinically significant PHT is also found to be associated with poor long-term survival in this meta-analysis. Likewise, similar statistically significant differences between patients with and without clinically significant PHT are observed in Child-Pugh class A patients. All of these results confirm that indirect clinical parameters are appropriate surrogate markers of clinically significant PHT, and emphasize the conclusion drawn by the Barcelona group that presence of clinically significant PHT is a powerful predictor for both post-operative complications and poor long-term survival.

Predictive value of clinically significant PHT for outcomes after hepatectomy was also confirmed by some studies using other ways to detect PHT. Increasing portal vein pressure, obtained by direct measurement during surgery, was found associated with both high rate of post-operative liver failure and poor long-term survival (Chen et al., 2012; Hidaka et al., 2012). Liver stiffness measurement (LSM) using transient elastography is a new non-invasive method, and shows a linear correlation with portal pressure (Ziol et al., 2005; Vizzutti et al., 2007). In a recent study, LSM >12.0 kPa was found to be an independent predictor for major postoperative complications by multivariate analysis (Wong et al., 2013). It suggested that LSM may be a good surrogate marker of PHT. However, there were only a few studies like that have been conducted to investigate the predictive value of LSM for outcomes after hepatectomy.

Many other risk factors, such as pre-operative bilirubin, cirrhosis and extent of hepatectomy, have also been found to be associated with post-hepatectomy complications (Schindl et al., 2005; van den Broek et al., 2008), and another factors, including microvascular invasion, AFP > 800 ng/ml, and multiple tumors, are considered to be independent risk factors for postoperative recurrence of HCC (Li et al., 2013; Zhu et al., 2013). Subgroup analyses may need to eliminate the influence of these factors in this meta-analysis. But unfortunately, most including studies did not provide such subgroup data. Further more, the aetiologies of cirrhosis were different greatly between the eastern and the western. The bias caused by this cirrhotic aetiological discrepancy is uncertain. Thus, our results should be interpreted cautiously for a population with specific aetiology of cirrhosis. In addition, some important outcome measures, including intraoperative blood loss, post-operative esophageal bleeding and long-term recurrence rate, were not presented by enough studies so that we could not extract them for meta-analysis. Finally, like most meta-analyses, our results should be interpreted with caution because the methodological limitations and the small number of included studies.

In conclusion, this meta-analysis suggests that presence of oesophageal varices and/or splenomegaly associated with thrombocytopenia is associated with higher rates of post-operative complications and poor long-term survival after hepatectomy for HCC. Portal hypertension should be considered an absolute contraindication to hepatectomy in cirrhotic patients.

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