Int J Clin Exp Med 2015;8(11):21044-21052
www.ijcem.com /ISSN:1940-5901/IJCEM0013866

Original Article

Combined portal vein resection for hilar cholangiocarcinoma

Tao Bai[1,3*], Jie Chen[1,3*], Zhi-Bo Xie[1,3], Liang Ma[1,3], Jun-Jie Liu[1,2], Shao-Liang Zhu[1,3], Fei-Xiang Wu[1,3], Le-Qun Li[1,3]

Departments of [1]Hepatobiliary Surgery, [2]Ultrasound Diagnosis, Affiliated Tumor Hospital of Guangxi Medical University, Nanning 530021, P. R. China; [3]Guangxi Liver Cancer Diagnosis and Treatment Engineering and Technology Research Center, Nanning 530021, P. R. China. [*]Equal contributors.

Received August 3, 2015; Accepted October 4, 2015; Epub November 15, 2015; Published November 30, 2015

Abstract: Background: Surgery is the only curative therapy for patients with hilar cholangiocarcinoma (HCCA). Combined portal vein resection (PVR) could achieve negative resection margins in HCCA patients with portal vein invasion. This systematic review aimed to analysis the efficiency of combined PVR for HCCA. Methods: MEDLINE, EMBASE, the Cochrane Library, the Chinese National Knowledge Infrastructure database, and clinical trial registries were searched through April 2015. Risk ratios (RRs), and 95% confidence intervals (CIs) were calculated. Results: The analysis included 21 retrospective studies, altogether involving 2403 patients (patients with PVR, n=637; patients without PVR, n=1766). Patients with PVR were likely to have more advanced HCCA (lymphatic invasion: RR=1.14, 95% CI 1.02 to 1.28; perineural invasion: RR=1.31, 95% CI 1.05 to 1.63) and suffered less curative resections (RR=0.89, 95% CI 0.75 to 0.99). Postoperative morbidity was similar between patients with or without PVR (RR=1.06, 95% CI 0.94 to 1.02). Patients with PVR suffered higher mortality rate (RR=1.52, 95% CI 1.06 to 2.18), and worse 5-year survival rate (RR=0.67, 95% CI 0.49 to 0.91). Conclusion: Combined PVR for HCCA patients would not increase postoperative morbidity rate. However, ascribed to PVR group concluded more advanced HCCA patients; patients with PVR had increased postoperative mortality rate and worse survival rate. The results still need further high quality trails for validation.

Keywords: Portal vein resection, hilar cholangiocarcinoma, meta-analysis, liver resection, survival

Introduction

Hilar cholangiocarcinoma (HCCA) also known as Klatskin tumor, which accounts for 60% of all biliary tract cholangiocarcinomas [1]. The possible therapeutic option for HCCA patients is surgery, whereas no adjuvant therapies are effective for them [2]. Extremely high range morbidity rate (>40%) is reported after liver resection [3-5].

Portal vein invasion previously remains a main cause for unresectability of HCCA which several authors demonstrate as a contraindication to surgery [6, 7]. This philosophy has become outdated when portal vein resection (PVR) have been advocated as an aggressive surgical strategy by numerous studies [8-12]. Initial resection for HCCA patients were consisted mainly of resections of the biliary tree and bilioenteric anastomosis to the intrahepatic ducts [13]. Nowadays, hepatectomy combined with PVR is becoming increasing popular which is in order to obtain negative margins [14, 15]. Nevertheless, the safety and efficiency remains debating when studies show confused results. Studies detected significantly higher mortality rate in patients with PVR [16], whereas some other studies found no significance between HCCA patients with or without PVR [17, 18]. Several studies figured out HCCA patients with PVR decrease survival periods [9, 16, 19] while others demonstrate no significant difference comparing with HCCA patients without PVR [20, 21].

Therefore, we performed this systematic review of previously published relevant literature to

comprehensively compare the safety and efficacy of combined PVR with hepatectomy in patients with HCCA.

Methods

This meta-analysis was conducted according to PRISMA guidelines (Checklist S1).

Literature search strategy

Following electronic databases were systematically researched through April 2015 without language restrictions (study year was from 1990 to 2015): MEDLINE, EMBASE, the Cochrane Library, and the Chinese National Knowledge Infrastructure (CNKI). Also, five primary clinical trial registries recognized by the WHO International Clinical Trial Registry Platform was searched: Australia and New Zealand Clinical Trial Registry (www.anzctr.org.au/), Chinese Clinical Trial Register (www.chictr.org), ISRCTN (www.controlled-trials.com/isrctn/), U.S. National Institutes of Health Clinical Trials Database (www.clinicaltrials.gov/), and Clinical Trials Registry-India (www.ctri.in:8080/Clinicaltrials/index.jsp). We conducted same methods in our previous studies [22]. Eligible studies were identified using any of the following index words: hilar cholangiocarcinoma *or* HCCA *or* hilar bile duct cancer *or* Klatskin tumor, portal vein resection *or* vascular resection. Relevant reviews and meta-analyses comparing the safety and efficiency of combined PVR in HCCA patients were examined manually to identify additional eligible studies.

Inclusion and exclusion criteria

For inclusion in our analysis, studies had to satisfy the following criteria: (1) analyzed the postoperative outcomes in HCCA patients undergoing surgery therapy; (2) HCCA patients should be treated with hepatectomy combined with PVR versus without PVR; (3) data from the same institution should not be repeated publication (if patients did not overlap according to different reports, all of the studies were included).

Trails without controls, without detailed data reported (abstract without full text, reviews and case reports) were excluded.

Types of outcome measures

Primary outcomes evaluated in the meta-analysis were survival rate (1-year, 3-year and 5-year survival rate). Secondary outcomes were postoperative morbidity (overall complications, bacteremia, wound infection, postoperative liver failure, and postoperative bile leakage), postoperative mortality and postoperative pathological outcomes (lymphatic invasion, portal vein invasion, perineural invasion and curative resection).

Data extraction and quality assessment

Two reviewers (J.C. and T.B.) independently screened each potentially eligible study and independently extracted the data below: authors, publication year, research design, and patient characteristics in all study arms, interventions, and outcomes. Disagreements about study eligibility or extracted data were arbitrated by a third reviewer (L.Q.L) [22].

Two reviewers (J.C. and T.B.) independently used Newcastle-Ottawa Scale (NOS) [23] scoring standard to evaluate all the included studies quality.

Statistical analysis

All statistical calculations were performed using Review Manager 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). Mantel-Haenszel risk ratios (RR) with corresponding 95% confidence interval (CI) were used. Heterogeneity was assessed by calculating I^2. A fixed-effects model was used for meta-analysis when I^2 was less than 50%, while a random-effects model was used when I^2 was more than 50%. In addition, I^2<25% was defined to represent low heterogeneity, moderate heterogeneity was defined as a value between 25 and 50%, and I^2>50% was of a high heterogeneity [24]. We repeated all meta-analyses by converting the model (fixed- or random-effects) in order to evaluate the robustness of meta-analysis results. If both models gave the similar results, the result was reliable. Publication bias was assessed using Egger's test and funnel plots [25, 26] in Stata 12.0 (Stata Corp, College Station, TX, USA).

Results

Characteristics of the included studies

After systematically and carefully searching of literature databases and trial registries, finally 21 published clinical studies [9, 10, 16-21, 27-39] were included (**Figure 1**). Among 2403 included HCCA patients, 637 of them were with

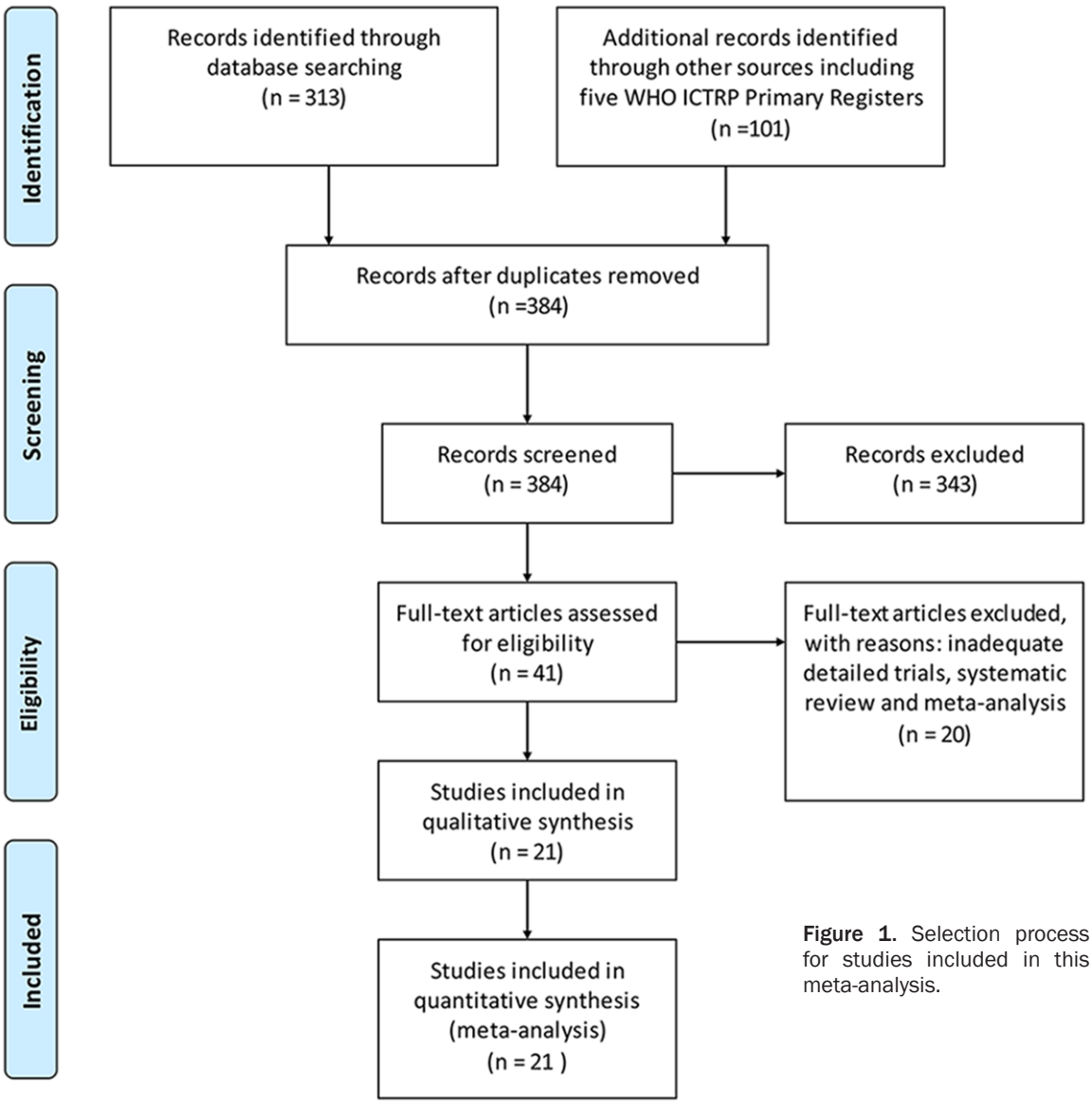


Figure 1. Selection process for studies included in this meta-analysis.

PVR, another 1766 were without PVR. All included studies were retrospective, and all of them were considered as high risk of bias. The characteristics of the included studies are shown in **Table 1**.

Outcomes

Survival: Together 8 studies [17, 18, 21, 29, 33, 35, 38, 39] estimated 1-year survival, and found no significant difference between HCCA patients with or without PVR (RR=0.93, 95% CI 0.75 to 1.14, *P*=0.49, I^2=65%). Totally 10 studies [9, 17-19, 21, 29, 32, 33, 38, 39] estimated 3-year survival, and found HCCA patients with PVR had significantly worse survival when compared with HCCA patients without PVR (RR=0.67, 95% CI 0.56 to 0.81, P<0.001, I^2=46%). Also, patients without PVR have better 5-year survival rate which estimated in 14 studies [9, 16-21, 30, 32-35, 38, 39] (RR=0.67, 95% CI 0.49 to 0.91, P=0.01, I^2=54%) (**Figure 2**).

Postoperative morbidity: Overall complications were assessed by 12 studies [16-19, 21, 27-29, 31, 36-38]. No significant difference was found between HCCA patients with or without PVR (RR=1.06, 95% CI 0.94 to 1.02, *P*=0.35, I^2=0%) (Supplementary Figure 1).

Six studies [16, 17, 19, 21, 36, 39] mentioned postoperative liver failure, the pooled result showed that it did not differ significantly

Table 1. Characteristics of included studies

Reference	Year	Enrolled patients (n)	Patients (n)		Type of study	Quality score
			With PVR (n)	Without PVR (n)		
Dinant *et al.*	2006	37	7	30	Retrospective study	6
Ebata *et al.*	2003	160	52	108	Retrospective study	7
Gerhards *et al.*	2000	108	10	98	Retrospective study	6
Han *et al.*	2007	47	11	35	Retrospective study	5
Hemming *et al.*	2006	60	26	34	Retrospective study	7
Hemming *et al.*	2011	95	42	53	Retrospective study	7
Hirano *et al.*	2010	126	64	61	Retrospective study	6
Igami *et al.*	2010	245	69	176	Retrospective study	6
Konstadoulakis *et al.*	2008	49	14	35	Retrospective study	7
Lee *et al.*	2000	111	29	82	Retrospective study	7
Lee *et al.*	2010	302	40	262	Retrospective study	7
Miyazaki *et al.*	2007	152	34	118	Retrospective study	7
Muñoz *et al.*	2002	28	10	18	Retrospective study	7
Neuhaus *et al.*	1999	95	23	43	Retrospective study	6
Nimura *et al.*	2000	142	43	99	Retrospective study	6
Shimada *et al.*	2003	26	9	24	Retrospective study	6
Song *et al.*	2009	259	51	208	Retrospective study	7
Tamoto *et al.*	2013	49	36	13	Retrospective study	6
Young *et al.*	2010	51	21	30	Retrospective study	7
Yu *et al.*	2014	238	25	174	Retrospective study	7
Zhou *et al.*	2008	96	21	65	Retrospective study	7

between with or without PVR group (RR=0.91, 95% CI 0.58 to 1.42, P=0.68, I^2=18%). Five studies [17, 19, 21, 36, 39] refer to postoperative bile leakage, the pooled result was similar (RR=1.33, 95% CI 0.73 to 2.41, P=0.84, I^2=0%). Totally 2 trails [19, 21] reported postoperative wound infection, the pooled result showed that HCCA patients with PVR had similar risk as patients without PVR (RR=0.79, 95% CI 0.50 to 1.27, P=0.24, I^2=29%). The result is also similar between 2 groups in bacteremia reported by 3 studies [19, 36, 39] (RR=1.29, 95% CI 0.66 to 2.54, P=0.45, I^2=0%).

Mortality: In our research, 15 studies [10, 17-21, 27-30, 34-37, 39] represented postoperative mortality. The pooled results showed patients with PVR had significantly higher mortality rate (RR=1.52, 95% CI 1.06 to 2.18, P=0.02, I^2=28%) (Supplementary Figure 2).

Postoperative pathological outcomes

There were 6 studies [16-19, 21, 39] reported lymphatic invasion, the results showed patients with PVR had significantly higher rate of lymphatic invasion (RR=1.14, 95% CI 1.02 to 1.28, P=0.02, I^2=3%). Totally 4 studies [16, 17, 19, 21] mentioned portal vein invasion, the pooled results were similar between patients with or without PVR (RR=1.33, 95% CI 0.71 to 2.49, P=0.38, I^2=95%). Perineural invasion was reported by 5 studies [16-19, 21], patients with PVR has significantly higher perineural invasion rate than that in patients without PVR (RR=1.31, 95% CI 1.05 to 1.63, P=0.01, I^2=79%). There were 7 studies [16, 17, 19, 21, 27, 35, 39] mentioned curative resections, patients with PVR has significantly lower rate of curative resection (RR=0.89, 95% CI 0.79 to 0.99, P=0.03, I^2=0%).

Sensitivity analysis

In order to test whether our meta-analysis results were skewed. We converted all the model, and found results were similar to previous ones except portal vein invasion (RR=1.30, 95% CI 1.13 to 1.49, P<0.001, I^2=95%). The heterogeneity of this result is relatively high which I^2 is 95%. It showed us that the result of

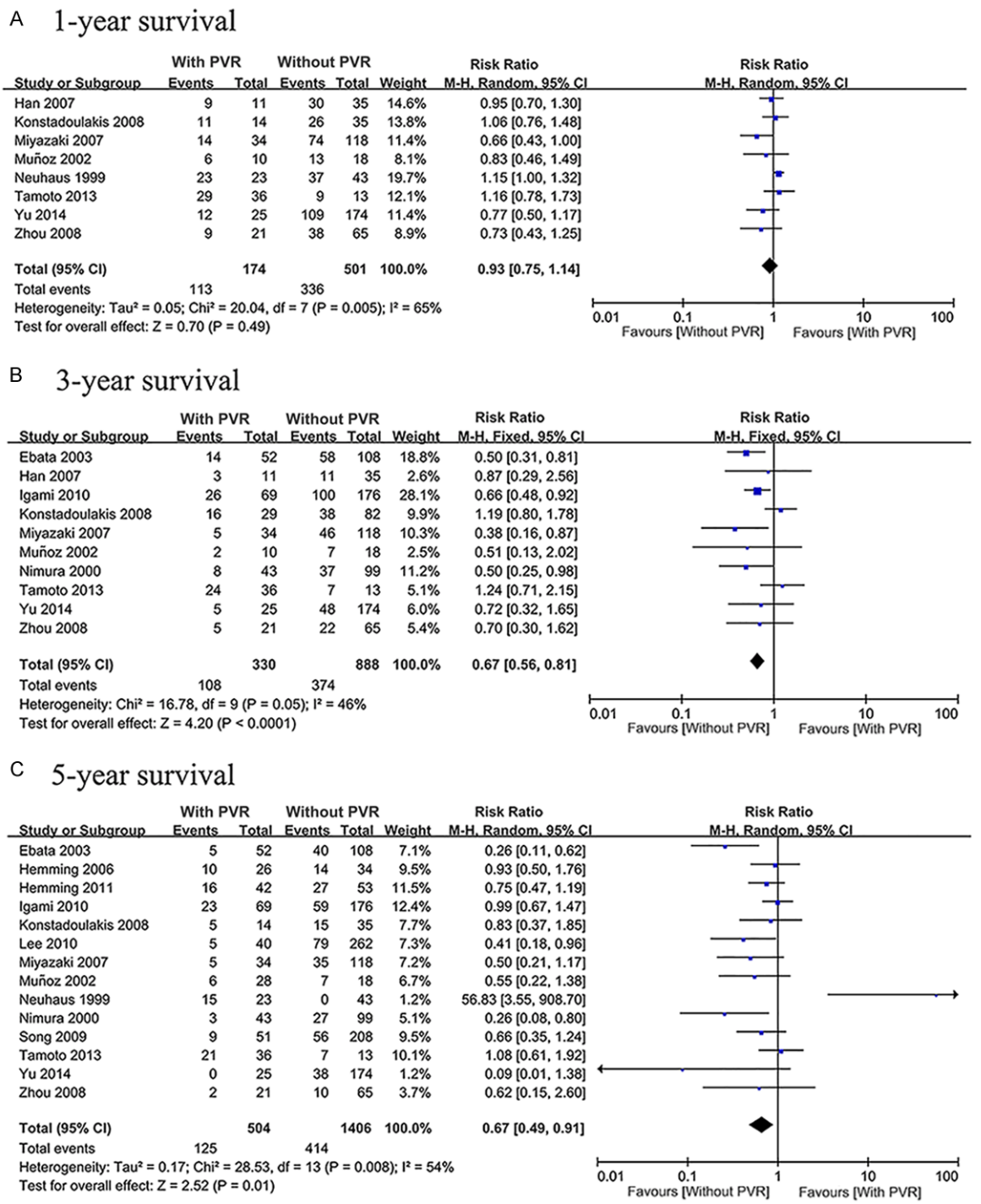


Figure 2. Meta-analysis of data on survival for patients undergoing surgery with and without combined portal vein resection for hilar cholangiocarcinoma.

this analysis still needed further concerns. Other results after converting is similar as the previous ones suggesting that our meta-analyses were reliable.

Publication bias

Funnel plots were generated and analyzed using Egger's tests in order to assess the risk

of publication bias in all included studies. The funnel plots for 5-year survival appeared to be symmetrical, suggesting the absence of bias. This was corroborated by Egger's test (t=-0.90, *P*=0.384) (Supplementary Figure 3).

Discussion

Combined PVR for advance HCCA patients with portal vein involvement is to increase surgical resection rate and survival benefit [35]. However, significantly higher mortality [16] and postoperative liver failure rate in patients with PVR give us the controversial idea of the safety and efficiency of PVR. Here we systematically reviewed and meta-analyzed the literature to address this question.

After systematically and carefully literature searching, we found three similar systematic review [38, 40, 41]. In Wu *et al.* [41], the result of postoperative morbidity [odds ratio (OR) =1.15, 95% CI 0.75-1.75], mortality (OR=2.31, 95% CI 1.21-4.43), and perineural invasion (OR=4.36, 95% CI 1.32-14.38) is similar with us. However, the 5-year survival rate (OR=0.66, 95% CI 0.36-1.21) and some pathological results (R0 resection, OR=0.57, 95% CI 0.29-1.11 and status of lymph nodes, OR=1.46, 95% CI 0.90-2.37) are different from us. In their review, the subgroup analysis depending on sample size and publish year needs further consideration. The cutoff point is the mean value of the sample size and publish year. The definition of cutoff point is difficult to understand. Since cutoff point should be the demarcation between 2 subgroups which is to distinguish the homogeneity and heterogeneity. In Chen *et al.* [40], their result of postoperative morbidity (OR=1.30, 95% CI 0.89-1.88), postoperative liver failure (OR=0.83, 95% CI 0.48-1.43), postoperative bile leakage (OR=1.31, 95% CI 0.65-2.64), curative resection (OR= 0.65, 95% CI 0.46-0.92), lymph node metastasis (OR=1.50, 95% CI 1.06-2.13), and perineural invasion (OR=2.95, 95% CI 1.80-4.84) is similar with us. However, the result of mortality (OR=1.60, 95% CI 0.90-2.86) and survival (hazad ratio=1.90, 95% CI 1.59-2.28) is different from us. In addition, publication bias test result was presented in neither studies. Attributed to all above mistakes and bias, the different results were presented. Moreover, another meta-analysis conducted by Yu *et al.* [38], approved our results (morbidity, OR=1.27, 95% CI 0.91 to 1.77; mortality, OR=2.05, 95% CI 1.33 to 3.15; 5-year survival rate, OR=0.42, 95% CI 0.24 to 0.73).

In order to solve these limitations, we conducted our systematic review. In our analysis, we carefully searched the literatures. We added several new articles, represented the exact data, conducted sensitivity test and presented publication bias test result. We finally found patients with PVR were likely to suffer less curative resections. However, curative resection rate has been an independent prognostic factors for long survival [16, 30, 34, 42]. Increased evidence showed dismal prognostic significance of pathologically proven nodal metastases [4, 42-45]. Kitagawa *et al. [46].* reported a 30.5% and 14.7% 5-year survival rate in HCCA patients with negative node metastases and with regional nodal metastases respectively. All the evidence suggested that patients with these prognostic factors usually suffered worse survival outcomes. In our analysis, patients with PVR were likely to have more advanced HCCA (more lymphatic invasion, more perineural invasion). The significant differences of pathological results would potentially reduce overall survival in the PVR cohort. In our analysis, patients with PVR suffered a worse 5-year survival rate and a higher mortality rate. The reliability of the possible correlation between combined PVR and worse survival results would be impaired by above evidence.

Combined PVR for patients with HCCA may prolong the operation time and intraoperative hepatic inflow occlusion time. Therefore, the risk of postoperative liver failure and postoperative complications should increase attribute to the ischemic damage of the residual liver [47, 48]. Nevertheless, postoperative morbidity rate and different postoperative complications were similar between 2 groups according to our analysis. Our results revealed that combined PVR have little association with postoperative complications. In addition, the development of preoperative biliary drainage and portal vein embolization, has decreased postoperative mortality rate [49]. With all these improvement, combined PVR is safe and reliable.

The biggest limitation in our systematic review is the included studies were retrospective, non-randomized studies which would increase the selection bias. Moreover, the sample size is

small which decrease the reliability of the final results. We select studies carefully with strict include and exclude criteria. Newcastle-Ottawa quality assessment tool [23] was performed to evaluate the quality which our final quality is high. Sensitivity analysis was conducted to conform the reliability of the pooled estimates in the meta-analysis. Publication bias is of no significance in our review. Thus, the selection bias would play little role in our final results.

In conclusion, there is no significant difference in the overall postoperative morbidity and postoperative complications between patients with PVR and without PVR. In more advance HCCA patients, a significantly higher mortality rate and worse survival could be detected. However, owing to the low level of clinical evidence available to date, the results requires further high-quality randomized, and controlled clinical studies for validation.

Acknowledgements

This study was supported by Guangxi Natural Science Foundation (no. 2011GXNSFD018032), HCC Bridge Study (no. CA182023) and Self-Funded Research Project of Guangxi Zhuang Autonomous Region National Health and Family Planning Commission (no. Z2015710).

Disclosure of conflict of interest

None.

Address correspondence to: Le-Qun Li and Fei-Xiang Wu, Department of Hepatobiliary Surgery, Affiliated Tumor Hospital of Guangxi Medical University, He Di Rd. #71, Nanning 530021, P. R. China. Tel: + (86)-771-5330855; Fax: + (86)-771-5312000; E-mail: lilequngx@163.com (LQL); wufeixianggx@sina.com (FXW)

References

[1] Khan SA, Thomas HC, Davidson BR and Taylor-Robinson SD. Cholangiocarcinoma. Lancet 2005; 366: 1303-1314.

[2] Ito F, Cho CS, Rikkers LF and Weber SM. Hilar cholangiocarcinoma: current management. Ann Surg 2009; 250: 210-218.

[3] Sano T, Shimada K, Sakamoto Y, Yamamoto J, Yamasaki S and Kosuge T. One hundred two consecutive hepatobiliary resections for perihilar cholangiocarcinoma with zero mortality. Ann Surg 2006; 244: 240-247.

[4] Seyama Y, Kubota K, Sano K, Noie T, Takayama T, Kosuge T and Makuuchi M. Long-term outcome of extended hemihepatectomy for hilar bile duct cancer with no mortality and high survival rate. Ann Surg 2003; 238: 73-83.

[5] Jarnagin WR, Bowne W, Klimstra DS, Ben-Porat L, Roggin K, Cymes K, Fong Y, DeMatteo RP, D'Angelica M, Koea J and Blumgart LH. Papillary phenotype confers improved survival after resection of hilar cholangiocarcinoma. Ann Surg 2005; 241: 703-712; discussion 712-704.

[6] Launois B, Campion JP, Brissot P and Gosselin M. Carcinoma of the hepatic hilus. Surgical management and the case for resection. Ann Surg 1979; 190: 151-157.

[7] Hoevels J and Ihse I. Percutaneous transhepatic portography in bile duct carcinoma. Correlation with percutaneous transhepatic cholangiography and angiography. Rofo 1979; 131: 140-150.

[8] Gerhards MF, van Gulik TM, de Wit LT, Obertop H and Gouma DJ. Evaluation of morbidity and mortality after resection for hilar cholangiocarcinoma--a single center experience. Surgery 2000; 127: 395-404.

[9] Nimura Y, Kamiya J, Kondo S, Nagino M, Uesaka K, Oda K, Sano T, Yamamoto H and Hayakawa N. Aggressive preoperative management and extended surgery for hilar cholangiocarcinoma: Nagoya experience. J Hepatobiliary Pancreat Surg 2000; 7: 155-162.

[10] Lee SG, Lee YJ, Park KM, Hwang S and Min PC. One hundred and eleven liver resections for hilar bile duct cancer. J Hepatobiliary Pancreat Surg 2000; 7: 135-141.

[11] Nishio H, Kamiya J, Nagino M, Kanai M, Uesaka K, Sakamoto E, Fukatsu T and Nimura Y. Value of percutaneous transhepatic portography before hepatectomy for hilar cholangiocarcinoma. Br J Surg 1999; 86: 1415-1421.

[12] Tsuzuki T, Ueda M, Kuramochi S, Iida S, Takahashi S and Iri H. Carcinoma of the main hepatic duct junction: indications, operative morbidity and mortality, and long-term survival. Surgery 1990; 108: 495-501.

[13] Bismuth H and Corlette MB. Intrahepatic cholangioenteric anastomosis in carcinoma of the hilus of the liver. Surg Gynecol Obstet 1975; 140: 170-178.

[14] Bismuth H. Surgical anatomy and anatomical surgery of the liver. World J Surg 1982; 6: 3-9.

[15] Kondo S, Katoh H, Hirano S, Ambo Y, Tanaka E and Okushiba S. Portal vein resection and reconstruction prior to hepatic dissection during right hepatectomy and caudate lobectomy for hepatobiliary cancer. Br J Surg 2003; 90: 694-697.

[16] Song GW, Lee SG, Hwang S, Kim KH, Cho YP, Ahn CS, Moon DB and Ha TY. Does portal vein resection with hepatectomy improve survival in locally advanced hilar cholangiocarcinoma? Hepatogastroenterology 2009; 56: 935-942.

[17] Miyazaki M, Kato A, Ito H, Kimura F, Shimizu H, Ohtsuka M, Yoshidome H, Yoshitomi H, Furukawa K and Nozawa S. Combined vascular resection in operative resection for hilar cholangiocarcinoma: does it work or not? Surgery 2007; 141: 581-588.

[18] Munoz L, Roayaie S, Maman D, Fishbein T, Sheiner P, Emre S, Miller C and Schwartz ME. Hilar cholangiocarcinoma involving the portal vein bifurcation: long-term results after resection. J Hepatobiliary Pancreat Surg 2002; 9: 237-241.

[19] Ebata T, Nagino M, Kamiya J, Uesaka K, Nagasaka T and Nimura Y. Hepatectomy with portal vein resection for hilar cholangiocarcinoma: audit of 52 consecutive cases. Ann Surg 2003; 238: 720-727.

[20] Hemming AW, Kim RD, Mekeel KL, Fujita S, Reed AI, Foley DP and Howard RJ. Portal vein resection for hilar cholangiocarcinoma. Am Surg 2006; 72: 599-604; discussion 604-595.

[21] Tamoto E, Hirano S, Tsuchikawa T, Tanaka E, Miyamoto M, Matsumoto J, Kato K and Shichinohe T. Portal vein resection using the no-touch technique with a hepatectomy for hilar cholangiocarcinoma. HPB (Oxford) 2014; 16: 56-61.

[22] Xie ZB, Wang XB, Peng YC, Zhu SL, Ma L, Xiang BD, Gong WF, Chen J, You XM, Jiang JH, Li LQ and Zhong JH. Systematic review comparing the safety and efficacy of conventional and drug-eluting bead transarterial chemoembolization for inoperable hepatocellular carcinoma. Hepatol Res 2015; 45: 190-200.

[23] GA W, Shea BO, DC, Peterson J, Welch V, Losos M and Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed February 29 2012.

[24] JP H and SG. Cochrane handbook for systematic reviews of interventions version 5.1.0. March 2011. Cochrane Collaboration, 2011. Available at: http://www.cochrane-handbook.org. Accessed March 29 2012.

[25] Stuck AE, Rubenstein LZ and Wieland D. Bias in meta-analysis detected by a simple, graphical test. Asymmetry detected in funnel plot was probably due to true heterogeneity. BMJ 1998; 316: 469; author reply 470-461.

[26] Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, Carpenter J, Rucker G, Harbord RM, Schmid CH, Tetzlaff J, Deeks JJ, Peters J, Macaskill P, Schwarzer G, Duval S, Altman DG, Moher D and Higgins JP. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011; 343: d4002.

[27] Dinant S, Gerhards MF, Rauws EA, Busch OR, Gouma DJ and van Gulik TM. Improved outcome of resection of hilar cholangiocarcinoma (Klatskin tumor). Ann Surg Oncol 2006; 13: 872-880.

[28] Gerhards MF, van Gulik TM, de Wit LT, Obertop H and Gouma DJ. Evaluation of morbidity and mortality after resection for hilar cholangiocarcinoma-a single center experience. Surgery 2000; 127: 395-404.

[29] Han F, Zhou JX, Zhang L and Han YZ. [Hepatectomy with portal vein resection and reconstruction in the treatment of hilar cholangiocarcinoma]. Zhonghua Wai Ke Za Zhi 2007; 45: 763-765.

[30] Hemming AW, Mekeel K, Khanna A, Baquerizo A and Kim RD. Portal vein resection in management of hilar cholangiocarcinoma. J Am Coll Surg 2011; 212: 604-613; discussion 613-606.

[31] Hirano S, Kondo S, Tanaka E, Shichinohe T, Tsuchikawa T, Kato K, Matsumoto J and Kawasaki R. Outcome of surgical treatment of hilar cholangiocarcinoma: a special reference to postoperative morbidity and mortality. J Hepatobiliary Pancreat Sci 2010; 17: 455-462.

[32] Igami T, Nishio H, Ebata T, Yokoyama Y, Sugawara G, Nimura Y and Nagino M. Surgical treatment of hilar cholangiocarcinoma in the "new era": the Nagoya University experience. J Hepatobiliary Pancreat Sci 2010; 17: 449-454.

[33] Konstadoulakis MM, Roayaie S, Gomatos IP, Labow D, Fiel MI, Miller CM and Schwartz ME. Aggressive surgical resection for hilar cholangiocarcinoma: is it justified? Audit of a single center's experience. Am J Surg 2008; 196: 160-169.

[34] Lee SG, Song GW, Hwang S, Ha TY, Moon DB, Jung DH, Kim KH, Ahn CS, Kim MH, Lee SK, Sung KB and Ko GY. Surgical treatment of hilar cholangiocarcinoma in the new era: the Asan experience. J Hepatobiliary Pancreat Sci 2010; 17: 476-489.

[35] Neuhaus P, Jonas S, Bechstein WO, Lohmann R, Radke C, Kling N, Wex C, Lobeck H and Hintze R. Extended resections for hilar cholangiocarcinoma. Ann Surg 1999; 230: 808-818; discussion 819.

[36] Shimada H, Endo I, Sugita M, Masunari H, Fujii Y, Tanaka K, Misuta K, Sekido H and Togo S. Hepatic resection combined with portal vein or hepatic artery reconstruction for advanced carcinoma of the hilar bile duct and gallbladder. World J Surg 2003; 27: 1137-1142.

[37] Young AL, Prasad KR, Toogood GJ and Lodge JP. Surgical treatment of hilar cholangiocarcinoma in a new era: comparison among leading Eastern and Western centers, Leeds. J Hepatobiliary Pancreat Sci 2010; 17: 497-504.

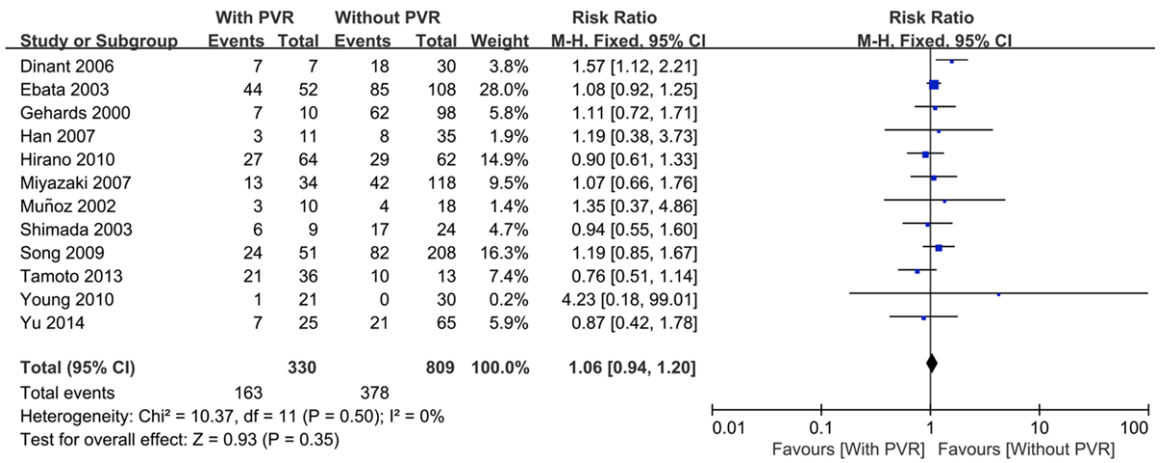
[38] Yu W, Gu Z, Shi S, Shen N and Zhang Y. Effect evaluation of vascular resection for patients with hilar cholangiocarcinoma: original data and meta-analysis. Cell Biochem Biophys 2014; 69: 509-516.
[39] Zhou LX, Xu ZY, Guo JM and Zhang ZW. [The role of vascular resection and reconstruction in the treatment of hilar cholangiocarcinoma]. Zhonghua Zhong Liu Za Zhi 2008; 30: 310-313.
[40] Chen W, Ke K and Chen YL. Combined portal vein resection in the treatment of hilar cholangiocarcinoma: a systematic review and meta-analysis. Eur J Surg Oncol 2014; 40: 489-495.
[41] Wu XS, Dong P, Gu J, Li ML, Wu WG, Lu JH, Mu JS, Ding QC, Zhang L, Ding Q, Weng H and Liu YB. Combined portal vein resection for hilar cholangiocarcinoma: a meta-analysis of comparative studies. J Gastrointest Surg 2013; 17: 1107-1115.
[42] de Jong MC, Marques H, Clary BM, Bauer TW, Marsh JW, Ribero D, Majno P, Hatzaras I, Walters DM, Barbas AS, Mega R, Schulick RD, Choti MA, Geller DA, Barroso E, Mentha G, Capussotti L and Pawlik TM. The impact of portal vein resection on outcomes for hilar cholangiocarcinoma: a multi-institutional analysis of 305 cases. Cancer 2012; 118: 4737-4747.
[43] Regimbeau JM, Fuks D, Le Treut YP, Bachellier P, Belghiti J, Boudjema K, Baulieux J, Pruvot FR, Cherqui D, Farges O; AFC-HC study group. Surgery for hilar cholangiocarcinoma: a multi-institutional update on practice and outcome by the AFC-HC study group. J Gastrointest Surg 2011; 15: 480-488.
[44] Nishio H, Nagino M and Nimura Y. Surgical management of hilar cholangiocarcinoma: the Nagoya experience. HPB (Oxford) 2005; 7: 259-262.
[45] Rea DJ, Munoz-Juarez M, Farnell MB, Donohue JH, Que FG, Crownhart B, Larson D and Nagorney DM. Major hepatic resection for hilar cholangiocarcinoma: analysis of 46 patients. Arch Surg 2004; 139: 514-523; discussion 523-515.
[46] Kitagawa Y, Nagino M, Kamiya J, Uesaka K, Sano T, Yamamoto H, Hayakawa N and Nimura Y. Lymph node metastasis from hilar cholangiocarcinoma: audit of 110 patients who underwent regional and paraaortic node dissection. Ann Surg 2001; 233: 385-392.
[47] Nagino M, Kamiya J, Uesaka K, Sano T, Yamamoto H, Hayakawa N, Kanai M and Nimura Y. Complications of hepatectomy for hilar cholangiocarcinoma. World J Surg 2001; 25: 1277-1283.
[48] Launois B, Terblanche J, Lakehal M, Catheline JM, Bardaxoglou E, Landen S, Campion JP, Sutherland F and Meunier B. Proximal bile duct cancer: High resectability rate and 5-year survival. Ann Surg 1999; 230: 266-275.
[49] Sano T, Shimada K, Sakamoto Y, Esaki M and Kosuge T. Changing trends in surgical outcomes after major hepatobiliary resection for hilar cholangiocarcinoma: a single-center experience over 25 years. J Hepatobiliary Pancreat Surg 2007; 14: 455-462.

Checklist S1. PRISMA 2009 Checklist

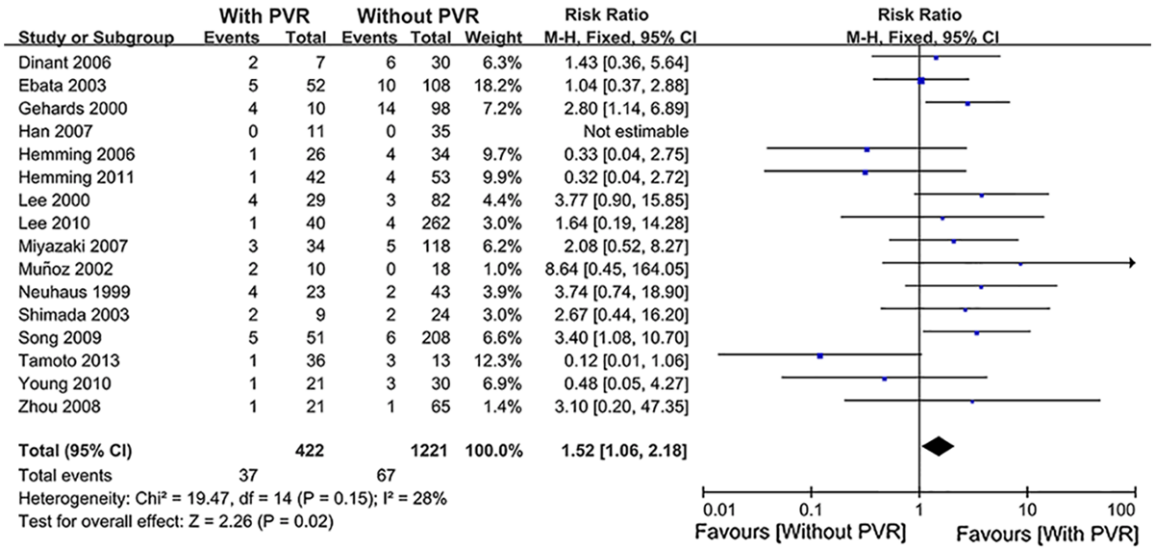
Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5

Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8-9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8-9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6-8
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11-12
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

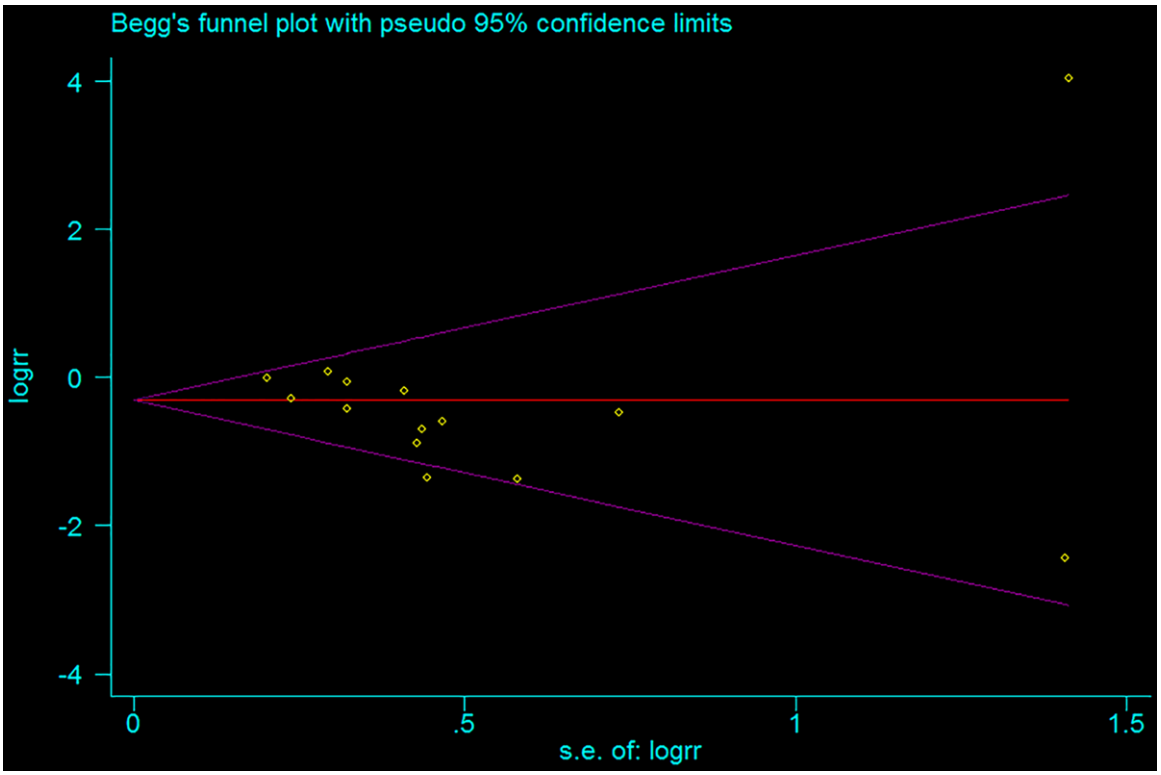
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit: www.prisma-statement.org.



Supplementary Figure 1. Meta-analysis of data on postoperative morbidity for patients undergoing surgery with and without combined portal vein resection for hilar cholangiocarcinoma.



Supplementary Figure 2. Meta-analysis of data on postoperative mortality for patients undergoing surgery with and without combined portal vein resection for hilar cholangiocarcinoma.



Supplementary Figure 3. Funnel plot of pooled relative risk estimates comparing 5-year survival of for patients undergoing surgery with and without combined portal vein resection for hilar cholangiocarcinoma.