Left-Side vs. Right-Side Hepatectomy for Hilar Cholangiocarcinoma: A Meta-Analysis

Wenxuan Wu
First Hospital of Zhejiang Province: Zhejiang University School of Medicine First Affiliated Hospital
Qiyang Cheng
First Hospital of Zhejiang Province: Zhejiang University School of Medicine First Affiliated Hospital
Junru Chen
First Hospital of Zhejiang Province: Zhejiang University School of Medicine First Affiliated Hospital
Diyu Chen
First Hospital of Zhejiang Province: Zhejiang University School of Medicine First Affiliated Hospital
Xiaode Feng
First Hospital of Zhejiang Province: Zhejiang University School of Medicine First Affiliated Hospital
Jian Wu (drwujian@zju.edu.cn)
First Hospital of Zhejiang Province: Zhejiang University School of Medicine First Affiliated Hospital

Research

Keywords: Hilar cholangiocarcinoma, Perihilar cholangiocarcinoma, Left-side hepatectomy, Right-side hepatectomy, Meta-analysis

Posted Date: January 8th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-141177/v1

Version of Record: A version of this preprint was published at World Journal of Surgical Oncology on April 10th, 2021. See the published version at https://doi.org/10.1186/s12957-021-02213-6.

Abstract

Goals: We aim to draw a conclusion which side of hepatectomy could be the priority for hilar cholangiocarcinoma patients.

Background: Surgery is established as only potentially curative treatment for hilar cholangiocarcinoma. However, whether hepatectomy should be preferred to the left-side hepatectomy, which contains left hemihepatectomy, extended left hemihepatectomy and left trisectionectomy, or right-side hepatectomy, which represents right hemihepatectomy, extended right hemihepatectomy and right trisectionectomy, is debated. In this meta-analysis, we evaluated and compared the efficacy and safety of left-side hepatectomy and right-side hepatectomy in patients with hilar cholangiocarcinoma.

Study: We systematically retrieved the MEDLINE, PubMed and Cochrane library and related bibliography up to February 2020. The primary outcome is overall survival, and secondary outcomes include 1-, 3-, and 5-Year survival rates, morbidity, mortality, R0 resection rate and operation time. Based on heterogeneity, fixed-effects model or random-effects models were established through meta-analysis.

Results: Eleven studies (11 cohort studies, totally 1031 patients) were involved in this study. The overall survival of patients underwent left-side hepatectomy was comparable to that of patients underwent right-side hepatectomy (hazard ratio, 1.27 [95% confidence interval, 0.98-1.63]). And there was no significant difference observed in 1-year (relative risk, 1.01 [95% CI, 0.89-1.15]), 3-year (relative risk, 0.94 [95% confidence interval, 0.80-1.11]), and 5-year survival (relative risk, 0.82 [95% confidence interval, 0.67-1.01]) rates between left-side hepatectomy group and the right-side hepatectomy group. Comparing with right-side hepatectomy cluster, the hilar cholangiocarcinoma patients in left-side hepatectomy cluster presented better overall postoperative morbidity (relative risk, 0.82 [95% confidence interval, 0.71-0.96]) and major postoperative morbidity (relative risk, 0.73 [95% confidence interval, 0.56-0.95]). The post-hepatectomy liver failure rate (relative risk, 0.22 [95% confidence interval, 0.09-0.56]) and procedure-related mortality (relative risk, 0.41 [95% confidence interval, 0.23-0.70]) in left-side hepatectomy group was better than that of right-side hepatectomy group. Besides, the R0 resection rate was similar between left-side hepatectomy group and right-side hepatectomy group (relative risk, 0.95 [95% confidence interval, 0.87-1.03]). And the operation time for left-side hepatectomy were significantly longer than those for right-side hepatectomy (mean difference, 38.68 [95% confidence interval, 7.41-69.95]).

Conclusion: Through meta-analysis, we explored the comparable long-term outcomes and better short-term outcomes in left-side hepatectomy group as is compared to right-side hepatectomy group of hilar cholangiocarcinoma patients. In this study, the evidence obtained might indicate that the choice of left-side hepatectomy or right-side hepatectomy had better depend on the specific situation of every patients of hilar cholangiocarcinoma.

Introduction

Hilar Cholangiocarcinoma (HCCA), a type of cholangiocarcinoma, is classified based on anatomical location and is located to the area between the second degree bile ducts and the insertion of the cystic duct into the common bile duct[1]. The prognosis of HCCA patients is poor. Radical surgery with negative margins(R0) is the only potentially curative treatment for this disease However, frequent metastasis and recurrence remain the major obstacle for the prognosis of HCCA patients underwent surgical resection (1-year survival rate of 80% and a 5-year survival rate of 39%)[2,3]. Recently, it is considered to be the standard surgical procedure of HCCA, which includes bile duct resection combined with major hepatectomy, caudate lobe resection, lymph node dissection, and vascular resection when necessary, resulting in improved R0 resection rate and long-term survival[4–8].

Up to now, RH is recognized as an accepted option for major liver resection in HCCA treatment[9,10]. Tumor location is a major factor in operation methods selection for HCCA, and the following factors also should be considered: (1) Length of hepatic duct: the extrahepatic portion of left hepatic duct is longer than the right one; (2) Oncological characteristic: due to the vertical spread characteristic of HCCA, the right hepatic artery is susceptible to be invaded. Moreover, the right hepatic artery usually travels behind the proximal bile duct near the hepatic hilum, making RH more advantageous in terms of radicality; (3) The anatomical structure on the right side of the hepatic hilum is complicated, with many anatomical variations;(4) it is easier to complete caudate lobectomy[10–13]. However, RH is confirmed to be the risk of future liver remnant (FLR) deficiency and even postoperative liver failure (PHLF). Although preoperative biliary drainage and portal vein embolization (PVE) were utilized into the HCCA preoperative management, it is still unclear whether these measurements could improve in postoperative morbidity and mortality [14,15].

Whereas left-side hepatectomy (LH) is more complicated and sometimes arterial reconstruction is needed during the operation [16], it is still an essential option for the HCCA located in left liver[17,18]. Generally, because of the anatomical structure, the patients underwent LH possess more FLR volume, which means it could take patients from less PHLF risk.

Many studies reported that RH can achieve better long-term survival resulted from higher R0 resection rate[13,16]. Nevertheless, Govil et al.[19] research reveals that LH is comparable to RH in long-term survival. Due to the rarity of HCCA and the small number of cases, the comparison between the effects of LH and RH remains unknown.

The aim of this meta-analysis is to conduct a statistical evaluation based on the existing studies, to clarify the long-term outcome of the LH and RH of HCCA, and to compare the differences of short-term outcome, R0 resection rate and operation time,in order to provide evidence for clinical application.

Materials And Methods

Search strategy

This meta-analysis followed the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement[20] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[21] A comprehensive systematic search was performed on PubMed, EMBASE, and Cochrane

Library through to February 3, 2020. The search strategy was to combine keywords including “hilar cholangiocarcinoma”, “klatskin tumor”, “left-side hepatectomy” and “right-side hepatectomy” into various combinations. To identify more relevant literature, manual search was performed on references of all included literature. Restrictions were not placed on any point of the search. In addition, the search process was completed independently by two authors (Wenxuan Wu and Qiyang Cheng), and the disagreement reached consensus through discussion.

Inclusion Criteria And Exclusion Criteria

Two authors (Wenxuan Wu and Qiyang Cheng) independently screened the titles and abstracts of all literatures, and reviewed further full texts if appropriate. Literature that reported the outcomes of left-side hepatectomy versus right-side hepatectomy in patients with HCCA and met the following criteria were included:(i)randomized controlled trials (RCTs), cohort studies or case-control studies;(ii)adult patients with HCCA;(iii) language-free publication comparing left-side hepatectomy and right-side hepatectomy for HCCA;(iv) include at least one of the following endpoints: overall survival (OS), 1-year survival rate, 3-year survival rate,5-year survival rate, operating time, R0 resection rate, postoperative morbidity, PHLF, procedure-related mortality. Exclusion criteria include the following:(i) study design type without explicit accountability;(ii) patients with intrahepatic cholangiocarcinoma, distal cholangiocarcinoma, and gallbladder carcinoma;(iii) no controls;(iv) duplicates;(v) unable to extract valid outcome data from the literature;(vi) conference, editorials, reviews, case reports, commentaries, letters, research involving animal experiments, cohorts with fewer than 10 cases and full text was not available.

Data Abstraction And Quality Assessment

For each literature included, data were extracted independently by two authors (Wenxuan Wu and Junru Chen) using a pre-made spreadsheet. The data to be extracted include: (i) General information: first author, year of publication, country;(ii) Study characteristics: study design, study period, sample size, duration of follow-up;(iii) Patient and preoperative characteristics: gender, age, bismuth classification, proportion of biliary drainage including percutaneous biliary drainage(PDB) and endoscopic biliary drainage(EBD) before surgery, proportion of portal vein embolization(PVE);(iv) Operative data: type of resection, operation time, R0 resection rate, proportion of caudate lobectomy;(5)Postoperative data: overall survival (OS), 1-year survival rate, 3-year survival rate,5-year survival rate, postoperative morbidity, PHLF, procedure-related mortality.

The primary endpoints of analysis were OS. OS was calculated from the time of surgery to death or last contact. Postoperative morbidity includes overall morbidity and major morbidity (according to Clavien-Dindo classification, Dindo grades III–V). Procedure-related mortality was considered to include operative mortality, postoperative mortality, in-hospital mortality, and 90-day mortality. Hazard ratio (HR) is most appropriate for analyzing time-to-event outcomes. Given that only two literatures reported the values directly, this meta-analysis used the method of Parmar et al.[22] to extracted data from the Kaplan-Meier curve, and then used the Excel sheet published by Tierney et al.[23] to calculated HR.

Similarly, two authors (Wenxuan Wu and Junru Chen) independently assessed the quality of each literature. The Newcastle–Ottawa Quality Assessment Scale (NOS)[24]was used to assess quality of the cohort study. This tool includes three categories of selection, comparability and outcome, with a maximum score of 9 stars, and more than 6 stars are considered as high quality.

Statistical analysis

To compare OS, we used HR and its 95% confidence interval (CI), and the other dichotomous data were calculated using relative risk (RR) and its 95% CI. Continuous data were presented as mean difference (MD) with 95% CI. Some literatures used the median and range to describe continuous data. In order to calculate uniformly, we used the formulas and tables provided by Luo et al.[25] and Wan et al.[26] to convert the data into mean and standard deviation(SD). Heterogeneity among the included studies was assessed using the Q test, and $P < 0.1$ was considered heterogeneous. The value of I^2 is used to quantify the degree of heterogeneity, specifically, when the I^2 values were 25%, 50%, and 75%, the corresponding heterogeneity is low, medium, and high.[27] Fixed-effect model was selected when there is no heterogeneity, otherwise random effects model was considered for pool data. Subgroup analyses were performed to assess the impact of region and year of publication on surgical outcome and survival, taking into account differences in treatment and surgical outcomes between the Eastern and Western centers, as well as the ongoing development of modern surgical techniques. The cut-off point for subgroup analysis is the mean of the year of publication. Plotting a funnel plot and visually evaluate the symmetry of the funnel plot to saw if there were publication biases. Begg's Test and Egger's test were also conducted to explore potential publication bias, with a cutoff level of $P < 0.05$. Unless otherwise noted, two-sided P values < 0.05 were considered statistically significant. All statistical analyses for the meta-analysis were generated using STATA/MP software (version 14.0).

Results

Literature search

Through a comprehensive search in PubMed, EMBASE, and Cochrane Library databases, a total of 694 citations were identified. Subsequently, after excluding 198 duplicate articles, our analysis removed 155 citations including case reports, reviews, conference papers, animal experiments, and research on children (Figure 1). Base on screening the title and abstract, an additional 322 citations were excluded, and finally 19 unique citations entered the full-text review. In order to retain the most recent and complete data, three studies based on the same population were eliminated after the further discussion by the two authors (Diyu Chen and Xiaode Feng). Eventually, 11 eligible cohort studies were included in this analysis.[15,19,28-36]

Characteristics of included studies and assessment of methodological quality

The 11 eligible retrospective-prospective cohort studies were carried between 2001-2020, including a total of 1031 patients. All studies were single-center studies, most of them (7/11) were performed in Asian populations (Japan, Korea, and India), and the rest (4/11) were based on Western populations (Germany, Italy, and USA). Seven studies were published before 2014, and four after 2014.Nine cohorts involved in our study represent the usage of PVE, seven of which conducted PVE before RH, while two of which conducted it not only before RH but also before LH. As for caudate lobectomy, all patients underwent caudate lobectomy in six of eleven papers, and the four studies only performed a caudate lobectomy in part of patients and the remaining one study describe unclearly about this. The specific characteristics and data of the included studies were shown in the Table 1.

After quality evaluation, the scores of our included studies ranging from 6 to 8, based on the Newcastle-Ottawa Scale. As shown in the e-Table 1, there were 3 Literatures with <7 points and 8 Literatures with ≥7 points.

Primary outcomes: overall survival

In order to evaluated the prognosis of patients in different surgery, we analyzed the overall survival data from ten cohorts (including 859 patients) in this study, and the data were visualized by forest plots in Figure 2. The pooled HR estimated based on the fixed-effect model and the random-effect model were both 1.27（95%CI：0.98-1.63; P =0.066）, indicating that the difference between LH and RH was not statistically significant. No significant difference was observed among studies in the estimates for OS (I2= 0%, P heterogeneity= 0.840). Subgroup analysis showed that the analysis results did not change due to the region, year of publication and the number of cases of left-side hepatectomy, and the differences between LH and RH remained not significant (Table 2).

Secondary outcomes

1-, 3-, and 5-Year survival rates

1-year survival data included in five studies containing 576 patients, it was 79.0% (188 of 238) in the LH group and 78.7% (266 of 338) in the RH group；3-year survival data included in seven studies containing 662 patients, it was 46.2% (121 of 262) in the LH group and 49.0% (196 of 400) in the RH group; 5-year survival data included in eight studies containing 798 patients, it was 28.8% (95 of 330) in the LH group and 35.5% (166 of 468) in the RH group. The results of the pooled 1-year, 3-year, and 5-year survival rates for LH vs. RH are shown in Figure 3. Based on the random-effects model, the pooled RR for the 1-year survival rates was 1.01（95%CI：0.89-1.15;P = 0.835）; the pooled RR for the 3-, and 5-year survival rates calculated using the fixed-effects model were 0.94（95%CI：0.80-1.11;P = 0.49）, and 0.82（95%CI：0.67-1.01;P =0.067）, respectively.

The results indicated that there was no statistically significant difference in the 1-, 3-, and 5-year survival rates between LH and RH. All studies on 1-year survival had no obvious heterogeneity (I^2= 48.3%, $P_{heterogeneity}$= 0.102). No statistically significant heterogeneity was observed for all studies on 3-year and 5-year survival rates (I^2= 0%, $P_{heterogeneity}$= 0.519; I^2= 0%, $P_{heterogeneity}$= 0.643, respectively).

Subgroup analysis demonstrated that despite the different publication years and the number of cases of left-side hepatectomy, the results of 1-,3- and 5-year survival showed no obvious difference, which was the same as the results of 1- and 3-year survival under the subgroup of different regions. However, patients undergoing LH in western centers were associated with poor 5-year survival results (Table 2).

Overall postoperative morbidity and major postoperative morbidity

Five studies with 590 patients provide information on overall postoperative morbidity, with rates of 50.4% (132 of 262) in the LH group and 61.9% (203 of 328) in the RH group. As shown in Figure 4A, the pooled RR was 0.82(95%CI, 0.71-0.96; P = 0.014), and the overall morbidity of the LH group was significantly lower than that of the RH group. The heterogeneity between the studies was not obvious (I^2= 13.9%, $P_{heterogeneity}$= 0.323). Major postoperative morbidity was mentioned in five studies with 315 patients, major morbidity occurred in 34.5% (48 of 139) of patients in the LH group and 45.5% (80 of 176) in the RH group. The pooled RR was 0.73 (95%CI, 0.56-0.95; P = 0.020; Figure 4B). The results suggested that RH group had a higher risk of serious postoperative complications, and there was no heterogeneity among the studies (I2= 0%, $P_{heterogeneity}$= 0.544).

Subgroup analysis indicated that LH was associated with reduced overall morbidity in post-2014, Western Central studies and less experienced centers (≤ 41cases). However, in Eastern Center and pre-2014 studies, there was no relationship between the two procedures and overall morbidity. All major morbidity data were collected from the studies published after 2014. The results of the Western Center studies and less experienced centers were consistent with the meta-analysis, but no significant differences were observed in the Eastern Center studies (Table2).

Post-hepatectomy liver failure and procedure-related mortality

Four studies reported the data about post-hepatectomy liver failure in 373 patients. In the LH and RH group, PHLF rate was 2.5% (4 of 161), and 12.7% (27 of 212) respectively. Figure 5A shows the pooled results of the fixed effects model, the pooled RR for PHLF was 0.22(95%CI, 0.09-0.56; P = 0.002). These results showed that performing LH could reduce the possibility of post-hepatectomy liver failure. Nine studies with 976 patients reported perioperative mortality. The mortality rates in the LH group and the other group were 3.9% (16 of 411) and 8.8% (47 of 535), respectively. As depicted in the forest plots, the pooled RR was 0.41(95%CI, 0.23-0.70; P = 0.001), LH significantly reduces perioperative mortality relative to RH (Figure 5B). For post-hepatectomy liver failure and postoperative mortality, no heterogeneity was observed between different studies (I2= 0%, P heterogeneity= 0.625; I2= 0%, P heterogeneity= 0.954, respectively).

In subgroup analysis, the results of the Eastern Center and less experienced centers showed that LH can reduce the incidence of PHLF. Regarding mortality, regardless of changes in region and publication year, LH was significantly associated with lower mortality. And in centers where LH was performed in more than 41 cases, the mortality rate was lower with LH (Table 2).

R0 resection rate

A total of 7 studies reported R0 resection rate of 885 HCCA patients. In the LH group, 70.8% (267 of 377) of patients achieved negative margin, while in the RH group, the data was 76.2% (387 of 508). The pooled analysis results showed that the RR of R0 resection rate was 0.95（95％CI：0.87-1.03; P = 0.179）without heterogeneity (I2= 0%, P heterogeneity= 0.607; Figure 6A). No statistical difference in R0 resection rate between LH and RH was identified. Subgroup analysis showed that the results of the Western Center were inconsistent with the meta-analysis, that is, a higher R0 resection rate could be obtained by RH (Table 2).

Operation time

A total of 846 patients reported operating time in nine studies. Based on the fixed-effects model, there was a low level of heterogeneity between the studies (I^2 = 45.1%, $P_{heterogeneity}$ =0.078). Considering I^2 critical 50%, the random-effects model was used to pooled the studies in a more conservative way. As shown in Figure 6B, the pooled MD was 38.68(95％CI,7.41-69.95; P = 0.015), indicating that the operation time in the LH group was significantly longer than that in the RH group.

Publication bias

Figure 7 shows a funnel plot of OS. Neither the Begg's test nor the Egger's test found significant publication bias, that is, the P values for the outcome was greater than 0.05. Since the number of studies included in other endpoints in the meta-analysis was small, funnel plots, Begg's Test, and Egger's test were not performed to assess publication bias.

Discussion

The evidence indicated that the effect of palliative treatment for HCCA was limited, and surgery is the only treatment that can improve long-term survival. Bile duct resection combined with major hepatectomy has been regarded as the standard surgical method for HCCA. In order to compare the efficacy and safety of LH and RH, we performed this meta-analysis. The results of our analysis show that LH is comparable to RH in terms of long-term survival. However, comparing with RH, LH presented better in terms of reduced overall morbidity, major morbidity, postoperative liver failure, and mortality rates, which spent longer operation time. Furthermore, it has been found no significant difference existed in the rate of R0 resection between LH and RH.

Due to technical limitations and anatomical disadvantages, many surgeons choose RH[10,12]. But recently, more centers began to take LH into the HCCA clinical treatment. The present study showed that the long-term survival of LH is not worse than RH. Subgroup analysis demonstrated that only Western Central group performed better on 5-year survival after RH. The results of the Eastern Central group, the different publication years and different cases of LH were involved in meta-analysis. Some authors thought that R0 resection was the most important factor for improving survival after surgical resection[4,37]. The direction of R0 resection rate was always the same as that of long-term survival in our meta-analysis and subgroup analysis. The present results provided convincing evidence that there is a positive effect of R0 resection on long-term survival. Therefore, it is reasonable to assume that in addition to tumor location, R0 resection rate is also a determinant of surgical procedure.

Neuhaus et al.[38] recommended additional caudate lobectomy to increase radicality, while more supporters believed that caudate lobectomy should be performed routinely based on anatomical and histopathological perspectives.[39,40]. Birgin et al[41]. presented a pooled RR value of 1.40, which was based on the 4 studies, reflecting a higher risk of residual tumors at the resection margin in patients without the caudate lobectomy. In the studies we included, all of them performed caudate lobe resection to varying degrees. In view of partial incomplete data and unclear implementation criteria, the subgroup analysis based on caudate lobectomy was regrettably not performed.

Analysis of morbidity and mortality revealed that LH was associated with better short-term outcomes, with both overall and major morbidity, postoperative liver failure, and mortality- being significantly lower in the LH group than in the RH group. Subgroup analysis also confirms this result. Of note, the overall morbidity of the LH group is only lower in studies published after 2014 and in the Western Center. The similar finding was observed in the analysis of major morbidity, with a significant improvement in major morbidity compared to RH, when LH was performed in Western Centers. The differences in the eastern and western treatment strategies could be further investigated to provide ideas for further optimization of surgery. It was interesting that the PHLF rate of the Eastern Centers group after performing LH was significantly reduced which was considered to be related to the active biliary drainage and PVE in the Eastern Center[42]. However, there is only one study in the Western Centers group in the subgroup analysis, so the results should be interpreted with cautiously. In addition, the date of major morbidity and PHLF were provided by studies published after 2014. It was not clear whether advances in technology and perioperative management in recent years have improved major morbidity and PHLF. When reporting mortality, the criteria for statistical days were not uniformed. In the subgroup analysis with different numbers of LH cases, in the more experienced centers, the mortality rate of LH was lower than that of RH group, which is also consistent with our conventional understanding. However, for the mortality rate including PHLF, the centers with the number of examples < 41 cases can obtain better results in the LH group. We consider that these centers have less experience, so they will be more cautious in surgery and in more detailed surgery management, but the final mortality rate may still be related to experience. Since the number of studies included in the meta-analysis is essentially not sufficient, the understanding of the results needs to be more cautious, and we hope that there will be more related study to be included in the future. In theory, 30 days had a reduced mortality rate compared to 90 days, which in turn underestimated the statistical results.

The PHLF caused by insufficient residual liver volume after major hepatectomy is the most fatal complication, with a mortality rate of 52–68%[43]. Kawasaki et al[12]. showed that patients with HCCA routinely performed biliary drainage and PVE before extensive hepatectomy, and the hospital mortality rate can be reduced to as low as 1.3%. Preoperative drainage is thought to improve liver function in patients with jaundice, which could reduce PHLF and death. Endoscopic biliary drainage and endoscopic nasobiliary drainage are superior to percutaneous transhepatic biliary drainage because they can reduce the incidence of tumor spread. And given the increase in major morbidity, routine preoperative drainage is not recommended[44]. PVE is believed to increased FLR, but there is no consensus on the indication criteria. In this meta-analysis, various studies conducted biliary drainage and PVE under the premise of different standards, hoping to further clarify the indications of biliary drainage and PVE in the future.

This meta-analysis has some limitations. Firstly, due to the rarity of HCCA, the included studies were all cohort studies, and there are no randomized controlled trials, which would cause selection bias. In some studies, the sample size is small, and differences in treatment experience may affect the accuracy of the results. Secondly, there was heterogeneity among the studies on 1-year survival rate and operation time, but the degree was low. Thirdly, the bismuth classification of tumors in each study is also different, but the data is not sufficient for subgroup analysis based on bismuth classification. It is hoped that further analysis based on different bismuth classification would be conducted in the future.

In conclusion, the present meta-analysis suggests that for resectable HCCA patients, LH and RH have comparable survival benefits and R0 resection rates, and lower morbidity and mortality. LH is safe and feasible. We recommend that the choice of LH or RH should be based on the specific anatomy of the tumor and to achieve radical cure as much as possible, while optimizing perioperative management to reduce postoperative morbidity and mortality.

To the best of our knowledge, this is the first meta-analysis comparing the outcomes of LH and RH to date. Given the low incidence of HCCA, further randomized trials in the real-world may be needed.

Abbreviations

HCCA, hilar cholangiocarcinoma; LH, left-side hepatectomy; RH, right-side hepatectomy; OS, overall survival; HR, hazard ratio; RR, relative risk; MD, mean difference; CI, confidence interval; FLR, future liver remnant; PHLF, postoperative liver failure; P VE, portal vein embolization; PRISMA, preferred reporting items for systematic review and meta-analyses; MOOSE, meta-analysis of observational studies in epidemiology; RCTs, randomized controlled trials; PDB, percutaneous biliary drainage; EBD, endoscopic biliary drainage; PVE, portal vein embolization; NOS, newcastle
ottawa quality assessment scale; SD, standard deviation;

Declarations

Acknowledgments

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare.

Guideline Checklist: The authors have completed the PRISMA guideline checklist (Appendix 1).

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Founding: This work was supported by the National Natural Science Foundation of China [No.81874228].

References

1. Razumilava N, Gores GJ. Cholangiocarcinoma. The Lancet. 2014;383(9935):2168–79.
2. Cillo U, Fondevila C, Donadon M, Gringeri E. Surgery for cholangiocarcinoma. Liver Int. 2019;39(Suppl 1(Suppl Suppl 1):143–55.
3. Bhardwaj N, Garcea G, Dennison AR, Maddern GJ. The Surgical Management of Klatskin Tumours: Has Anything Changed in the Last Decade? World J Surg. 2015;39(11):2748–56.
4. Zhang XF, Squires MHr, Bagante F, Ethun CG, Salem A. The Impact of Intraoperative Re-Resection of a Positive Bile Duct Margin on Clinical Outcomes for Hilar Cholangiocarcinoma. Ann Surg Oncol. 2018;25(5):1140–9.
5. Nagino M, Ebata T, Yokoyama Y, Igami T, Sugawara G. Evolution of surgical treatment for perihilar cholangiocarcinoma: a single-center 34-year review of 574 consecutive resections. Ann Surg Oncol. 2013;258(1):129–40.
6. Ito F, Agni R, Rettammel RJ, et al. Resection of hilar cholangiocarcinoma: concomitant liver resection decreases hepatic recurrence. Ann Surg. 2008;248(2):273–9.
7. Ramos E. Principles of surgical resection in hilar cholangiocarcinoma. World J Gastrointest Oncol. 2013;5(7):139–46.
8. Xiang F, Hu ZM. Chance and challenge of associating liver partition and portal vein ligation for staged hepatectomy. Hepatobiliary Pancreat Dis Int. 2019;18(3):214–22.
9. Miyazaki M, Yoshitomi H, Miyakawa S, et al. Clinical practice guidelines for the management of biliary tract cancers 2015: the 2nd English edition. J Hepatobiliary Pancreat Sci. 2015;22(4):249–73.
10. Natsume S, Ebata T, Yokoyama Y, Igami T, Sugawara G. Clinical significance of left trisectionectomy for perihilar cholangiocarcinoma: an appraisal and comparison with left hepatectomy. Ann Surg. 2012;255(4):754–62.
11. Shimizu H, Kimura F, Yoshidome H, Ohtsuka M, Kato A. Aggressive surgical resection for hilar cholangiocarcinoma of the left-side predominance: radicality and safety of left-sided hepatectomy. Ann Surg. 2010;251(2):281–6.
12. Kawasaki S, Imamura H, Kobayashi A, Noike T, Miwa S, Miyagawa S. Results of surgical resection for patients with hilar bile duct cancer: application of extended hepatectomy after biliary drainage and hemihepatic portal vein embolization. Ann Surg. 2003;238(1):84–92.

13. Uesaka K. Left hepatectomy or left trisectionectomy with resection of the caudate lobe and extrahepatic bile duct for hilar cholangiocarcinoma (with video). J Hepatobiliary Pancreat Sci. 2012;19(3):195–202.
14. Farges O, Regimbeau JM, Fuks D, et al. Multicentre European study of preoperative biliary drainage for hilar cholangiocarcinoma. Br J Surg. 2013;100(2):274–83.
15. Jo H-S, Kim D-S, Yu Y-D, Kang W-H, Yoon KC. Right-side versus left-side hepatectomy for the treatment of hilar cholangiocarcinoma: a comparative study. World J Surg Oncol. 2020;18(1):3–3.
16. Yasuda Y, Larsen PN, Ishibashi T, Yamashita K, Toei H. Resection of hilar cholangiocarcinoma with left hepatectomy after pre-operative embolization of the proper hepatic artery. HPB (Oxford). 2010;12(2):147–52.
17. Hosokawa I, Shimizu H, Yoshidome H, Ohtsuka M, Kato A. Surgical strategy for hilar cholangiocarcinoma of the left-side predominance: current role of left trisectionectomy. *Ann Surg* 2014;*259:1178–1185.* 2014;259(6):1178–1185.
18. Nagino M. Perihilar cholangiocarcinoma: a surgeon's viewpoint on current topics. J Gastroenterol. 2012;47(11):1165–76.
19. Govil S, Bharatan A, Rammohan A, et al. Liver resection for perihilar cholangiocarcinoma – why left is sometimes right. HPB (Oxford). 2016;18(7):575–9.
20. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of internal medicine. 2009;151(4):264–9.
21. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D. Meta-analysis of Observational Studies in Epidemiology. JAMA. 2000;283(15):2008–12.
22. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. STATISTICS IN MEDICINE. 1998;17:2815–34.
23. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007;8:16.
24. Wells GA, Shea BJ, O'Connell D, Smitch M. The Newcastle-Ottawa scale (NOS) for assessing the quality of non-randomized studies in meta-analysis. Applied Engineering in Agriculture. 2014;18:727–34.
25. Luo D, Wan X, Liu J, Smitch M, Hirata K. Optimally estimating the sample mean from the sample size, median, mid-range and/or mid-quartile. Statistical Methods in Medical Research. 2016;0(0):1–21.
26. Wan X, Wang W, Liu J, Tong AK. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135.
27. Higgins JP, Thompson SG, Deeks JJ, Smitch M. Measuring inconsistency in meta-analyses. British Medical Journal. 2003;327:557–60.
28. Bednarsch J, Czigany Z, Lurje I, et al. Left- versus right-sided hepatectomy with hilar en-bloc resection in perihilar cholangiocarcinoma. *HPB (Oxford).* 2019:S1365-1182 × (1319)30617 – 30613.
29. Hong SS, Han DH, Choi GH, Choi JS. Comparison study for surgical outcomes of right versus left side hemihepatectomy to treat hilar cholangiocellular carcinoma. Ann Surg Treat Res. 2020;98(1):15–22.
30. Lee Y, Choi D, Han S, Han IW, Heo JS, Choi SH. Comparison analysis of left-side versus right-side resection in bismuth type III hilar cholangiocarcinoma. Ann Hepatobiliary Pancreat Surg. 2018;22(4):350–8.
31. Otto G, Heise M, Hoppe-Lotichius M, Pitton M, Hansen T. Hilar cholangiocarcinoma: right versus left hepatectomy. Zentralbl Chir. 2012;137(6):535–40.
32. Ratti F, Cipriani F, Piozzi G, Catena M, Paganelli M, Aldrighetti L. Comparative Analysis of Left- Versus Right-sided Resection in Klatskin Tumor Surgery: can Lesion Side be Considered a Prognostic Factor? J Gastrointest Surg. 2015;19(7):1324–33.
33. Shimizu H, Kimura F, Yoshidome H, et al. Aggressive surgical resection for hilar cholangiocarcinoma of the left-side predominance: radicality and safety of left-sided hepatectomy. Ann Surg. 2010;251(2):281–6.
34. Sugiura T, Okamura Y, Ito T, et al. Left Hepatectomy with Combined Resection and Reconstruction of Right Hepatic Artery for Bismuth Type I and II Perihilar Cholangiocarcinoma. World J Surg. 2019;43(3):894–901.
35. Konstadoulakis MM, Roayaie S, Gomatos IP, et al. Aggressive surgical resection for hilar cholangiocarcinoma: is it justified? Audit of a single center's experience. Am J Surg. 2008;196(2):160–9.
36. Yamanaka N, Yasui C, Yamanaka J, et al. Left hemihepatectomy with microsurgical reconstruction of the right-sided hepatic vasculature. A strategy for preserving hepatic function in patients with proximal bile duct cancer. Langenbecks Arch Surg. 2001;386(5):364–8.
37. Moris D, Kostakis I, Machairas D, Prodromidou N, Tsilimigras A, Ravindra DI. K, V. Comparison between liver transplantation and resection for hilar cholangiocarcinoma: A systematic review and meta-analysis. PLoS One. 2019;14(7):e0220527.
38. Neuhaus P, Thelen A, Jonas S, Puhl G, Denecke T. Oncological superiority of hilar en bloc resection for the treatment of hilar cholangiocarcinoma. Ann Surg Oncol. 2012;19(5):1602–8.
39. Xiang S, Lau W, Chen Y. X, P. Hilar cholangiocarcinoma: controversies on the extent of surgical resection aiming at cure. Int J Colorectal Dis. 2015;30(2):159–71.
40. Kambakamba P, DeOliveira ML. Perihilar cholangiocarcinoma: paradigms of surgical management. Am J Surg. 2014;208(4):563–70.
41. Birgin E, Rasbach E, Reissfelder C, Rahbari N. N. A systematic review and meta-analysis of caudate lobectomy for treatment of hilar cholangiocarcinoma. Eur J Surg Oncol. 2020;46(5):747–53.
42. Franken L, Schreuder C, Roos AM. E, et al. Morbidity and mortality after major liver resection in patients with perihilar cholangiocarcinoma: A systematic review and meta-analysis. Surgery. 2019;165(5):918–28.

43. Olthof P, Wiggers B, Groot JK, Coelen KB, Allen RJ, Besselink PJ. M, G. Postoperative Liver Failure Risk Score: Identifying Patients with Resectable Perihilar Cholangiocarcinoma Who Can Benefit from Portal Vein Embolization. J Am Coll Surg. 2017;225(3):387–94.
44. Mehrabi A, Khajeh E, Ghamarnejad O, et al. Meta-analysis of the efficacy of preoperative biliary drainage in patients undergoing liver resection for perihilar cholangiocarcinoma. Eur J Radiol. 2020;125:108897.

Tables

Table 1. Characteristics of the Included Studies

Study	Study Design	Location/ Period	Follow-up Months*	No. of Patients (Male, %)	Age, Years*	No. of Stage I/II/III/IV	No. of Biliary drainage (EBD/PBD)	No. of PVE	caudate lobectomy, %	Main Findings
Bednarsch et al.[28] (2019)	cohort study	Germany/ 2011-2016	28 (0-90)	LH:36(63.9)	67 ± 9	1/0/23/12	35(27/8)	0	100	3-,5-year OS rate, LH=62%,30% vs. RH=51%,46%; R0,LH=69.4% vs. RH=75.6%
				RH:45(68.9)	67 ± 11	2/6/23/14	46(35/11)	37	100	
Govil et al.[19] (2016)	cohort study	India/ 2009-2015	14 (3-64)	LH:23(NR)	58 (20-74)	0/0/28/8	8(0/8)	0	NR	2-year-OS rate, LH=39%vs. RH=44%,R0,NR
				RH:13(NR)			6(0/6)	0	NR	
Hong et al.[29] (2020)	cohort study	Korea/ 2000-2018	NR	LH:82(68.3)	63.46±10.38	5/6/43/28	60	2	100	1,3-,5-year OS rat LH=87.3%,38.2% vs. RH=77.2%,41 26.8% ; R0,LH=75.6% vs. RH=72.8%
				RH:114(66.7)	63.64± 8.72	4/13/75/22	93	45	100	
Jo et al.[15] (2020)	cohort study	Korea/ 2010-2017	19 (1-97)	LH:24(62.5)	71 (53-83)	IV:7	22(14/8)	0	100	1,3-,5-year OS rat LH=82.6%,50.6% vs. RH=69.3%,48 37.7%; R0,LH=75% vs. RH=75.8%
				RH:33(66.6)	66 (42-79)	IV:12	29(20/9)	6	100	
Study	Study Design	Location/ Period	Follow-up Months*	No. of Patients (Male, %)	Age, Years*	No. of Stage I/II/III/IV	No. of Biliary drainage (EBD/PBD)	No. of PVE	caudate lobectomy, %	Main Findings
Lee et al.[30] (2018)	cohort study	Korea/ 1995-2012	NR	LH:35(57.1)	61.0±8.1	IIIb:35	23	0	94.3	1,3-,5-year OS rat LH=80%,47%,35% RH=85%,47%, 33%; R0,LH=85.7% vs. RH=82.5%
				RH:103(66)	62.1±9.2	IIIa:103	71	24	86.4	
Otto et al.[31] (2012)	cohort study	Germany/ 1998-2011	NR	LH:68(75)	64 (39-83)	0/0/35/33	NR	0	100	1,5-year OS rate, LH=72%,22% vs. RH=73%,29%; R0,LH=72.1% vs. RH=82.4%
				RH:68(66.2)	62 (44-82)	1/0/37/30	NR	4	100	
Ratti et al.[32] (2015)	cohort study	Italy/ 2004-2014	23(3-98)	LH:44(68.1)	59 (36-79)	1/17/13/13	23(6/16)†	0	97.7	3-,5-year OS rate, LH=49.5%,35.3% RH=53.2%, 42.8%; R0,LH=61.4% vs. RH=75.4%
				RH:61(50.8)	62 (41-82)	1/20/15/25	39(9/22)†	29	93.4	
Shimizu et al.[33] (2010)	cohort study	Japan/ 1984-2008	NR	LH:88(69.3)	67.0±8.9	IIIb:88	NR	5	100	1,3-,5-year OS rat R0,LH=63.6% vs. RH=69.1%
				RH:84(56)	67.1±8.0	IIIa +V:84	NR	32	100	
Study	Study Design	Location/ Period	Follow-up Months*	No. of Patients (Male, %)	Age, Years*	No. of Stage I/II/III/IV	No. of Biliary drainage	No. of PVE	caudate lobectomy, %	Main Findings

							(EBD/PBD)			
Sugiura et al.[34] (2018)	cohort study	Japan/ 2002-2013	NR	LH:12(91.7)	65 (58-84)	2/10/0/0	NR	0	100	3-,5-year OS rate, LH=66.7%,41.7% RH=70.8%, 49%; R0,NR
				RH:24(75)	68 (37-81)	8/16/0/0	NR	24	100	
Konstadoulakis et al.[35] (2008)	cohort study	USA/ 1988-2006	NR	LH□29	NR	NR	NR	0	77.6	1,3-,5-year OS rat LH=66.7%,33.3% vs. RH= 85%,63.2%,50%; R0,NR
				RH□20	NR	NR	NR	1		
Yamanaka et al.[36] (2001)	cohort study	Japan/ 1980-1998	NR	LH:11(54.5)	60±11	NR	NR	NR	100	OS, HR, 0.53 95% 0.02-15.24; R0,NI
				RH:14(64.3)	55±10	NR	NR	NR	93	

*Sign indicates median (range) ; otherwise, data are expressed as mean±SD.

†In addition to EBD and PBD, biliary drainage also includes EBD + PBD

Abbreviation: NR, not reported in the text; EBD: endoscopic biliary drainage; PBD: percutaneous biliary drainage; PVE: portal venous embolization.

Table 2. Subgroup analyses

Variable	Subgroup	OS	1-year survival	3-year survival	5-year survival	Overall morbidity	Major morbidity	PHLF	Mortality	R0 resection
Region	Western	HR=1.34; 95 % CI, 0.95-1.89; P=0.097; n=4	RR=0.90; 95 % CI, 0.72-1.13; P=0.354 n=2	RR=0.93; 95 % CI, 0.73-1.19; P=0.552 n=3	RR=0.70; 95 % CI, 0.52-0.94; P= **0.018** n=4	RR=0.70; 95 % CI, 0.57-0.87; P= **0.001** n=2	RR=0.62; 95 % CI, 0.42-0.91; P= **0.015** n=2	RR=0.40; 95 % CI, 0.09-1.82; P= 0.233 n=1	RR=0.39; 95 % CI, 0.17-0.88; P= **0.024** n=3	RR=0.87; 95 % CI, 0.76-0.99; P=**0.038** n=3
	Eastern	HR=1.19; 95 % CI, 0.82-1.73; P=0.362; n=6	RR=1.08; 95 % CI, 0.93-1.24; P=0.315 n=3	RR=0.96; 95 % CI, 0.77-1.19; P=0.681 n=4	RR=0.97; 95 % CI, 0.72-1.30; P=0.836 n=4	RR=0.92; 95 % CI, 0.74-1.14; P=0.434 n=2	RR=0.88; 95 % CI, 0.61-1.26; P= 0.477 n=3	RR=0.16; 95 % CI, 0.05-0.55; P= **0.003** n=3	RR=0.42; 95 % CI, 0.20-0.88; P= **0.021** n=6	RR=1.00; 95 % CI, 0.90-1.10; P= 0.958 n=4
Year of publication	≤2014	HR=1.39; 95 % CI, 0.92-2.10; P=0.113; n=3	RR=0.90; 95 % CI, 0.72-1.13; P=0.354 n=2	RR=0.53; 95 % CI, 0.29-0.96; P= 0.037 n=1	RR=0.63; 95 % CI, 0.39-1.00; P= 0.051 n=2	RR=0.86; 95 % CI, 0.61-1.20; P=0.377 n=1	n=0	n=0	RR=0.32; 95 % CI, 0.13-0.77; P= **0.011** n=3	RR=0.90; 95 % CI, 0.78-1.04; P=0.141 n=2
	□2014	HR=1.20; 95 % CI, 0.87-1.65; P=0.276; n=7	RR=1.08; 95 % CI, 0.93-1.24; P=0.315 n=3	RR=0.99; 95 % CI, 0.84-1.18; P= 0.917 n=6	RR=0.89; 95 % CI, 0.70-1.12; P= 0.307 n=6	RR=0.81; 95 % CI, 0.68-0.97; P=**0.018** n=3	n=5	n=4	RR=0.47; 95 % CI, 0.23-0.96; P= **0.038** n=6	RR=0.97; 95 % CI, 0.88-1.07; P= 0.582 n=5
Cases	□ 41cases	HR=1.24; 95 % CI, 0.92-1.66; P=0.154; n=3	RR=1.08; 95 % CI, 0.93-1.25; P=0.303 n=2	RR=0.93; 95 % CI, 0.72-1.21; P=0.594 n=2	RR=0.84; 95 % CI, 0.62-1.13; P= 0.248 n=3	RR=0.85; 95 % CI, 0.70-1.03; P= 0.102 n=3	RR=0.76; 95 % CI, 0.46-1.27; P= 0.295 n=2	RR=0.38; 95 % CI, 0.11-1.32; P= 0.127 n=2	RR=0.32; 95 % CI, 0.14-0.72; P= **0.006** n=4	RR=0.95; 95 % CI, 0.85-1.06; P=0.369 n=4
	≤ 41cases	HR=1.35; 95 % CI, 0.82-2.23; P=0.231; n=7	RR=0.96; 95 % CI, 0.77-1.19; P=0.688 n=3	RR=0.95; 95 % CI, 0.77-1.18; P=0.656 n=5	RR=0.81; 95 % CI, 0.61-1.08; P=0.148 n=5	RR=0.74; 95 % CI, 0.60-0.91; **P=0.004** n=1	RR=0.71; 95 % CI, 0.52-0.97; P=**0.029** n=3	RR=0.12; 95 % CI, 0.03-0.55; P= **0.006** n=2	RR=0.52; 95 % CI, 0.24-1.10; P= 0.086 n=5	RR=0.94; 95 % CI, 0.84-1.05; P= 0.289 n=3

Data are presented as HR or RR (95 % CI); P value; number of included studies (n)

Abbreviation: OS, overall survival; PHLF: postoperative liver failure.

Figures

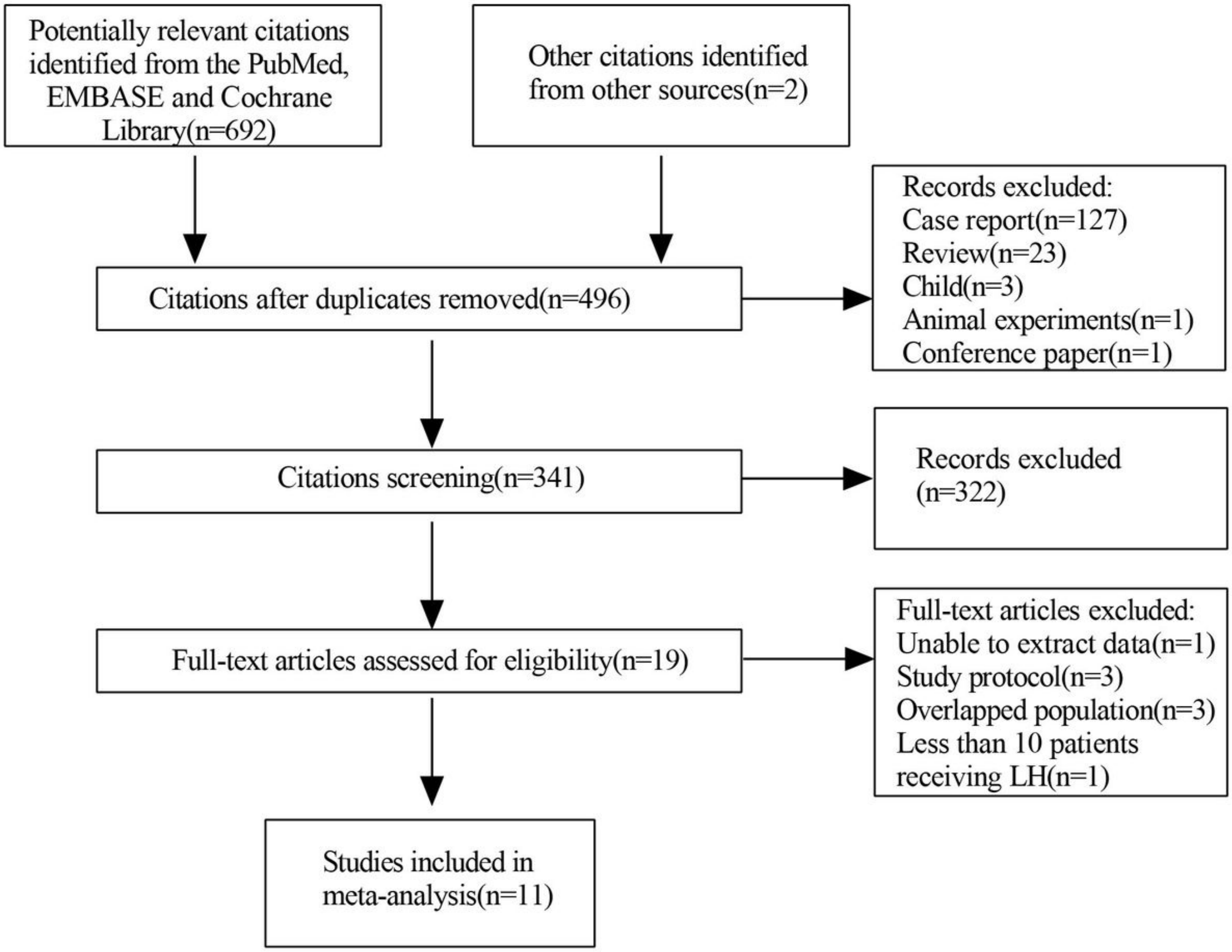

Figure 1

PRIMSA flow diagram of study selection

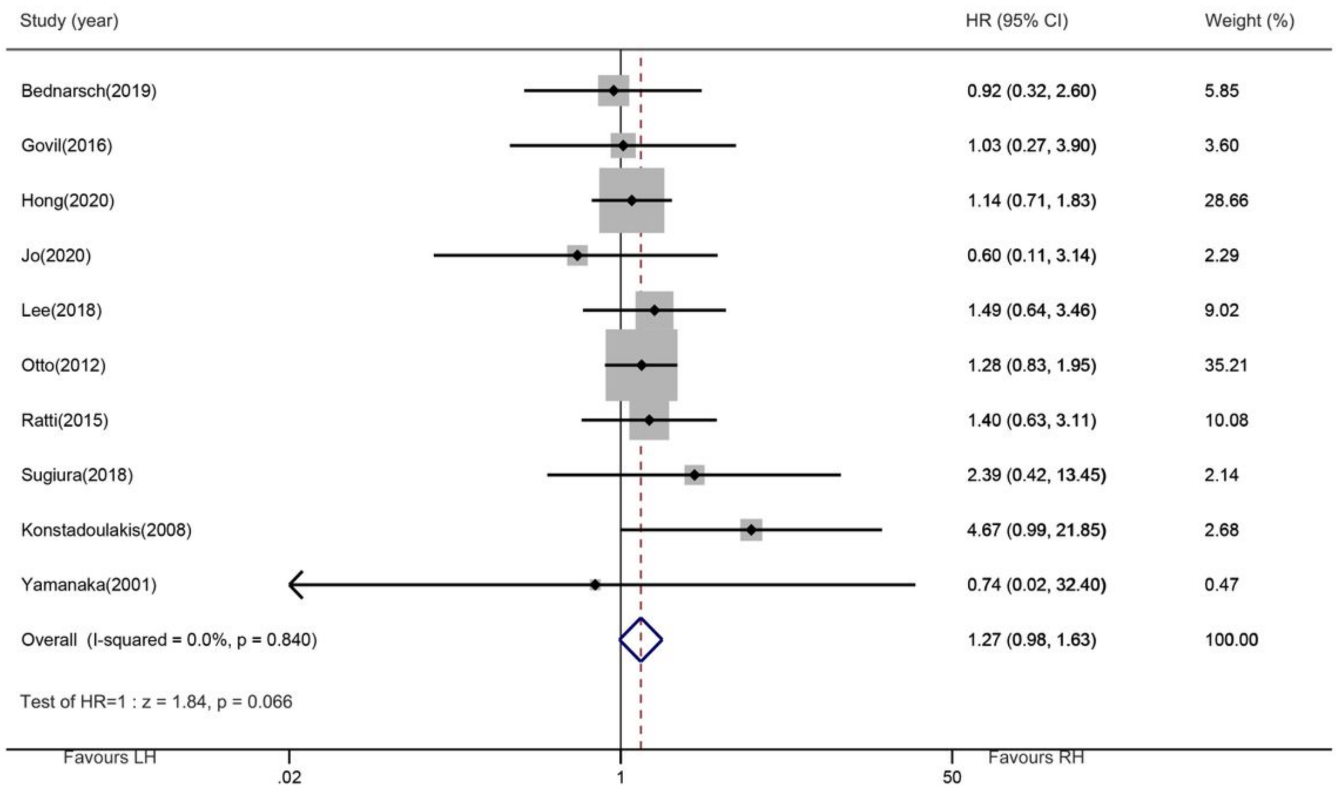

Figure 2

Forest plots of overall survival (left-side hepatectomy vs. right-side hepatectomy)

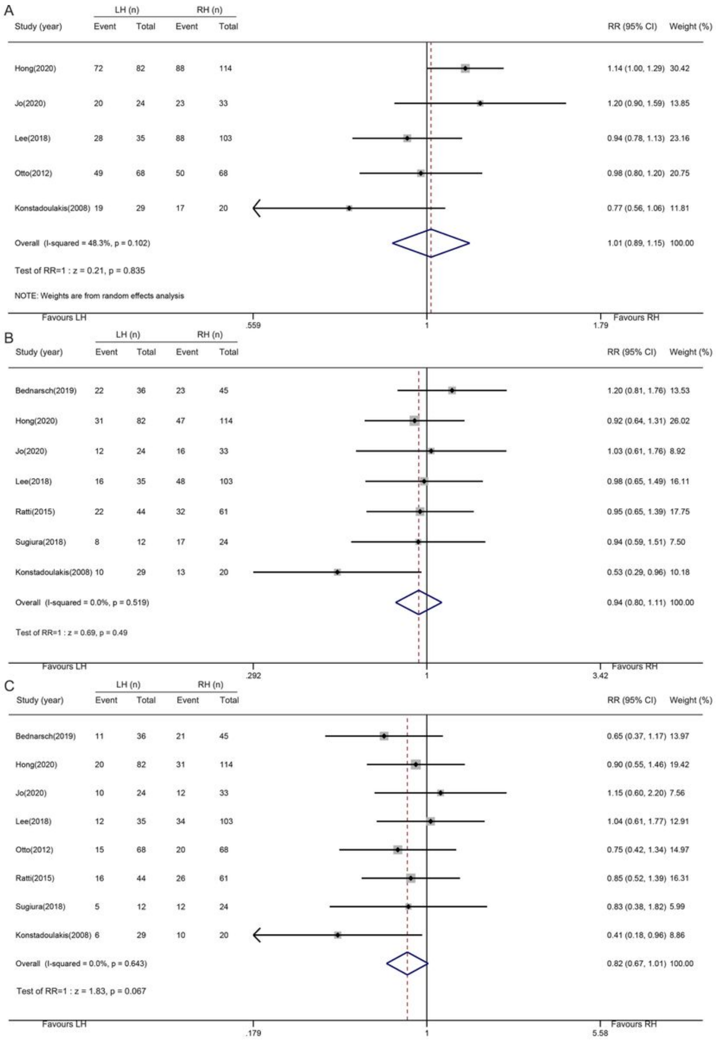

Figure 3

Forest plots of 1-, 3-, and 5-year survival rates (left-side hepatectomy vs. right-side hepatectomy) (A) 1-year survival rate (B) 3-year survival rate (C) 5-year survival rate

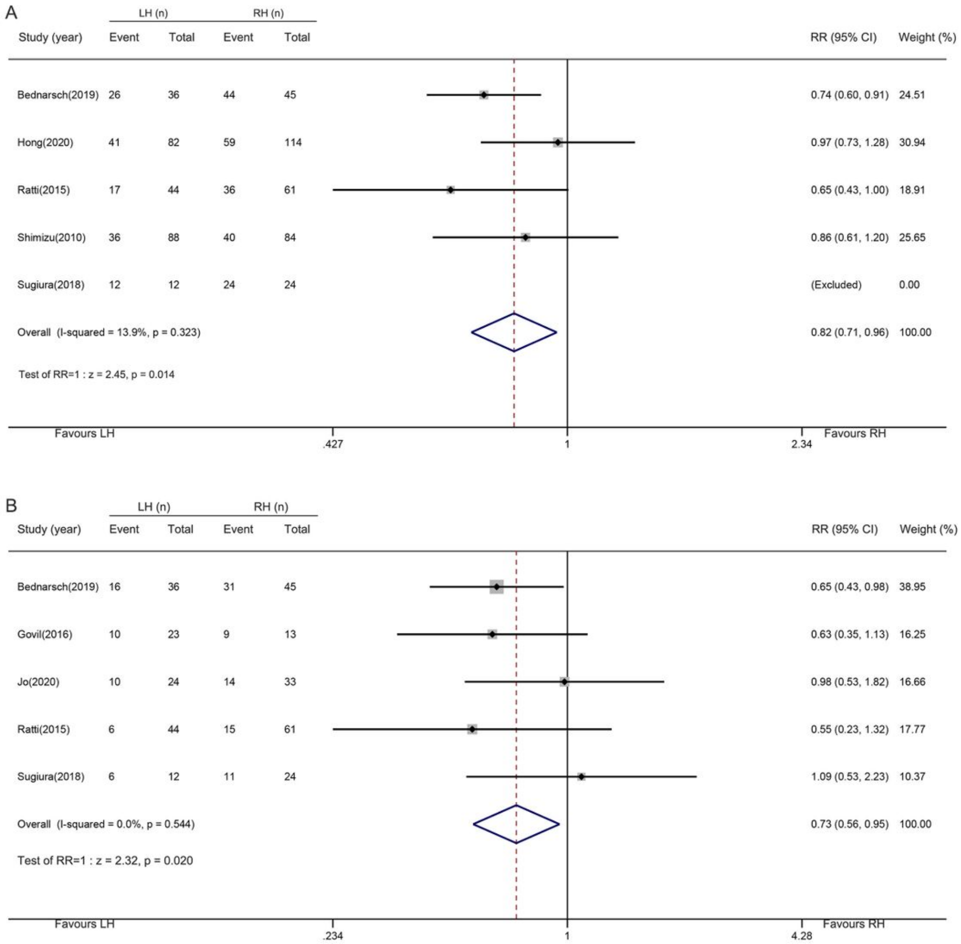

Figure 4

Forest plots of Overall postoperative morbidity and major postoperative morbidity (left-side hepatectomy vs. right-side hepatectomy) (A) Overall postoperative morbidity (B) Major postoperative morbidity

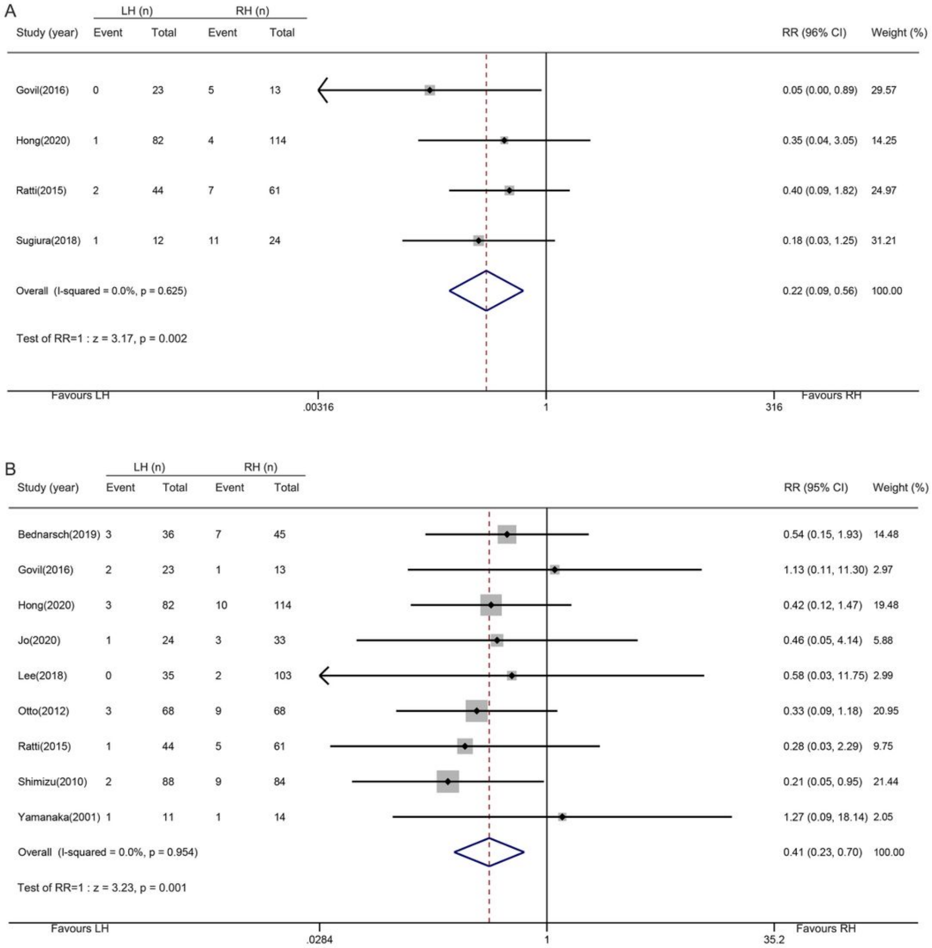

Figure 5

Forest plots of Post-hepatectomy liver failure and procedure-related mortality (left-side hepatectomy vs. right-side hepatectomy) (A) Post-hepatectomy liver failure (B) Procedure-related mortality

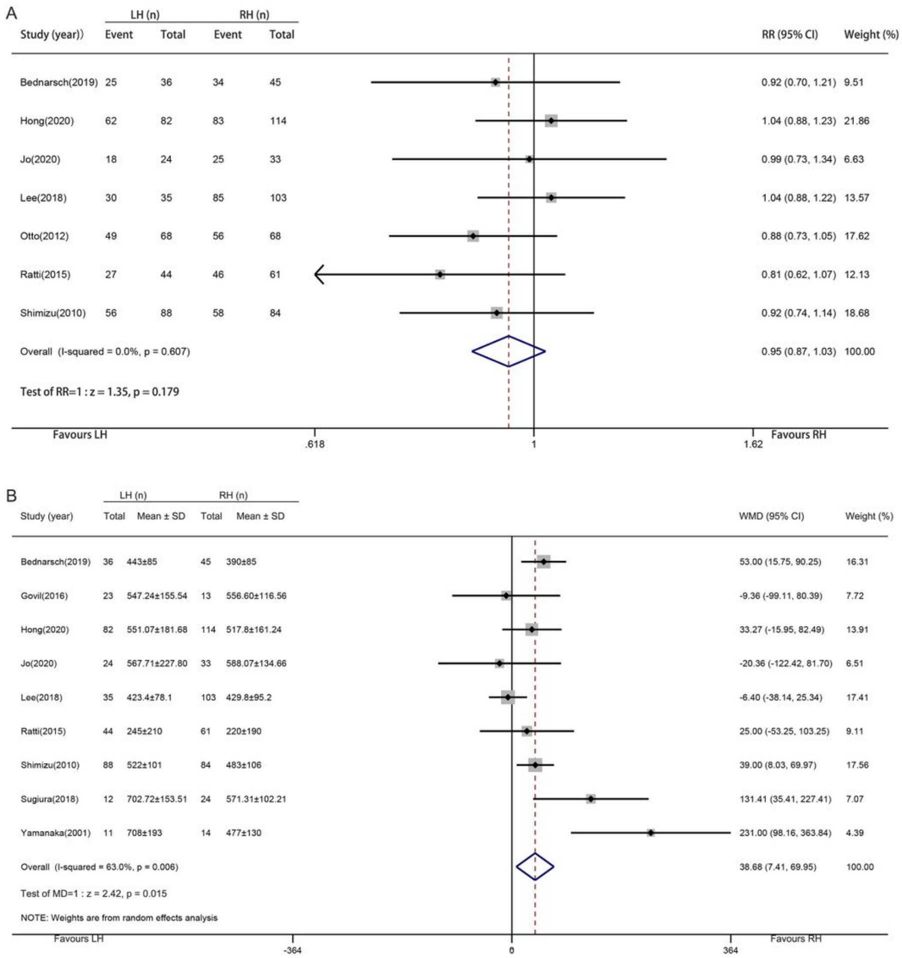

Figure 6

Forest plots of R0 resection rate and operating time (left-side hepatectomy vs. right-side hepatectomy) (A) R0 resection rate (B) operating time

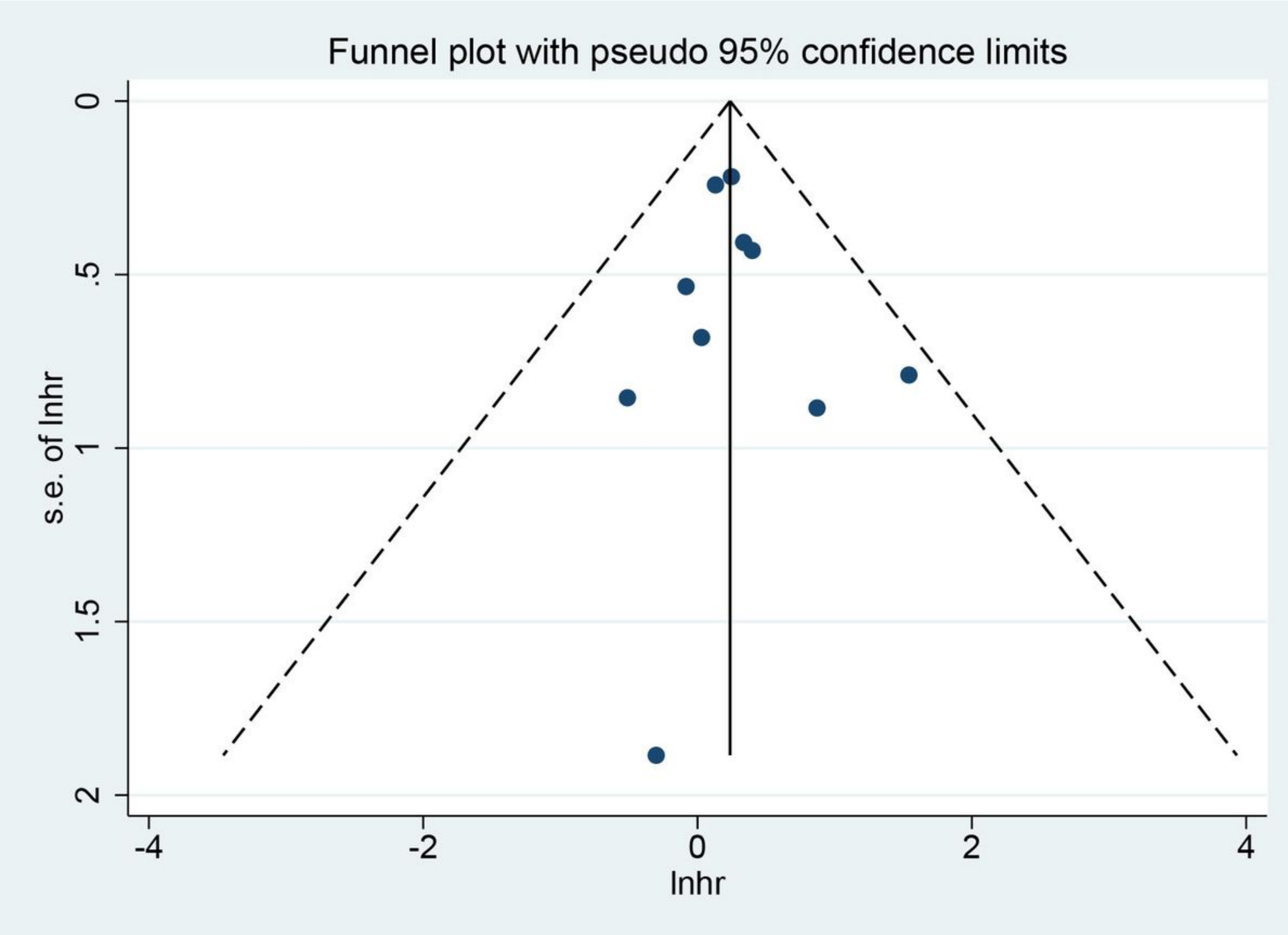

Figure 7

Funnel plot of overall survival

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- eTable1.doc
- Appendix1.pdf
- SupplementaryTable1.docx