Oncology and Translational Medicine
DOI 10.1007/s10330-019-0390-0
December 2019, Vol. 5, No. 6, P–P

ORIGINAL ARTICLE

Value of partial hepatectomy for the treatment of hilar cholangiocarcinoma: A meta-analysis study*

Ming Yang[1], Yanhong Zhang[1], Miaohang Cui, Jianhua Chen[2], JinLong Liu[1] (✉)

[1] Department of General Surgery, The Affiliated Hospital of Chengde Medical College, Chengde 067000, China
[2] Department of General Surgery, Kuancheng County Traditional Chinese Medicine Hospital, Chengde 067000, China

Abstract

Objective To discuss the value of partial hepatectomy in patients with hilar cholangiocarcinoma.
Methods English articles related to hilar cholangiocarcinoma were screened from January 1, 1990 to May 12, 2019 in the PubMed, MEDLINE, EMBASE, and Cochrane Library databases. Information on postoperative radical cure, survival, morbidity, and mortality after surgery were extracted from articles that met the inclusion criteria for the meta-analysis.
Results Twenty-two articles that met the inclusion criteria were classified into 4 study groups: the hepatectomy radical cure group (19 articles), the hepatectomy survival group (16 articles), the hepatectomy morbidity group (9 articles), and the hepatectomy mortality group (17 articles). We found that the rate of radical cure after partial hepatectomy (odds ratio [OR] 0.32, 95% confidence interval [CI] 0.20–0.51) and the survival rate (hazard ratio [HR] 0.67, 95% CI 0.58–0.79) were significantly higher than after simple bile duct resection, but that morbidity (OR 1.99, 95% CI 1.37–2.90) and mortality (OR 2.71, 95% CI 1.47–4.98) in patients within the partial hepatectomy group were also higher than in the simple bile duct resection group, taking into account the significant heterogeneity in the articles pertaining to the hepatectomy radical cure group (I^2 = 68.3%, P = 0.000), a sub-group analysis was subsequently conducted. Its results showed that when the branches of the secondary bile ducts were not involved during hilar cholangiocarcinoma, then a bile duct resection had a similar radical cure outcome as combined partial hepatectomy (OR 0.94, 95% CI 0.54–1.65).
Conclusion Partial hepatectomy can increase the proportion of radical cure in patients with hilar cholangiocarcinoma and extend the survival time after surgery. However, the morbidity and mortality after surgery are higher than those in simple bile duct resections. Therefore, simple bile duct resection is still a relevant and efficient tool in the treatment of Bismuth-Corlette Type I and II hilar cholangiocarcinomas.
Key words: hilar cholangiocarcinoma; partial hepatectomy; prognosis; meta-analysis

Received: 10 November 2019
Revised: 24 November 2019
Accepted: 13 December 2019

Hilar cholangiocarcinoma (HCCA) is a malignant cancer that arises in the biliary confluence. These types of tumor were first described by Gerald Klatskin in 1965 [1] and designated as Klatskin tumors. Surgical resection of HCCA tumors remains a profound surgical challenge because of its biological characteristics and anatomical location. It is thought that the optimal surgical treatment for HCCA should not be limited to the reconstruction of the biliary drainage system, but also to completely excise the tumor, to minimize surgical trauma, reduce liver damage and incidence of postoperative complications and mortality. Combined hepatectomy can expand the scope of resection and increase the likelihood of complete tumor resection. However, it does have an associated risk of postoperative liver failure.

Due to the low incidence of HCCA and the challenges in its treatment, there is still a lack of large sample studies on the postoperative radical effects, long-term prognosis, postoperative complications, and surgical death after combined partial hepatectomy. Several issues remain unanswered such as whether the combination of partial liver resection prolongs the postoperative survival

✉ Correspondence to: Jinlong Liu. Email: liujl800813@163.com
* Supported by a grant from the Science and Technology Research and Development Project of Chengde (No. 201804A023).

period and improves the postoperative radical cure rate or whether the surgical trauma increases postoperative complications and mortality.

The purpose of this study is to explore the effects of different surgical resections by analyzing all current available literature, and to provide evidence-based medical data on the effectiveness of surgical treatments for HCCA.

Methods

Literature search

Studies were identified through a search of PubMed, MEDLINE, EMBASE, and Cochrane Library databases using the following retrieval formula: “hilar cholangiocarcinoma” or “Klatskin tumor”. The search included articles ranging from January 1st 1990 to May 12th 2019. The language of the articles was restricted to English. References and reviews were manually searched to detect additional studies.

Inclusion criteria

The systematic review generated a complete database from the published studies by analyzing the prognosis of patients with HCCA treated by bile duct resection with or without partial hepatectomy. Eligible studies met the following inclusion criteria: the subject of the study included patients with HCCA; all patients underwent surgical treatment; data included a prognosis analysis in patients with HCCA who underwent bile duct resection with or without combined partial hepatectomy (prognosis included at least one of four indexes: radical resection, long-term survival, postoperative complications and short-term mortality); hazard ratio (HR) and 95% confidence interval (CI) for survival were included according to patients’ survival status, either reported or extrapolated from the original data; in the case of patient duplication, the most recent report or the most informative report was included; and, finally, study quality with > 5 stars were included, according to the Newcastle-Ottawa quality assessment scale [2].

The exclusion criteria were as follows: prognostic effects were evaluated by a recurrence rate; prognosis of a single surgical treatment was reported without the inclusion of a control group; or letters, reviews, case reports, conference abstracts, editorials, and expert opinions.

Data extraction

Two investigators (Liu JL and Yang M) reviewed all articles. Data were extracted independently by two investigators (Liu JL and Chen JH) using a data extraction sheet. Data included the name of the first author, year of publication, ethnic origin of patients, number of patients, bile duct resection with or without combined partial hepatectomy, Bismuth-Corlette classification of patients undergoing different surgical procedures, number of radical resections, survival data (HR and 95% CI), number of postoperative complications and postoperative short-term mortality. When data was conflicting, the two data extractors would jointly resolve the problem.

Assessment of study quality

Study quality was assessed independently by two investigators (Liu JL and Chen JH), according to the Newcastle-Ottawa quality assessment scale. Briefly, the overall star system assesses three main categories: selection of cohort, comparability of cohort, and ascertainment of outcome. A study is awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars can be given for comparability. The total number of stars was evaluated, with higher stars reflecting higher methodological quality. A single study can be awarded a maximum of nine stars.

Statistical analysis

In this study, the odds ratios (OR) and 95% confidence intervals (CI) were used to evaluate the outcomes of the different surgical procedures on radical resection, postoperative complications and short-term mortality in patients with HCCA. HR and 95% CI were used to estimate the impact of different surgical procedures on survival. A HR below 1 was attributed when the survival time for the combined hepatectomy group was longer than for the bile duct resection group. Otherwise, the HR value was calculated using the formula: exp (LN (HR)).

When data for HR and 95% CI was not available, an estimated value was derived indirectly from the Kaplan-Meier curves using the previously described method by Tierney *et al* [3]. Kaplan-Meier curves were analyzed using the Engauge Digitizer version 4.1 (http://digitizer.sourceforge.net/) to retrieve the survival data, and the obtained values were entered in the spreadsheet appended in Tierney’s publication [3]. This work was performed by two independent researchers to increase the accuracy of the extracted survival rates.

To assess heterogeneity among the studies, we used the Cochran Q and I^2 statistics. For the Q statistic, a P value < 0.10 was considered statistically significant [4]. The random effects model was calculated according to the DerSimonian-Laird method [5]. Otherwise, the fixed-effects model (Mantel-Haenszel method) was used. For I^2, a value > 50% was considered a measure of severe heterogeneity [6]. For groups presenting with high heterogeneity, the source of heterogeneity was analyzed by single factor meta-regression analysis, and the subgroup analysis was carried out according to the source of heterogeneity. The funnel plot and Egger test were used to evaluate publication bias. A significant two-way P value for comparisons was defined as $P < 0.05$.

Literature Selection

A total of 1376 potentially relevant citations were retrieved after an initial database search. An additional 55 studies were found from the reference list of the articles and reviews or after a manual search of the journals. These were duplicates from the database search studies. Titles and abstracts of all relevant articles were read by two independent researchers (Liu JL and Yang M). One thousand and fourteen studies were excluded from the analysis after initial screening based on abstract or title, with a remaining 219 going through further full-text review. After applying the inclusion criteria, 197 studies were excluded. The final 22 studies fulfilled the inclusion criteria [7-28] and were subdivided into 4 study groups: the hepatectomy radical cure group (19 articles) [9–20, 22–28], the hepatectomy survival group (16 articles) [7–8, 10–13, 15–16, 19-21, 23-27], the hepatectomy morbidity group (9 articles) [9, 14–16, 19–20, 23, 26–27] and the hepatectomy mortality group (17 articles) [9,11–20, 22–24, 26–28] (Fig. 1).

Methodological quality of the studies

For all included studies, two researchers independently extracted the data and assessed the methodological quality using the Newcastle-Ottawa quality assessment scale. The scores are shown in Table 1. The studies included in our meta-analysis showed a high level of methodological quality (> 5 stars on the Newcastle-Ottawa scale).

Assessment of heterogeneity

The Q test and I^2 test were used to assess the heterogeneity between the study groups. We found that the hepatectomy survival group (I^2 = 41.7%, P = 0.041), the hepatectomy morbidity group (I^2 = 0.0%, P = 0.772), and the hepatectomy mortality group (I^2 = 0.0%, P = 0.979) did not show significant heterogeneity, unlike the hepatectomy radical cure group (I^2 = 68.3%, P = 0.000), which showed a significant heterogeneity.

Single factor meta-regression was used to investigate the source of heterogeneity in the hepatectomy radical cure group. Three factors were investigated: the ethnic origin of the patients (Asian or other), the year of publication (before or after 2005), and whether the indication of hepatectomy was explicitly outlined. Following single factor meta-regression analysis, we found that the indication of hepatectomy according to the Bismuth-Corlette classification was an important factor affecting heterogeneity (P = 0.007). According to these results, a subgroup analysis was further performed on the indications of hepatectomy.

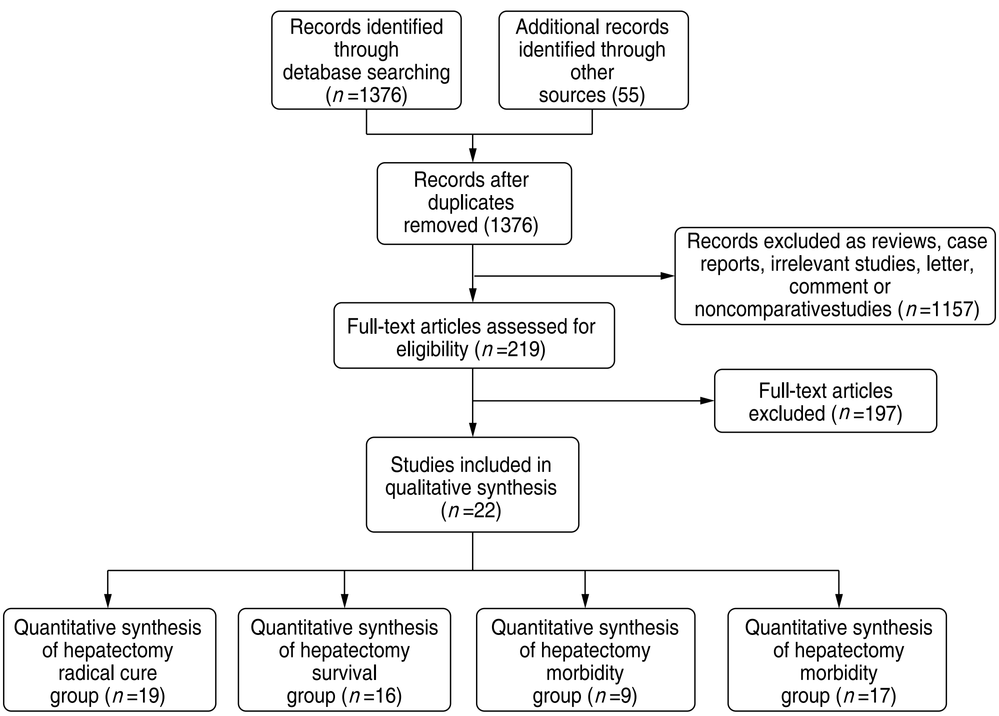

Fig. 1 Flow diagram representative of the study selection

Table 1 characteristics of include studies and the study groups belonged

First author	Newcastle-Ottawa Score	Publish year	Country	Study group
Capussotti L [8]	7	2002	Italy	2
Cho MS [10]	9	2012	South Korea	1, 2
de Jong MC [11]	7	2012	America	1, 2, 4
Hadjis NS [12]	7	1990	Britain	1, 2, 4
Jarnagin WR [15]	9	2001	America	1, 2, 3, 4
Klempnauer J [16]	7	1997	Germany	1, 2, 3, 4
Lim JH [19]	8	2013	South Korea	1, 2, 3, 4
Otani K [23]	8	2012	Japan	1, 2, 3, 4
Tabata M [26]	8	2000	Japan	1, 2, 3, 4
Lee SG [18]	7	2010	South Korea	1, 4
Ramesh H [24]	8	2004	India	1, 2, 4
Chen RF [9]	6	2007	China	1, 3, 4
Han SS [13]	7	2008	South Korea	1, 2, 4
Lee SG [17]	6	2000	South Korea	1, 4
Matsuo K [20]	8	2012	America	1, 2, 3, 4
Miyazaki M [21]	7	2007	Japan	2
Miyazaki M [22]	8	2010	Japan	1, 4
Song SC [25]	9	2013	South Korea	1, 2
Zervos EE [28]	6	2005	America	1, 4
Hirano S [14]	8	2010	Japan	1, 3, 4
Abd ElWahab [7]	7	2016	Egypt	2
Xiong J [27]	7	2015	China	1, 2, 3, 4

1, hepatectomy radical cure group; 2, hepatectomy survival group; 3, hepatectomy morbidity group; 4, hepatectomy morbidity group

Results

Meta-analysis for the hepatectomy radical cure group

In the 19 articles included in this group, a total of 2139 patients with HCCA were analyzed including 1648 patients who underwent combined partial hepatectomy and 491 patients who underwent simple bile duct resection. In the hepatectomy radical cure group, the collective radical cure rate was 76.09% (1254 / 1648) after combined partial hepatectomy, and the collective radical cure rate after simple bile duct resection was 51.93% (255 / 491). The radical resection rate in the combined partial hepatectomy group was significantly higher than in the simple bile duct resection group. The combined OR for the hepatectomy radical cure group was 0.32 (95% CI: 0.20–0.51) (Fig. 2). Out of the 19 articles, 6 reported surgical indications for different surgical procedures. One [23] reported combined hepatectomy for patients with Bismuth-Corlette III and IV HCCA, another article [24] reported simple bile duct resection for patients with Bismuth-Corlette I HCCA, and four articles [12, 14, 16, 28] reported simple bile duct resection for patients with Bismuth-Corlette I and II HCCA.

For the study group with high heterogeneity in the literature (I^2 = 68.3%, P = 0.000), we conducted a

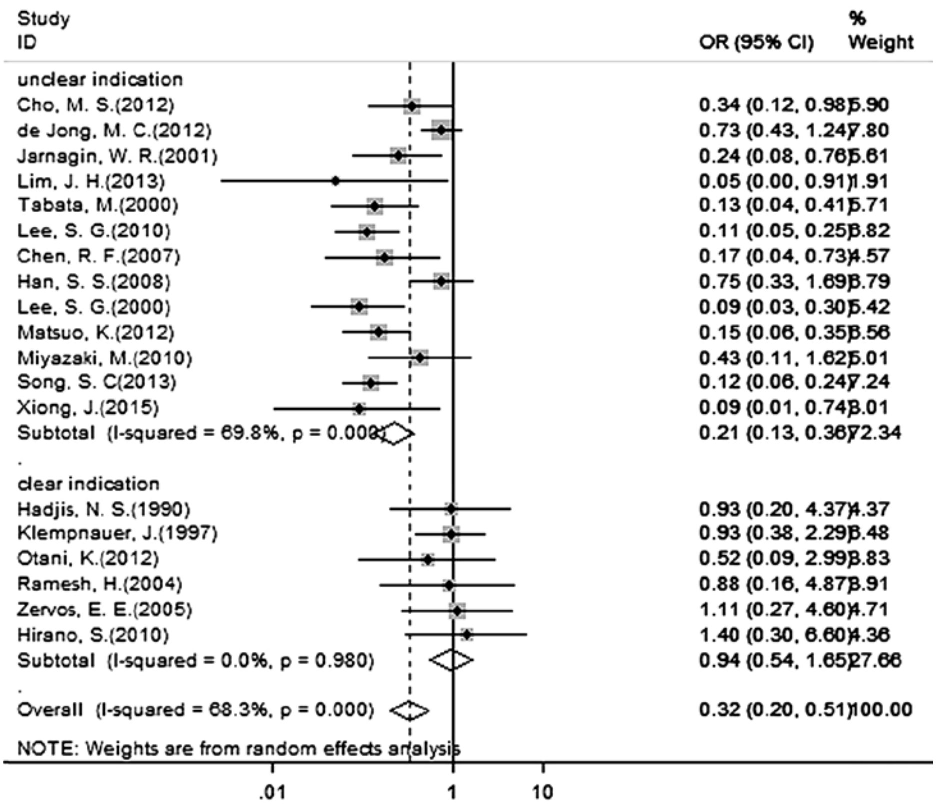

Fig. 2 Forest plot for the hepatectomy radical cure group Subgroup analysis according to the indication of hepatectomy is showed

meta-regression analysis based on the ethnic origin of patients (Asian or other), the year of publication (before or after 2005), and whether the indication of hepatectomy was explicitly expressed. We found that the indication of hepatectomy is an important factor affecting heterogeneity (P = 0.006). Subsequently, we used this factor as a grouping basis for the subgroup analysis. Subgroup analysis revealed that the heterogeneity was significantly reduced when combining the articles for the indication of hepatectomy (I^2 = 0.0%, P = 0.980) (Fig. 2). The pooled OR values suggest that when simple bile duct resection was chosen for patients with type I and II HCCA, this would not reduce the probability of radical resection due to the extent of resection (OR 0.94, 95% CI 0.54–1.65) (Fig. 2).

Meta-analysis for the hepatectomy survival group

In the 16 articles included in this group, a total of 1680 patients with HCCA were analyzed including 1188 patients who underwent combined partial hepatectomy and 492 patients who underwent simple bile duct resection. The reported 3-year survival rate for HCCA patients was between 30.5% [26] and 42%[25], and the 5-year survival rate between 20.2%[11] and 33%[25]. Out of the 16 articles, 7 [7, 10, 11, 15, 20, 21, 25] presented a HR value with a 95% CI. In the remaining 9 [8, 12, 13, 16, 19, 23, 24, 26, 27], we extrapolated the HR from the Kaplan-Meier curves using Tierney's method [3]. The collective HR from the 16 articles suggested that survival for HCCA patients after combined partial hepatectomy was significantly increased compared to that of patients who underwent simple bile duct resection (HR 0.67, 95% CI 0.58–0.79), (Fig. 3).

A subgroup analysis was subsequently performed according to the source of the HR. Following a Q test, the P value was lower than 0.10, therefore the fixed effect model was selected. Following the subgroup analysis, and regardless of whether HR were directly collected or extrapolated via indirect calculations, the collective HR suggested that survival for HCCA patients after partial hepatectomy was significantly increased compared to patients who underwent simple bile duct resection (Fig. 3).

Meta-analysis for the hepatectomy morbidity group

In the 9 included articles, a total of 782 patients with HCCA were analyzed including 583 patients who underwent combined partial hepatectomy and 199 patients who underwent simple bile duct resection.

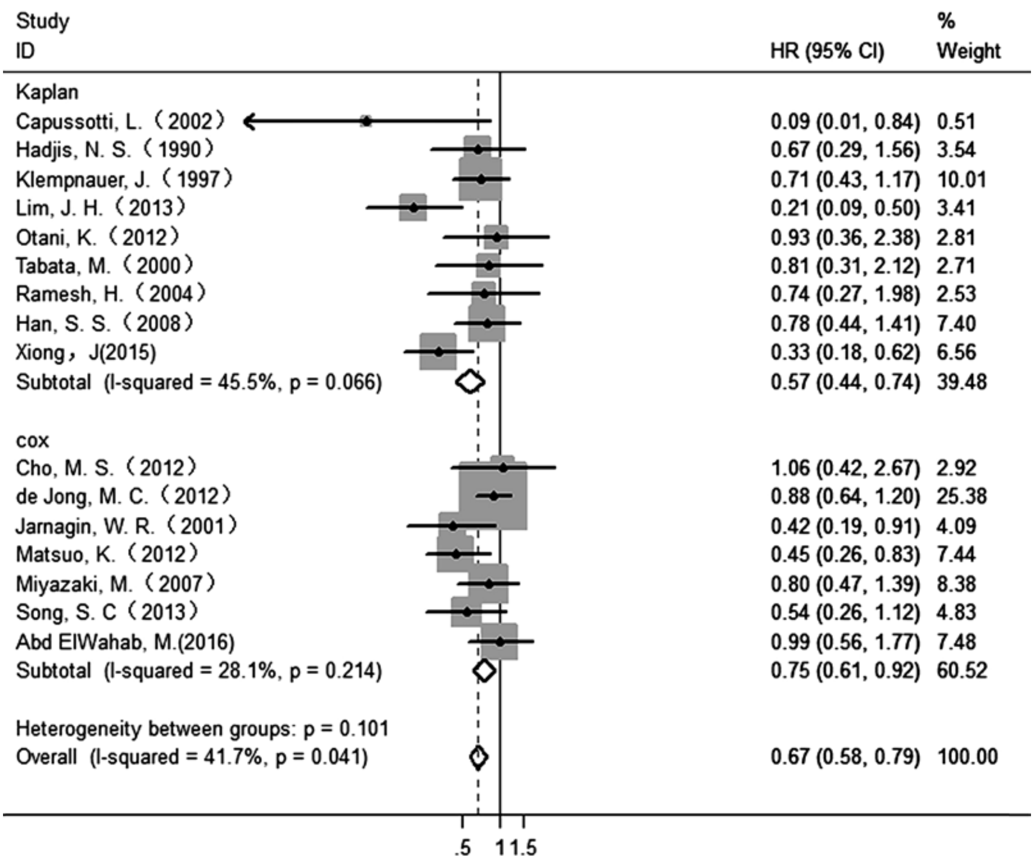

Fig. 3 Forest plot for the hepatectomy survival group Subgroup analysis according to the source of the HR value is showed.

Reported complications from surgery for HCCA included liver abscess, abdominal abscess, postoperative liver dysfunction, hyperbilirubinemia, intraperitoneal hemorrhage, bile leakage, portal vein thrombosis and others. To determine whether combined partial hepatectomy increased the risk of surgical complications, nine articles in the hepatectomy morbidity group were collectively evaluated. Following this analysis we found that complications occurred in 47.34% (276/583) of patients in the combined hepatectomy group, whereas they occurred in 30.15% (60/199) of patients in the simple bile duct resection group. The collective OR suggested that the risk of postoperative complications in the combined partial hepatectomy group was higher than in the simple bile duct resection group (OR 1.99, 95% CI 1.37–2.90) (Fig. 4).

In regards to the capabilities in the performance of the hepatectomy techniques and preoperative preparation techniques for the past ten years, a subgroup analysis was performed based on the year of publication of the articles, which were subdivided into two groups: publications before or after 2005. The calculated OR was 2.55 (95% CI 1.31–4.97) for the three studies published before 2005, and 1.76 (95% CI 1.12–2.77) for the five studies published after 2005 (including those published in 2005). The subgroup analysis showed that despite the risk of complications following combined partial hepatectomy being significantly higher than following simple bile duct resections after 2005, this risk was reduced when compared to those studies performed before 2005 (Fig. 4).

Meta-analysis for the hepatectomy mortality group

In the 17 articles included in this group, a total of 1792 patients with HCCA were analyzed including 1407 patients who underwent combined partial hepatectomy and 387 patients who underwent simple bile duct resection. Reported causes of death in HCCA patients included infections, liver failure and abdominal bleeding. To determine whether combined partial hepatectomy increased the risk of surgery-related mortality, 17 articles in the hepatectomy mortality group were collectively analyzed. After partial hepatectomy, 6.54% (92 / 1407) of patients with HCCA had died, compared to 2.07% (8 / 387) for patients in the simple bile duct resection group. One article [19] was excluded from this meta-analysis due to the absence of data on short-term postoperative death in both the reported groups. The collective OR suggested that the risk of short-term postoperative mortality in the combined partial hepatectomy group was higher than in the simple bile duct resection group (OR 2.71, 95% CI 1.47–4.98) (Fig. 5).

A subgroup analysis was performed based on the time of publication for each article, before or after 2005. The OR for the 6 papers published before 2005 was 3.43 (95% CI 1.33–8.84), and 2.25 (95% CI 1.01–5.00) for the 11

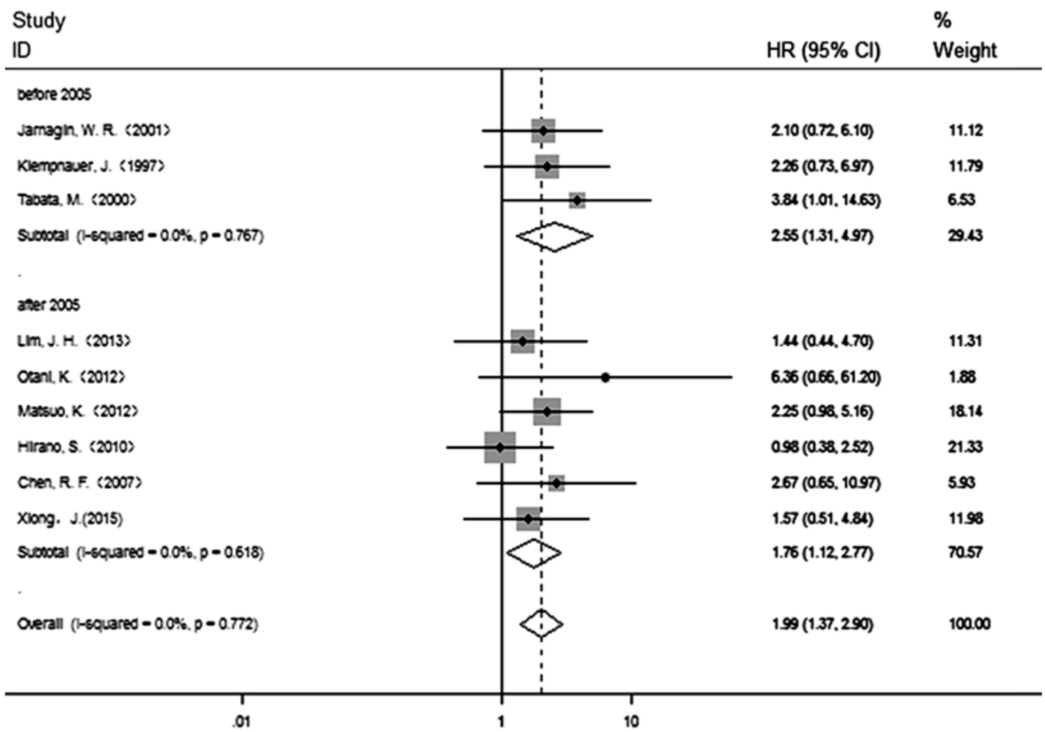

Fig. 4 Forest plot for the hepatectomy morbidity group Subgroup analysis according to the published date of the articles (before and after 2005) is showed

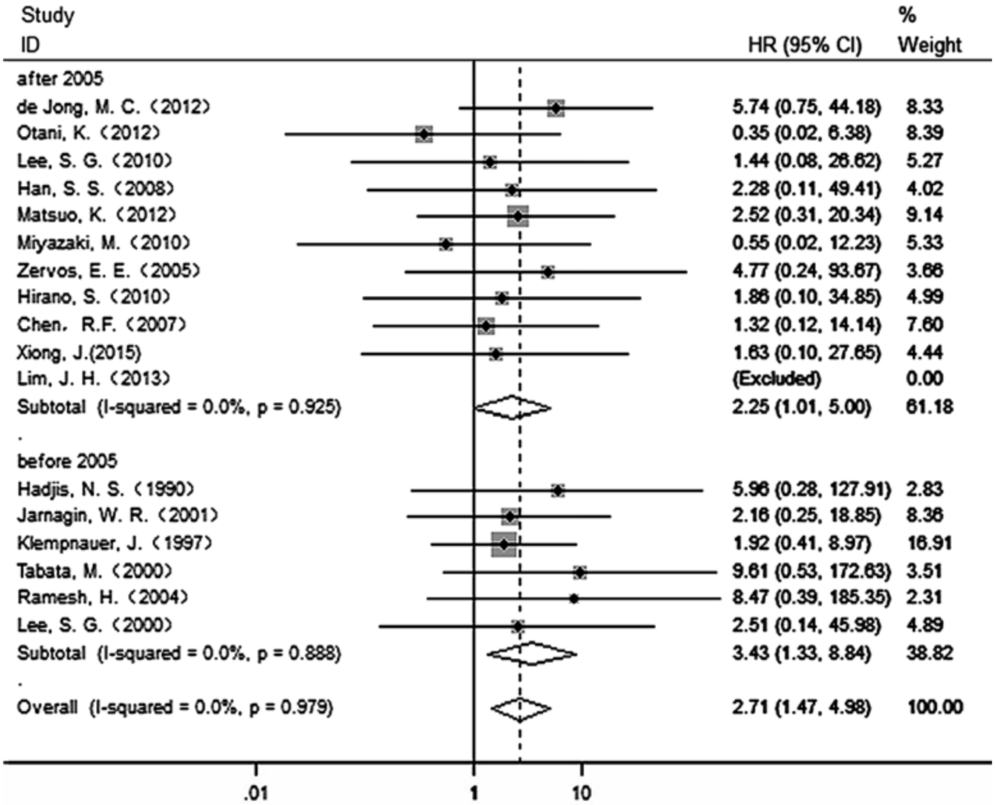

Fig. 5 Forest plot for the hepatectomy mortality group Subgroup analysis according to the published date of the articles (before and after 2005) is showed. Studies by Lim JH were excluded from meta-analysis due to the absence of data on short-term postoperative deaths in both groups

papers published in or after 2005 (with exception of Lim, *et al*[19]). The subgroup analysis showed that although the risk of short-term postoperative mortality after combined partial hepatectomy was significantly higher than after simple bile duct resection after 2005, this was reduced when compared to studies published prior to 2005 (Fig. 5).

Publication bias

To determine the publication bias in the included articles for each of the above groups, funnel diagrams were drawn (Fig. 6–9). The symmetry state indicated no publication bias in the 4 study groups selected. We also performed the Egger's test using Stata 12.0. No publication bias was found for the hepatectomy radical

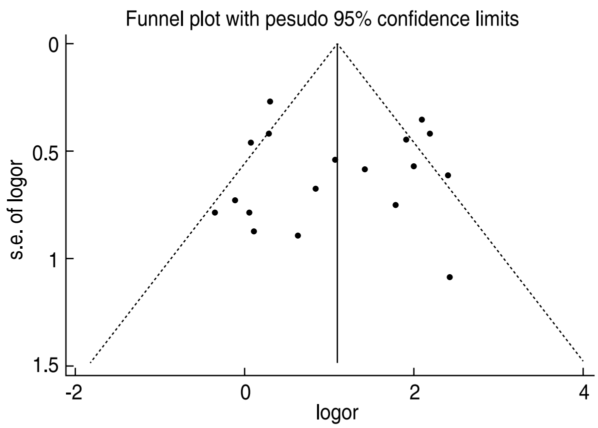

Fig. 6 Funnel plots for detection of publication bias in the hepatectomy radical cure group Studies are distributed symmetrically and suggest that publication bias is absent after meta-analysis

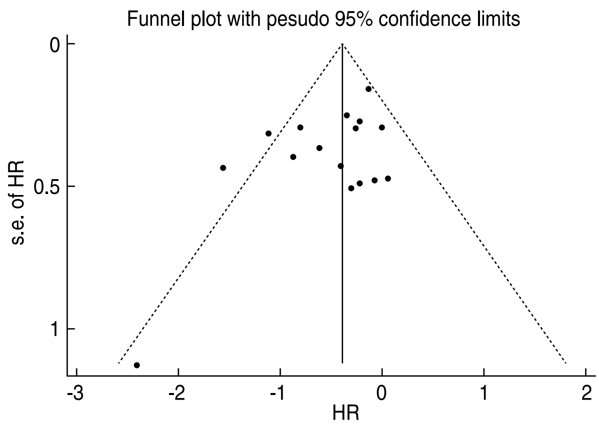

Fig. 7 Funnel plots for detection of publication bias in the hepatectomy survival group Studies are distributed symmetrically and suggest that publication bias is absent after meta-analysis

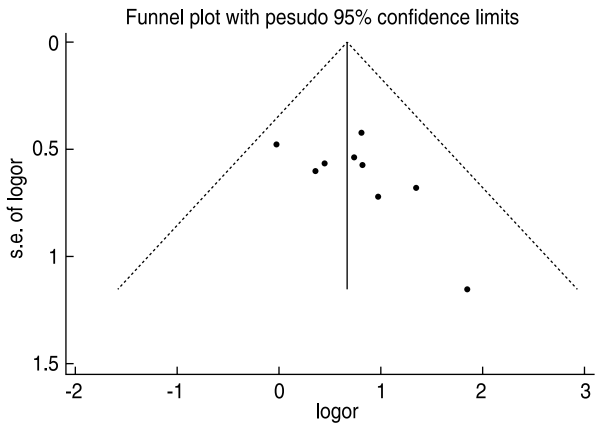

Fig. 8 Funnel plots for detection of publication bias in the hepatectomy morbidity group Studies are distributed symmetrically and suggest that publication bias is absent after meta-analysis

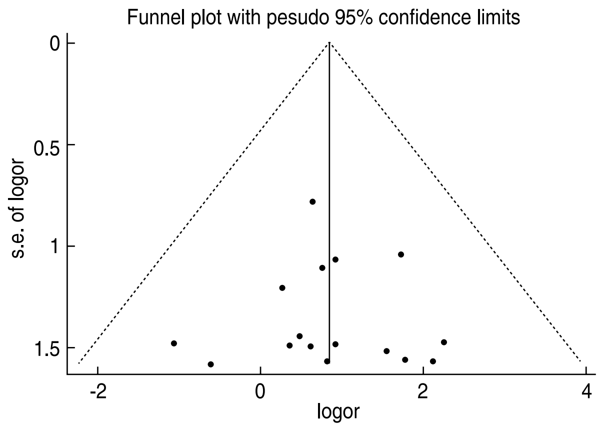

Fig. 9 Funnel plots for detection of publication bias in the hepatectomy mortality group Studies are distributed symmetrically and suggest that publication bias is absent after meta-analysis

cure group ($P = 0.686$), the hepatectomy survival group ($P = 0.082$), the hepatectomy morbidity group ($P = 0.109$) or the hepatectomy mortality group ($P = 0.991$).

Discussion

Altemeier *et al* [29] first reported 3 cases of primary sclerosing hilar cholangiocarcinoma in 1957. In the following decades, HCCA treatment strategies gradually improved. In 1965, Klatskin *et al* [30] first defined HCCA and described its clinical and pathological features in detail and systematically. In the 1970s, the treatment strategy for HCCA patients was to relieve the patient's jaundice using biliary drainage or U-tube drainage. Patients had a short overall survival, and high mortality rates after treatment [31–32]. In the 1980s, bile duct resection replaced bile duct drainage and achieved better outcomes for HCCA patients. However, due to limitations in the surgical resection range, the therapeutic outcomes for type III and IV HCCA patients were still unsatisfactory [33–34]. In the 1990s, Bismuth *et al* [35] proposed the use of simple cholecystectomy or partial hepatectomy for different types of HCCA to improve radical surgery and prolong patients' survival.

Currently, surgical methods used for HCCA patients include either extrahepatic biliary resection or biliary resection combined with hepatectomy. The extent of proximal bile duct resection includes a further 5-mm duct resection from the tumor site. The distal bile duct edge should be located at the upper edge of the pancreas. Extrahepatic biliary resection has a small resection range and may present with lower postoperative complications and low mortality. However, in the case of HCCA, the removal of the bile duct may not provide a R0 resection margin.

In this study, data derived from the hepatectomy radical cure group and the hepatectomy survival group showed that the cure rate for HCCA patients after partial hepatectomy was higher and survival times longer than after simple bile ducts resection. These results confirm that combined partial hepatectomy expands the extent of biliary resection, thereby increasing the chance of radical resection and prolonging postoperative survival.

Due to high heterogeneity in the hepatectomy radical cure group, we performed a subgroup analysis based on the Bismuth-Corlette classification. We found that when HCCA did not invade the second bile duct bifurcation, the choice of simple bile duct resection would achieve a similar outcome as a partial hepatectomy. Our study showed that simple bile duct resection remains a good option for the treatment of Bismuth-Corlette I, II, and well-differentiated HCCA, but this observation will need further confirmation in future clinical studies.

To ensure an R0 resection for HCCA, the location of the proximal bile duct resection is often higher or expands into the liver, resulting in higher incidences of bile leakage after bile duct anastomosis, with reported cases increased by 25.56% [36]. Combined partial hepatectomy may require removal of the left or right portion of the liver, and this can increase the risk of biliary fistula, hemorrhage and liver failure. In addition, some patients often present with endotoxemia, malnutrition, or anemia prior to surgery and subsequently, surgical trauma, and postoperative complications may directly lead to death in those patients. After review of the literature, postoperative complication rates for the combined hepatectomy group were found to be as high as 46.54%, and the postoperative mortality rates were 6.62%. Following a meta-analysis, the resulting OR showed that the complication rates in patients who underwent partial hepatectomy were significantly higher than in patients who underwent simple bile ductectomy. Common postoperative complications reported in the literature included infections, bile leakage, and intra-abdominal hemorrhage. Additionally, liver failure and short-term postoperative deaths in patients with poor liver reserves were common. Combined partial hepatectomy reduced the difficulty of surgery, but increased the incidence of surgical trauma, postoperative complications and mortality.

In this study, we found that combined hepatectomy increased radical cure and prolonged survival in patients with HCCA. However, in patients with poor general condition and poor liver reserve function, the risk of surgery should be carefully considered. Simple bile duct resection has proven to be a valuable technique for the treatment of hilar cholangiocarcinoma of Bismuth-Corlette type I and II.

HCCA is a relatively rare disease, and therefore it is challenging to conduct large-scale clinical studies. This study used a screening and combinatorial approach where meta-analysis was performed with the extracted data to increase the sample size. The conclusions provided here are evidence based.

This study did have some limitations. The search strategy used in this study yielded a high number of preliminary screening documents (748 articles). Therefore, there is a possibility that relevant literature might have been missed despite it being analyzed by two independent investigators. Due to the nature of HCCA surgery, literature included in this study pertained to retrospective cohort studies only, which could affect the reliability of our conclusions. Lastly, studies included here did not compare the postoperative outcomes for each of the Bismuth-Corlette classifications, and therefore we were unable to draw direct conclusions based on the Bismuth-Corlette's optimal surgical options.

Ethical statement

No ethical approval was obtained because the study did not involve a prospective evaluation, did not involve laboratory animals and the data collected was confidential in nature.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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DOI 10.1007/s10330-019-0390-0
Cite this article as: Yang M, Zhang YH, Cui MH, *et al*. Value of partial hepatectomy for the treatment of hilar cholangiocarcinoma: A meta-analysis study. Oncol Transl Med, 2019, 5: –.