Systematic Review and Meta-Analysis

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Effect of preoperative cholangitis on prognosis of patients with hilar cholangiocarcinoma

A systematic review and meta-analysis

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Abstract

Background: The aim of this study was to compare the clinical outcomes between patients with preoperative cholangitis and noncholangitis patients to determine whether the preoperative cholangitis would be able to serve as an independent predictive factor on hilar cholangiocarcinoma (HCC) outcomes.

Methods: A systematic literature search for reported preoperative cholangitis in patients with hilar cholangiocarcinoma was performed in 4 databases: PubMed, Web of Science, Embase, and the Cochrane Library, published from 1979 to 2017.

Results: In total, the initial search identified 1228 articles. Of these studies only 9 studies met the inclusion criteria and were included in this analysis. Differences between preoperative cholangitis existing and noncholangitis patients were observed in terms of mortality (RR = 2.29; 95% CI = 1.48–3.52; $P = .0002$), overall morbidity (RR = 1.15;95% CI = 1.00–1.32; $P = .04$), Liver failure (RR = 1.15;95% CI = 1.00–1.32; $P = .04$), Infection (RR = 1.52;95% CI = 1.16–2.00; $P = .003$), sepsis (RR = 2.40;95% CI = 1.25–4.5; $P = .008$).

Conclusions: The results lend support to the notion that in hilar cholangiocarcinoma patients, the existence of preoperative cholangitis is statistically associated with the higher postoperative mortality and morbidity. Also that it increases the risk of liver failure and infection. therefore, it is very important to properly control the preoperative cholangitis before surgery.

Abbreviations: CI = confidence interval, DFS = disease-free survival, HCC = hilar cholangiocarcinoma, OS = overall survival, RR = relative risk, SSI = surgical site infection.

Keywords: hilar cholangiocarcinoma, morbidity, mortality, preoperative cholangitis, prognosis

1. Introduction

Hilar cholangiocarcinoma (HCC), also labeled as Klatskin tumor, was firstly reported by Altemeier et al[1] in 1957. It is a cholangiocarcinoma that occurs between the opening of the cystic duct and the secondary branches of the right and left hepatic ducts. According to the Bismuth-Corlette system HCC can be divided into 4 types: tumors for type I infiltrate the common hepatic duct, tumors for type II invade the hilus, tumors for type IIIA/B affect the right or left hepatic duct, and tumors for type IV symbolize both right and left hepatic ducts and the subsegments have been invaded,[2] which preoperative assessment aid us with evaluating local tumor spread and determining the extent of resection for HCC.[3] Studies have revealed that complete resection of HCC with histologically negative margins provides a better possibility for long-time survival postoperatively.[4,5]

Radical resection (R0 resection) appears to be the best approach to achieve higher long-term survival rate for patients with HCC.[6] It was reported that when the radical removal rate was 19% to 75%, the 5-year survival rate reached 10% to 44%.[7–9] Surgical radical resection should include hemihepatic, caudate resection, hepatic portal lymph node dissection, and vascular resection if vascular system was also involved.[10,11]

Diagnosis of preoperative cholangitis has traditionally been made by following the criteria: *Temperature*: body temperature is higher than 38°C. *Liver function*: abnormalities in liver function test results and exception of jaundice. *Symptoms*: the upper right abdominal pain in the presence of a positive bile culture.[12,13] It has been reported that the existence of preoperative cholangitis in patients with HCC is closely related to the incidence of postoperative complications such as liver failure, infection, sepsis, and persistent biliary anastomotic leakage.[14] It is even reported that preoperative cholangitis affected the postoperative survival of patients with HCC.[15] However, it has not been studied whether preoperative cholangitis will affect the prognosis of patients with HCC after radical resection.

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The aim of this study is to determine whether preoperative cholangitis will affect the mortality, morbidity, liver failure, infection, sepsis, and survival of patients with HCC after radical resection.

2. Methods

2.1. Literature research

A comprehensive literature search was performed using PubMed, EMBASE, the Cochrane Library and the Web of Science. The keywords and key phrases used for search include: "hilar bile duct neoplasms or hilar bile duct carcinoma or Klatskin tumor or perihilar cholangiocarcinoma or hilar cholangiocarcinoma" and "cholangitis or angiocholitis or choledochitis." According to the criteria of evaluation and exclusion, all titles and abstracts, full texts if needed, were reviewed. The differences are revealed by consensus. The papers include cross reference to find further relevant research. We also searched for the references contained in the original studies by hand to identify studies that were missing in the initial search. All procedures were approved by the ethics committee for human experiments of the First Hospital of Lanzhou University.

2.2. Study selection criteria

Whether the published studies included preoperative cholangitis and postoperative hilar cholangiocarcinoma related research. Those studies that have no enough data to extract, or unrelated cancers studies (for example, distal bile duct cancer, gallbladder cancer, pancreatic cancer), or HCC studies without operation information were excluded.

2.3. Data extraction

Data extraction was performed independently by 2 researchers (YW and WF), with the discrepancies resolved by the consensus of these 2 researchers (any differences on a contradictory research are solved through full discussion). Information includes authors, years of publication, countries, number of patients, average age range, gender, and postoperative outcomes. The main results were postoperative complications, including mortality, morbidity, infection, and liver failure.

2.4. Statistical analysis

The software Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration 2014) was used to do data analysis. The risk ratio (RR) for each trial was calculated from the number of evaluable patients. Also the RRs with their 2-sided 95 % confidence intervals (CIs) were used for dichotomous outcomes as the confirmatory effect size estimate and test criterion. The fixed-effect model was applied. The hypothesis tests were based on the 95 % CIs, and the P values were used for illustration. Funnel plots were also constructed to look for potential publication bias. We used the χ^2 test to evaluate heterogeneity between trials and the I^2 statistic to assess the extent of the inconsistency, wherein an I^2 test $>50\%$ suggests significant heterogeneity. Statistical heterogeneity was assessed using an I^2 test and was categorized into low ($<50\%$), moderate (51%–75%), or high ($>75\%$) groups according to predefined criteria.

3. Results

The initial search identified 1228 articles based on the search keywords and phrases. Around 9 retrospective cohort studies were eligible to be included in the study and the data were extracted for this systematic review and meta-analysis. Search procedure and the results are displayed in Figure 1. Of these data, the study reported by Michio et al[16] studying 118 patients with advanced carcinoma (the gallbladder and the proximal bile duct cancers) involved the hepatic hilus. Table 1 provides the detailed information about these 9 studies[14,16–23] that were included in the systematic review and meta-analysis. No randomized control trial was included, the quality of the studies included in the meta-analysis was assessed by the NOS scale. Overall, an average medium quality (5 out of 9 stars) was achieved in all studies (range 5–6). Table 2 illustrated the effect of preoperative cholangitis on patients with hilar cholangiocarcinoma.

3.1. Primary outcomes: morbidity and mortality

Postoperative morbidity was identified in 7 studies[14,16,18,19,21–23] (n = 638 patients) in total. The RR and 95% CI for each study and the pooled RR are shown in Figure 2. In https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5671862/figure/F2/the fixed effects model (RR = 1.15; 95% CI = 1.00–1.32), heterogeneity testing revealed $I^2 = 79\%$ and revealed a significant difference in the incidence of overall complications in favor of the no-cholangitis ($P = .04$).

Six out of the 7 studies[14,16–18,22,23] provided the data (n = 491 patients) on the incidence of mortality. The RR and 95% CI for each study and the pooled RR are shown in Figure 3. The overall summary estimated RR was 2.29 (95% CI: 1.48–3.52; $P = .0002$). Heterogeneity testing revealed $I^2 = 60\%$ and the P value for heterogeneity is .06, when analyzed using a fixed-effect model.

3.2. Secondary outcomes: the incidence of hepatic failure, infection and sepsis

3.2.1. Hepatic failure. Data were extracted from 7 studies[14,16,18,19,21–23] (n = 638 patients) on the incidence of hepatic failure. The RR and 95% CI for each study and the pooled RR are shown in Figure 4. The fixed effects model (RR = 1.15; 95% CI = 1.00–1.32) showed a significant difference in the incidence of hepatic failure, in favor of the no-cholangitis group ($P = .04$). Heterogeneity testing revealed $I^2 = 79\%$.

3.2.2. Infection. Four studies[14,16–18] provided the data (n = 360 patients) on the incidence of infection. Of them, one study reported by Jun et al[16] compared surgical site infection (SSI) between preoperative cholangitis and noncholangitis patients. The RR and 95% CI for each study and the pooled RR are shown in Figure 5. The fixed effects model (RR = 1.52; 95% CI = 1.16–2.00) showed a significant difference in the incidence of infection, in favor of the no-cholangitis group ($P = .003$). Heterogeneity testing revealed $I^2 = 74\%$.

3.2.3. Sepsis. Three studies[14,16,18] provided the data (n = 279 patients) on the incidence of sepsis. The RR and 95% CI for each study and the pooled RR are shown in Figure 6. The fixed effects model (RR = 2.40; 95% CI = 1.25–4.59) showed a significant difference in the incidence of sepsis in favor of the no-cholangitis group ($P = .008$). Heterogeneity testing revealed $I^2 = 79\%$.

3.2.4. Publication bias. The funnel plot (Fig. 7) showed no evidence of noticeable asymmetry. Egger test similarly showed no publication bias (Egger t value = −1.37 $P = .229$).

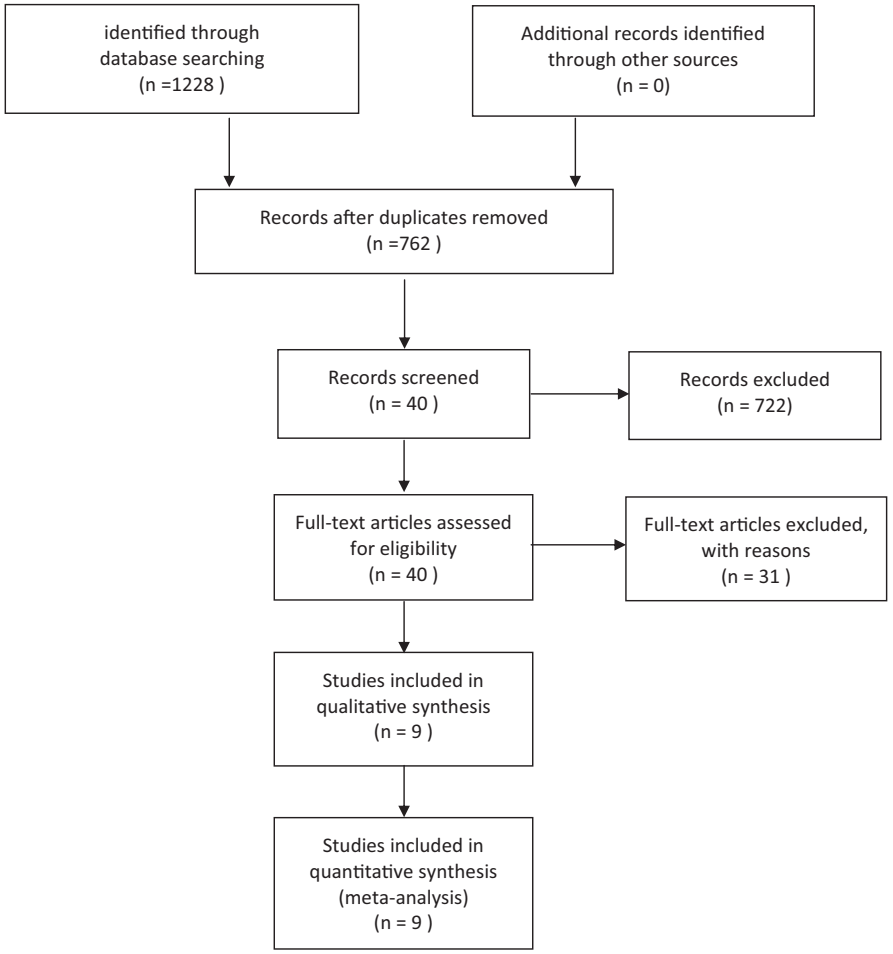

Figure 1. Search flow diagram.

4. Discussion

Radical resection is standard of care and is the only method of long-term survival for patients with HCC.[6] Surgical resection of hilar cholangiocarcinoma often requires hemi hepatectomy and complete caudate lobectomy in order to achieve R0 resection.[24] Some surgeons advocate that biliary drainage should be performed before surgery.[25] The biliary drainage method mainly includes percutaneous transhepatic biliary drainage (PTBD), endoscopic nasobiliary drainage (ENBD), and endoscopic biliary stenting (EBS). But most of these operations will induce cholangitis. Doctors have made some effort to avoid cholangitis, but the effect is not satisfactory. It is not clear whether preoperative cholangitis will lead to poor prognosis of patients with hilar cholangiocarcinoma after radical surgery. We found that (primary sclerosing cholangitis) PSC patients had significantly higher overall survival and disease-free survival compared with non-PSC patients.[26] However, some studies showed that preoperative cholangitis considered as an independent predictor of postoperative morbidity,[19,27] was associated with worse short-term outcomes such as postoperative hospitali-

Table 1

Characteristics of included studies.

Author	Year	Country	Years of study	Bismuth–Corlet type					Type of study	Mean age, years	Male/female	Score NOS
				I	II	IIIa	IIIb	IV				
Jun et al[17]	2009	Japan	1988–2005	4	14	30	11	22	R	68 (35–82)	52/29	6/9
Dario et al[14]	2016	America	1996–2013	NA	25	55	40	13	R	66 (35–84)	84/49	5/9
Tsuyoshi et al[19]	2006	Japan	2000–2004			NA			R	66 (34–78)	71/31	6/9
Yoh et al[18]	2000	Japan	1987–1998			NA			R	63.3	20/8	5/9
Michio et al[16]	1996	Japan	1979–1993			NA			R	60.3 (33–79)	63/55	6/9
Su et al[23]	1995	TaiWan China	1983–1995	8	11	10	17	3	R	62 (32–74)	34/15	6/9
Pim et al[20]	2017	The Netherlands	1997–2014	26	115		74	2	R	64.5 (56–74)	146/71	5/9
Satoshi et al[21]	2009	Japan	2001–2008	88				38	R	68.5 (40–82)	115/31	6/9
MichaeF et al[22]	2000	The Netherlands	1983–1998	14	38	28	26	4	R	59.9 (18–74)	69/43	6/9

NOS = Newcastle–Ottawa score, R = retrospective analysis, R = retrospective clinical study.

Table 2

The characteristics of preoperative cholangitis-related outcomes of included studies.

Author	Preoperative cholangitis	Morbidity n (%)	Mortality n (%)	Hepatic failure n (%)	SSI n (%)	Sepsis n (%)	DIC n (%)	Bile leakn (%)
Dario et al[14]	Yes	40 (95)	NA	14 (33)	NA	5 (12)	NA	13 (31)
	No	62 (68)	NA	15 (16)	NA	12 (13)	NA	20 (22)
Jun et al[17]	Yes	NA	4 (6)	NA	12 (80)	NA	NA	NA
	No	NA	5 (33)	NA	49 (74)	NA	NA	NA
Yoh et al[18]	Yes	13 (86.7)	5 (33.3)	8 (53)	NA	11 (85)	9 (60)	NA
	No	10 (76.9)	0	1 (8)	NA	0	3 (23)	NA
Michio et al[16]	Yes	13 (59)	8 (36.4)	11 (50)	NA	5 (22.7)	NA	NA
	No	32 (33.3)	15 (15.6)	23 (24)	NA	7 (7.3)	NA	NA
Tsuyoshi et al[19]	Yes	8 (89)	NA	NA	NA	NA	NA	NA
	No	43 (46)	NA	NA	NA	NA	NA	NA
Su et al[23]	Yes	81 (34.8)	2 (8.7)	NA	NA	NA	NA	NA
	No	15 (57.7)	3 (11.5)	NA	NA	NA	NA	NA
Pim et al[20]	Yes	28 (54)	NA	NA	NA	NA	NA	NA
	No	24 (16)	NA	NA	NA	NA	NA	NA
Satoshi et al[21]	Yes	7 (35)	NA	NA	NA	NA	NA	NA
	No	49 (46)	NA	NA	NA	NA	NA	NA
MichaeF et al[22]	Yes	10 (53)	3 (15)	NA	NA	NA	NA	NA
	No	45 (72)	14 (23)	NA	NA	NA	NA	NA

DIC = disseminated intravascular coagulation, NA = not available, SSI = surgical site infection.

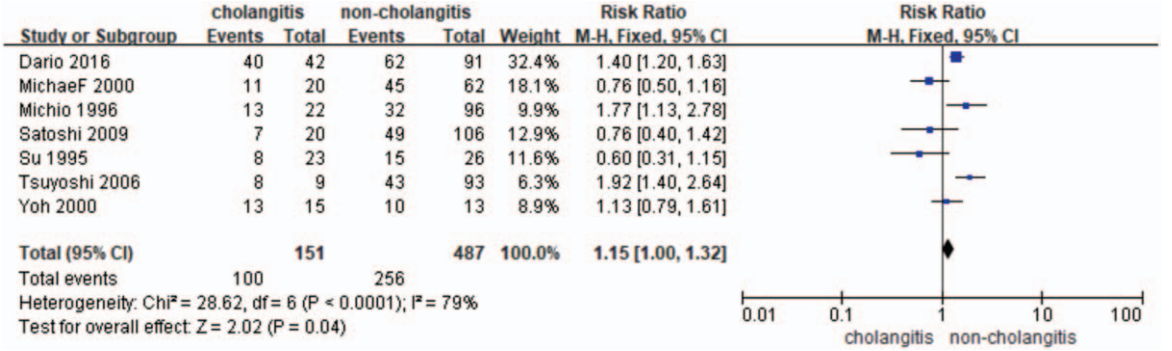

Figure 2. Forest plot for morbidity (cholangitis vs noncholangitis).

zation, in-hospital mortality, and postoperative infectious complications for patients with hilar cholangiocarcinoma after radical resection.[28,29] Therefore, more study needed to be done to draw a clearer conclusion.

The present study demonstrated that by controlling the incidence of preoperative cholangitis, postoperative morbidity and mortality reduced, and also improved long-term patient prognosis.[30] Therefore, sufficient management of preoperative cholangitis is highly recommended for HCC patients who has cholangitis. As such, the current study is important because the data demonstrated that through careful management of preoperative cholangitis, the margin of long-term survival

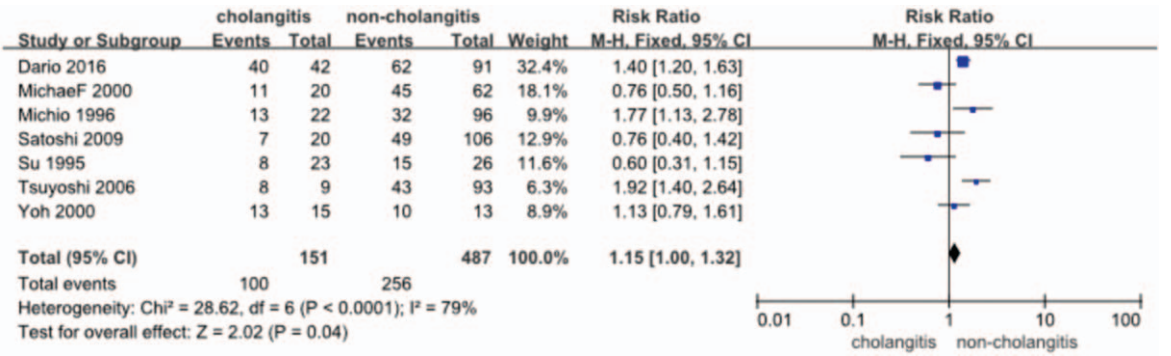

Figure 3. Forest plot for mortality (cholangitis vs noncholangitis).

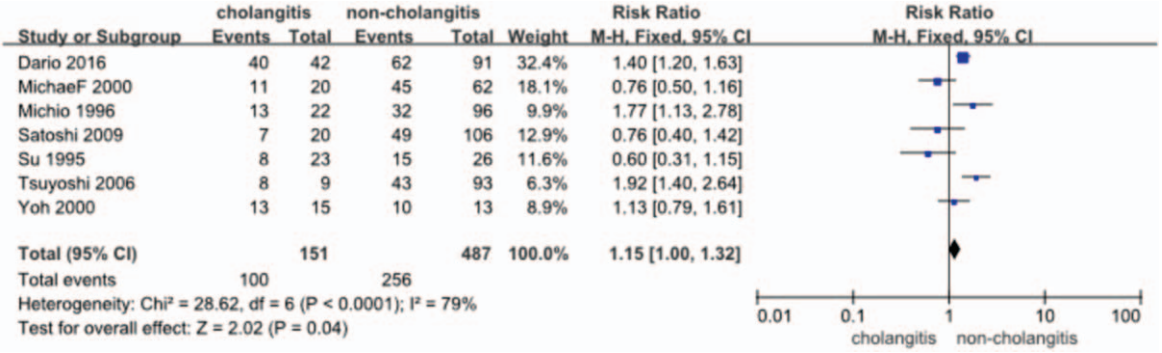

Figure 4. Forest plot for the incidence of hepatic failure (cholangitis vs noncholangitis).

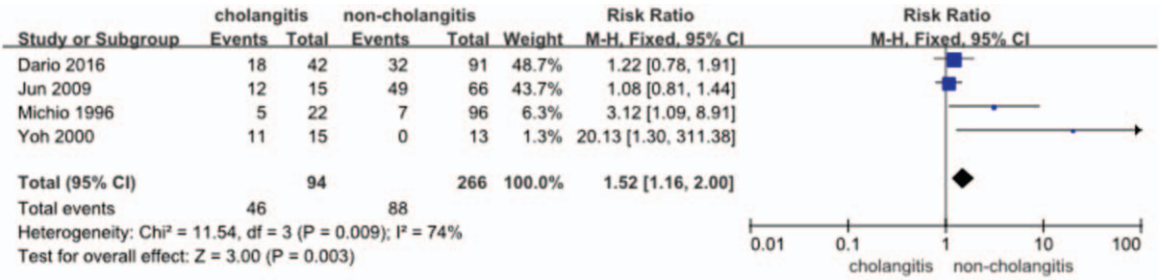

Figure 5. Forest plot for the incidence of infection (cholangitis vs noncholangitis).

without increasing postoperative morbidity can be achieved. No recommendations have been reached regarding to the most appropriate drainage method.[31] Tang et al[32] showed that PTBD should be used as the initial method of biliary drainage in type III or IV patients to reduce the incidence of procedure-related cholangitis, pancreatitis, and to improve the rates of palliative relief of cholestasis. For patients who had major hepatectomy, ENBD was recommended for biliary drainage to save the liver function due to its more sufficient potency and less preoperative cholangitis compared to endoscopic retrograde biliary drainage (ERBD).[33,34] Complete preoperative drainage of the FLR (future liver remnant) segments corelates with lower postoperative mortality in patients with an FLR volume below 50%. By contrast, there is lack of evidence to support preoperative biliary drainage in the presence of an FLR volume above 50%. For these patients, the risk of cholangitis and associated mortality developing after drainage seems to outweigh the questionable benefit of biliary decompression.[35]

In this meta-analysis, for the first time we extracted all qualified published data comparing the complications associated with preoperative cholangitis in patients with hilar cholangiocarcinoma and pooled them together. The primary outcome showed that preoperative cholangitis is closely associated with higher risk of morbidity and mortality in patients with hilar cholangiocarcinoma, compared to that of noncholangitis. Seven studies including 638 patients with hilar cholangiocarcinoma provide postoperative morbidity data. The postoperative overall morbidity was 66.23% (100/151) of patients in preoperative cholangitis group compared to 52.57% (256/487) in the noncholangitis group. Six studies including 491 patients with hilar cholangiocarcinoma provide postoperative mortality data. The postoperative mortality was 24.09% (33/137) in patients with preoperative cholangitis compared to the rate of 11.58% (41/354) in the noncholangitis group.

The second outcome demonstrated that the incidence of hepatic failure, infection, and sepsis were significantly higher in

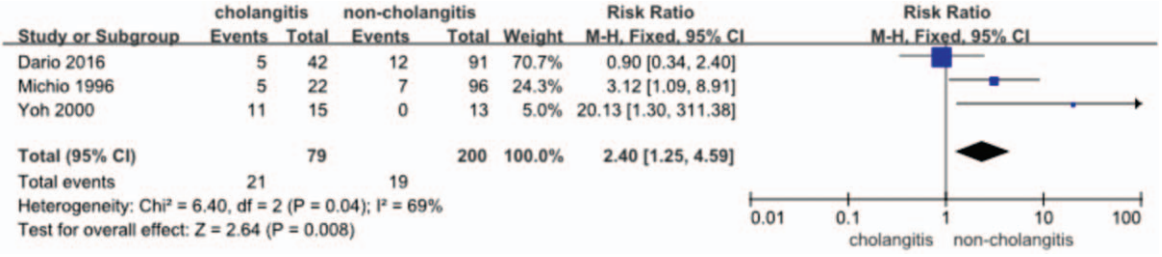

Figure 6. Forest plot for the incidence of sepsis (cholangitis vs noncholangitis).

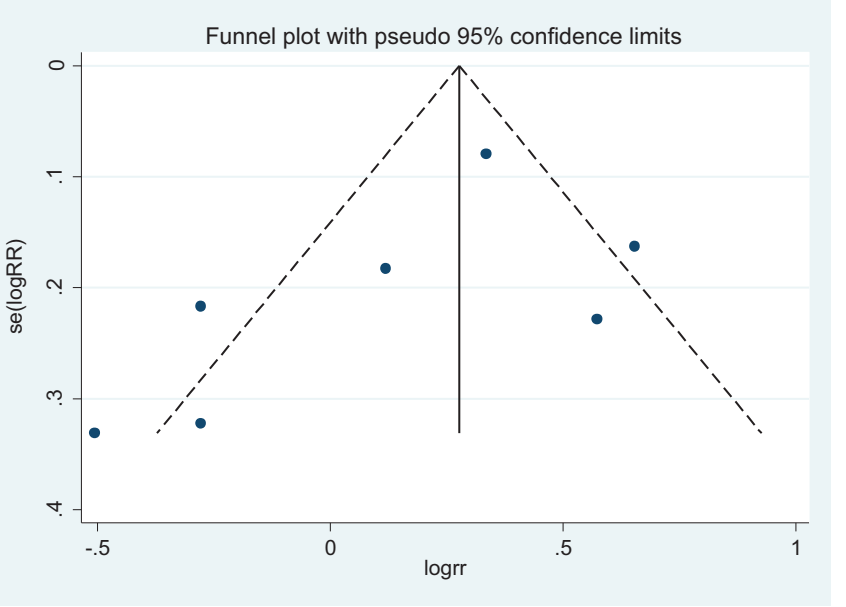

Figure 7. Funnel plot for publication bias (postoperative morbidity between cholangitis and noncholangitis).

the preoperative cholangitis group than those in the non-cholangitis group. Because the lack of sufficient studies to describe the overall survival, it is not possible to make Forest plot. In univariate analysis, preoperative cholangitis patients had significantly reduced overall survival (5-year estimate 29.9%) compared to noncholangitis patients (40.5%) ($P = .009$).[36] And cholangitis was associated with a significant decrease in both disease-free and overall survival.[30]

For the first time, we show here an independent and strong association of preoperative cholangitis with an increased risk of death and postoperative complications, such as liver failure, infection, sepsis, and persistent biliary anastomotic leakage, and a poor prognosis from R0 resection of hilar cholangiocarcinoma. That preoperative cholangitis frequently results in postoperative complications were shown in several studies, nevertheless, these previous studies failed to find a direct link between preoperative cholangitis and considerable risk of main complications or deaths after R0 resection, indicating that the exact effect of cholangitis on post-resection prognosis, in the light of these evidence, was poorly defined and difficult to evaluate.

This meta-analysis still has limitations. First, the included studies are retrospective and some of them with a limited sample size. Second, due to the paucity of data, we were not able to compare overall survival in patients with cholangitis versus no-cholangitis patients, and we were also unable to perform a subgroup analysis based on the type of malignancy, the method of surgery. Third, with the advances in technology, the result should also be affected in the different study period of the included studies (3 of these[16,22,23] were published before 2000).

The advantage of this meta-analysis was the use of the high-quality methodology of statistical analysis, which incorporated many patients associated with this study. The new test is included in this study, adding the latest published data, and this study still the first systematic analysis assessing the preoperative cholangitis-related complications for patients with HCC.

In conclusion, evidence was provided in this systematic review and meta-analysis that higher overall morbidity, mortality, and other complications were concerned with preoperative cholangitis. Additionally, further randomized control trials should be performed to confirm our conclusions. We confirm that preoperative cholangitis directly affects the outcomes after radical resection in patients with hilar cholangiocarcinoma, so, effective strategies should be carried out to reduce the risk of preoperative cholangitis and improve the prognosis of patients with HCC.

Author contributions

Wenbo Meng, Wence Zhou and Xun Li: study concept and design, study supervision, critical revision of the manuscript and funding obtaining.
Wengkang Fu: data collection, extraction, statistical analysis and interpretation; critical revision of the intellectual content of the manuscript.
Yudong Wang: study concept and design; data collection, extraction, statistical analysis and interpretation; manuscript drafting; critical revision of the intellectual content of the manuscript.
Zengwei Tang: critical revision of the intellectual content of the manuscript.
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Formal analysis: Yudong Wang, Wenkang Fu, Zengwei Tang.
Funding acquisition: Wenbo Meng.
Investigation: Yudong Wang, Wenkang Fu, Zengwei Tang.
Methodology: Yudong Wang, Wenkang Fu.
Resources: Yudong Wang, Wenkang Fu.
Software: Yudong Wang, Wenkang Fu.
Supervision: Wenbo Meng, Wence Zhou, Xun Li.
Writing – original draft: Yudong Wang.
Writing – review & editing: Yudong Wang, Wenkang Fu, Zengwei Tang, Wenbo Meng, Wence Zhou, Xun Li.

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