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REVIEW ARTICLE – HEPATOBILIARY TUMORS

Systematic Review and Meta-Analysis of Prognostic Factors for Early Recurrence in Intrahepatic Cholangiocarcinoma After Curative-Intent Resection

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ABSTRACT

Background. Recurrence rates of intrahepatic cholangiocarcinoma (iCCA) after curative hepatectomy are as high as 50% to 70%, and about half of these recurrences occur within 2 years. This systematic review aims to define prognostic factors (PFs) for early recurrence (ER, within 24 months) and 24-month disease-free survival (DFS) after curative-intent iCCA resections.

Methods. Systematic searching was performed from database inception to 14 January 2021. Duplicate independent review and data extraction were performed. Data on 13 predefined PFs were collected. Meta-analysis was performed on PFs for ER and summarized using forest plots. The Quality in Prognostic Factor Studies tool was used for risk-of-bias assessment.

Results. The study enrolled 10 studies comprising 4158 patients during an accrual period ranging from 1990 to 2016. In the risk-of-bias assessment of patients who experienced ER after curative-intent iCCA resection, six studies were rated as low risk and four as moderate risk (49.6%; 95% confidence interval [CI], 49.2–50.0). Nine studies were pooled for meta-analysis. Of the postoperative PFs, multiple tumors, microvascular invasion, macrovascular invasion, lymph node metastasis, and R1 resection were associated with an increased hazard for ER or a reduced 24-month DFS, and the opposite was observed for receipt of adjuvant chemo/radiation therapy. Of the preoperative factors, cirrhosis, sex, HBV status were not associated with ER or 24-month DFS.

Conclusion. The findings from this systematic review could allow for improved surveillance, prognostication, and treatment decision-making for patients with resectable iCCAs. Further well-designed prospective studies are needed to explore prognostic factors for iCCA ER with a focus on preoperative variables.

Intrahepatic cholangiocarcinoma (iCCA) is the second most common type of primary liver cancer, with an incidence of 0.85 per 100,000 annually.[1,2] Although iCCA is a rare and complex disease, its incidence in in North America has increased almost five-fold, and the reasons for this increase are not clear.[3,4] Surgery remains the mainstay therapy for curative intent, but only about 20% of iCCAs are surgically resectable at the time of diagnosis. In addition, the recurrence rates after liver resection (LR) are exceedingly high, reaching 50–70% and leaving limited treatment options.[5–7] In fact, most of the recurrence occurs relatively early, about 25% within 6 months and 50% within 2 years after surgery.[8]

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In the current literature, the definition of early recurrence (ER) after curative-intent surgery for iCCA varies from 12 to 24 months.[9,10] The identified risk factors for ER of iCCA are age, cirrhosis, hepatitis B (HBV), carbohydrate antigen 19-9 (CA19-9), tumor size, number of tumor lesions, and lymph node metastases (LNM).[8–11] The cited studies are limited by their small samples, with heterogenicity observed in the measured choice of prognostic factors.[12–14] Moreover, none of the few iCCA recurrence risk stratification tools described in the literature provides a comprehensive summary of the prognostic factors for ER.[15–21] The high recurrence rates underscore the need for better identification of patients with a greater risk for ER both before and after surgery who might benefit from alternative treatment sequencing strategies such as neoadjuvant and/or adjuvant chemotherapy.[22]

The primary objective of this systematic review and meta-analysis was to define prognostic factors for ER, within 24 months after surgery, in adult patients undergoing curative-intent resection of iCCA. The secondary objective was to define prognostic factors for 24-month disease-free survival (DFS) after curative-intent resection of iCCA. This report provides the most up-to-date evidence for identification of patients at highest risk for iCCA ER after curative-intent surgery.

METHODS

Protocol and Reporting

The protocol for this study was registered with PROSPERO (ID 247079).[23] This review was conducted according to the Cochrane Collaboration handbook guidelines and reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.

Eligibility Criteria

The included articles were randomized/quasi-randomized trials and cohort studies that evaluated the effect of any prognostic factor on the recurrence of iCCA within 24 months after curative intent surgery among adults 18 years of age or older. Studies were considered eligible for inclusion if they reported the absolute rate of iCCA recurrence stratified by a prognostic factor within 24 months after curative-intent surgery (primary outcome), or if they reported the absolute rate of other common cancer outcome measures such as DFS or recurrence-free survival (subsequently denoted as DFS) within 24 months after curative-intent surgery. The study excluded review articles, meta-analyses, case series, and cross-sectional studies, as well as research in progress, conference proceedings/abstracts, dissertations/theses, and book chapters.

The included studies were specific to histologically confirmed, de novo iCCA. Studies evaluating other common hepatobiliary malignancies such as extrahepatic cholangiocarcinoma, hilar cholangiocarcinoma, gallbladder cancer, hepatocellular carcinoma, or concomitant diseases were excluded.

Information Sources and Search Strategy

An academic hospital information specialist (M.E.) developed the search strategies in conjunction with all the authors (Appendix 1). Key search terms were determined from a scoping search of the literature and consultation with experts in the field. The databases Medline, Medline In-Process/ePubs, Embase, Cochrane Central Register of Controlled Trials (CCTR), and the Cochrane Database of Systematic Reviews (CDSR) all were searched via the Ovid platform from inception of the review to 14 January 2021. The search component blocks used were "cholangiocarcinoma" and "intrahepatic" and "recurrence" and "surgery," and "early." All the components included controlled vocabulary and text word terms. The searches were limited to humans and adults, with conference materials removed when possible. No language limits were applied. Citations of all the included studies were searched, and the first 100 hits from Google Scholar also were searched manually for augmenting studies. No gray literature was searched. Plans were made to contact study authors only if clarification was needed.

Study Selection Process

Article abstracts identified in the search were independently screened by two authors (W.J.C. and P.J.W.), and those not meeting the eligibility criteria were excluded (Fig. 1). The same two reviewers then assessed the full-text articles. Reviewer disagreements were resolved by consensus and involvement with a third reviewer (G.S.) as needed. Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) was used for screening and full-text selections.

Data Collection Process

The included studies had baseline characteristics and outcome data extracted in duplicate using a piloted, standardized template designed by the authors (W.J.C. and P.J.W.). The data were entered and maintained in Microsoft Excel (Microsoft, Redmond, WA, USA), and accuracy was verified by comparisons between authors.

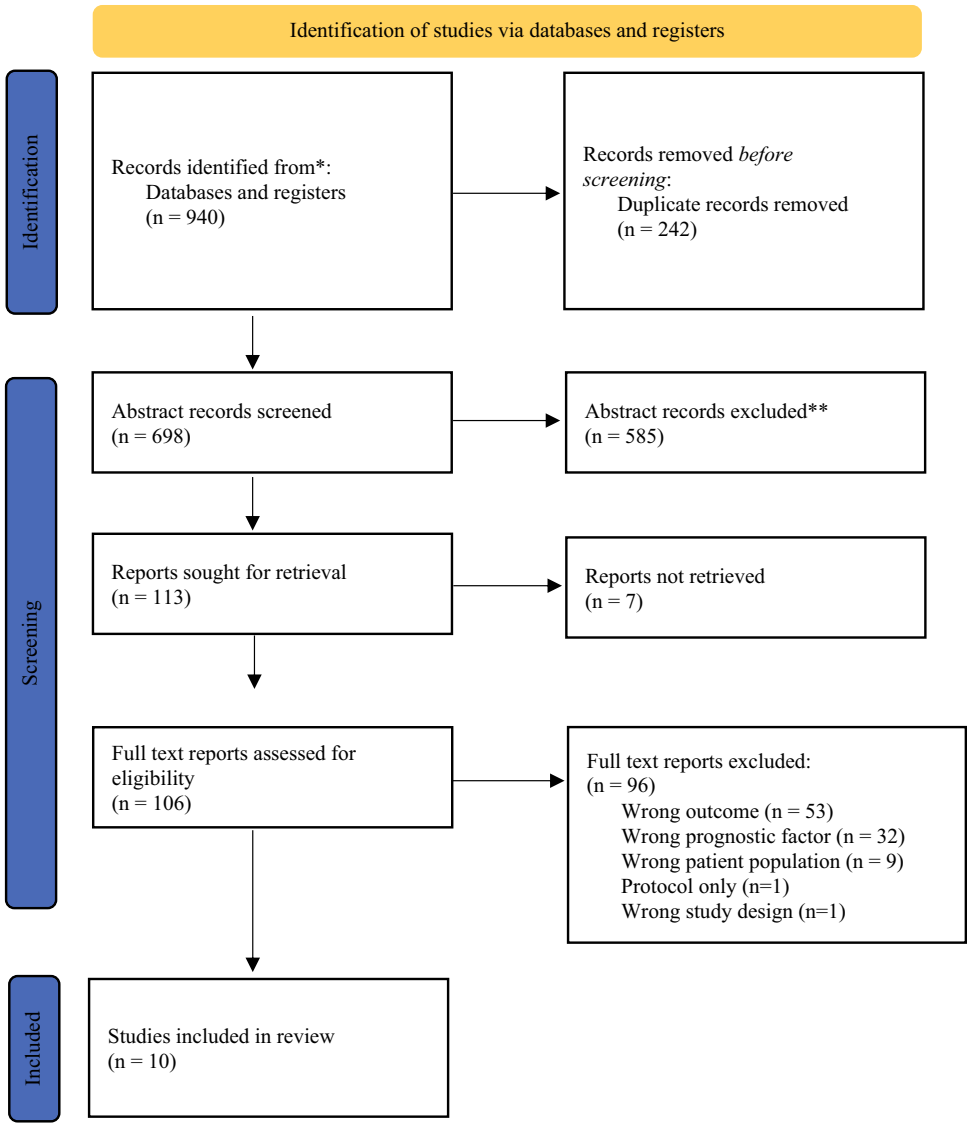

FIG. 1 PRISMA flowchart version 2020

Data Items

The primary outcome of interest in this review was ER, defined as the recurrence rate of iCCA within 24 months after curative-intent surgery. The secondary outcomes of interest were other composite measures of iCCA recurrence and survival within 24 months after curative-intent surgery and included DFS. A list of 13 prognostic factors was developed a priori based on expert consensus and a scoping review of the literature. Data regarding these variables were sought for each included study, and missing data were noted. These factors included patient demographics (age [continuous], sex [binary]), health measures (presence of hepatitis B and/or C infection [binary], cirrhosis [binary]), tumor factors (CA19-9 level [continuous], tumor size [binary, >5 vs. ≤5 cm], tumor number [continuous], tumor differentiation [poor vs moderate or good tumor differentiation], microvascular invasion [binary], macrovascular invasion [binary], and lymph node metastasis [binary]), and treatment factors (R0 resection [binary] and adjuvant chemotherapy or radiation therapy [binary]). Age, sex, hepatitis B virus (HBV) and/or hepatitis C virus (HCV), cirrhosis, and CA19-9 were categorized as preoperative prognostic factors. Tumor size, tumor number, tumor differentiation, microvascular invasion, macrovascular invasion, LNM, R0 resection, and adjuvant chemotherapy or radiation therapy were categorized as postoperative prognostic factors. Continuous variables were summarized as median (interquartile range) values and categorical variables as percentages.

Study Risk-of-Bias Assessment

The risk of bias was assessed for each included study by two independent reviewers (W.J.C. and P.J.W.) using the Quality in Prognostic Factor Studies (QUIPS) tool.[24,25] The QUIPS tool comprises six domains used to classify the risk of bias of prognostic factor studies.[24] These domains are study participation, study attrition, prognostic factor measurement, outcome measurement, adjustment for other prognostic factors, and statistical analysis and reporting. Each domain was assigned a risk-of-bias rating (high, moderate, or low), and an overall rating was subsequently applied (a rating of moderate/high risk of bias $\geq$1 domain[s] resulted in an overall rating of moderate/high risk of bias).[25] Disagreements between reviewers were resolved by discussion and consensus.

Synthesis of Results

If a prognostic factor associated with the primary or secondary outcome (recurrence or DFS within 24 months) was reported by two or more included studies, then that factor was considered for meta-analysis. When synthesis for extracted data was achievable, Review Manager (v5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used to perform meta-analyses.[26] The adjusted summary effects (either as odds ratio [OR] or hazard ratio [HR]) measured in their originally reported form were used. Unadjusted summary effects were used if adjusted summary effects were not available.

Statistical heterogeneity was assessed using the I^2 statistical estimate, and a random-effects model was used in anticipation of heterogeneity across studies. The study categorized I^2 as follows: 40% as low, 40–60% as moderate, 60–75% as substantial, and 75–100% as considerable heterogeneity. Prognostic factors were classified as either preoperative or postoperative, and forest plots were generated to display results.

For the secondary outcomes, HRs were estimated using the Parmar method at 24 months in the DFS Kaplan-Meier curves.[27] If studies were found using the same database, the degree of the database overlap was assessed based on sample size and study duration. For near complete overlap, the effect estimate was extracted from only one study in the order of preference of reporting (1: adjusted effect estimate; 2: analysis of a larger and more recent patient sample), and sensitivity analysis was conducted.

Reporting Bias

If prognostic factors were identified in more than 10 studies, the risk of reporting or publication bias was assessed using funnel plots.[28]

RESULTS

Study Selection

Our initial search strategy identified 940 studies, 242 of which were duplicates. After the initial title and abstract screening, 585 abstracts were excluded for not meeting our inclusion criteria. A total of 113 full-text articles were sought for retrieval, and 7 reports could not be retrieved with an information specialist's help. Of the 106 full-text articles screened, 96 were excluded. The reasons for the exclusions are demonstrated in the PRISMA flowchart (Fig. 1). Studies excluded for the reason of "wrong prognostic factor" mainly consisted of basic science, genetic, and radiologic analyses. The current study included 10 studies. Four studies met our primary objective of reporting ER,[8–10,29] and six studies met our secondary objective of reporting 24-month DFS.[30–35]

Study Characteristics

The characteristics of the 10 studies meeting our objectives are summarized in Table 1. These studies involved 4158 patients.[8–10,29–35] Nine of the studies were retrospective cohort studies, and the remaining study was a prospective cohort study. The publication years of the studies ranged from 2010 to 2020.

All the patients underwent curative-intent surgery for iCCA. Of the 10 studies, 4 were from Asia,[9,10,30] 2 were from Europe,[31,32] 1 was from Australia,[33] and 3 used the same multicenter database from which the research was conducted in the United States.[8,29,34] The patient accrual period for these 10 studies ranged from 1990 to 2016. The median patient follow-up period reported ranged from 19 to 44 months.[8,9,29] The three studies that used the same multicenter database comprised an average of 967 patients (range, 880–1089 patients).[8,29,34]

Definition and Reporting of Early Recurrence

Of the four studies that met our primary objective, two used 24 months from the time of surgery as the cutoff time point to define ER.[9,29] Wang et al.[10] used 12 months as the cutoff for ER, and Tsilimigras et al.[8] used a cutoff of 6 months to define "very early recurrence (VER). More than 49.6% (95% confidence interval [CI], 49.2–50.0%) of the patients experienced ER (within 12–24 months), and 22.3% experienced VER after curative-intent iCCA resection. The overall iCCA recurrence rate was reported as 59.3–78.8%. Of the patients who experienced ER, the 5-year overall survival (OS) ranged from 8.0 to 11.6%.[8–10]

TABLE 1 Included study characteristics

First author (year) country)	Study period	Study design	Inclusion criteria	Exclusion criteria	No. of patients	Median follow-up (months)	ER definition (months)	Overall recurrence rate (%)	ER rate (%)	5-year OS in ER group (%)
Primary objective: early recurrence: summary report for patients in the ER group										
Tsilimigras[8] USA, multicenter	1990–2016	RC	Curative-intent hepatectomy, histologic iCCA	Macroscopically positive surgical margins, lack of f/u data, death of loss to f/u without recurrence within 6 months	880	24	6	–	22.3	8.9
Wang[10] China	2005–2009	RC	Curative hepatectomy, pathology iCCA	HCC + iCCA, who died during f/u, incomplete data	259	–	12	78.8	50.2	8.0
Yang[9] China	2005-2011	RC	Curative hepatectomy	Preoperative TACE, RFA, PEI	322	44	24	59.3	52.2	11.6
Zhang[29] USA, multicenter	1990–2016	RC	Curative-intent hepatectomy, histologic iCCA	Extrahepatic metastasis, palliative resection, ablation, or intra-arterial therapy only, lost to f/u, missing data	933	22	24	73.4	57.9	-
Secondary objective: 24 months DFS: summary report for all patients in the study										
Ahn[35] Korea	2003–2012	RC	Curative hepatectomy	Combined HCC-CCA, intraductal growing type, periductal infiltrating, R1 resection	292	–	–	52.3	–	–
Hu[34] USA, multicenter	1990–2015	RC	Curative-intent hepatectomy, histologic iCCA	Palliative or R2 resection, ablation, or intra-arterial therapy, extrahepatic metastasis	1,089	35	–	66.9	–	–
Luvira[30] Thailand	2004–2009	RC	Curative-intent hepatectomy, histologic mass-forming iCCA	Periductal infiltration or intraductal tumor	50	–	–	80.0	–	–
Nickkholgh[32] Germany	2001–2015	PC	Hepatectomy, histologic iCCA	No TNM classification, combined HCC, papillary or mucinous adenocarcinoma	190	19	–	45.8	–	–
Nuzzo[31] Italy	1997–2008	RC	Hepatectomy, histologic iCCA	Primary extrahepatic tumors or metastases	55	28	6	61.8	38.2	–
Saxena[33] Australia	1990–2009	RC	Histologic iCCA referred	Perihilar tumors	88	31	–	68.0	–	–

CCA, cholangiocarcinoma; *DFS*, disease-free survival; *ER*, early recurrence; f/u, follow up; *HCC*, hepatocellular carcinoma; *iCCA*, intrahepatic cholangiocarcinoma; *med*, median; *OS*, overall survival; *PC*, prospective cohort; *PEI*, percutaneous ethanol injection; *RC*, retrospective cohort; *RFA*, radiofrequency ablation; any missing or not applicable parts were marked with "–"; *TACE*, transarterial chemoembolization; *TNM*, tumor-node-metastasis

Prognostic Factors

Before the review search, 13 prognostic factors of interest were identified. The 13 main prognostic factors are summarized in Tables 2 and 3, divided into pre- and postoperative factors. In the overall patient groups, the median age ranged from 41 to 63 years, and the proportion of patients with cirrhosis ranged from 11.5 to 31.7%. Multiple tumors were noted in 14.0% to 25.3% of the patients, and 4.7–33.2% of the patients had microvascular invasion. The presence of lymph node metastasis ranged from 15.5 to 64%.[8–10,29,30,33] The R0 rate for the ER group was reported in two studies and ranged from 30.0 to 87.4%.[8,29] A positive HBV status was reported in three studies, up to 22.8–40.5%.[9,10,31] Postoperative poor tumor differentiation ranged from 10.0 to 28.0% over five studies.[8,9,29,30,33]

Assessment on Risk of Bias in Studies

The risk-of-bias assessment result is presented in Table 4. Using the QUIPS tool,[24] 10 studies meeting the primary and secondary objectives were rated.[8–10,29] Six studies were rated as having an overall low risk of bias,[8,29–31,33,34] whereas four studies were rated as having moderate risk of bias.[9,10,32,35] No ratings of high risk were made, and no studies were excluded at this stage. Based on a moderate risk of bias present in at least one category, the overall rating of four studies was upgraded to moderate risk.

Meta-Analysis for Prognostic Factors

Nine studies with a total of 2189 patients were eligible for the meta-analysis, providing the estimated effects for at least one of the pre-specified prognostic factors for the correct recurrence analysis period (recurrence within 24 months or 24-month DFS).[9,10,29–35] One study was excluded from the meta-analysis for two reasons: (1) sole reporting of summary measures in operating rooms because it could not be pooled with the other studies that reported estimates as HRs and (2) overlapping database with two other studies that also investigated the same prognostic factors.[29,34]

Adjusted estimates were used wherever possible, and all results were presented as forest plots. The postoperative prognostic factors pooled by HRs included multiple tumors, poor tumor differentiation, microvascular invasion, macrovascular invasion, LNM, adjuvant chemotherapy (CT)/radiation therapy (RT), tumor size (>5 vs. ≤5cm), and R1 versus R0 resection (Fig. 2). The preoperative prognostic factors pooled by HRs were cirrhosis, sex, and HBV (Fig. 3).f The postoperative prognostic factors associated with an increased hazard of ER were multiple tumors (HR, 1.60; 95% CI, 1.09–2.37; I^2 = 21%), microvascular invasion (HR, 1.57; 95% CI, 1.17–2.10; I^2 = 0%), macrovascular invasion (HR, 1.76; 95% CI, 1.46–2.13; I^2 = 0%), LNM (HR, 1.42; 95% CI, 1.17–1.71; I^2 = 0%), and R1 resection (HR, 1.77; 95% CI, 1.29–2.43; I^2 = 0%]), whereas a reduced ER hazard was associated with adjuvant CT/RT (HR, 0.68; 95% CI, 0.49–0.93; I^2 = 0%). From the two studies included in the adjuvant CT/RT

TABLE 2 Preoperative prognostic factors for ER or 24-month DFS after curative-intent iCCA resection

First author (year) country	Median age (years)	Male (%)	HBV/HCV (%)	Cirrhosis (%)	CA19-9
Primary objective: early recurrence: summary report for patients in the ER group					
Tsilimigras[8] USA (multicenter)	55	58.7	–	19.4	60.9 U/ml, med
Wang[10] China	55	67.2	22.8/–	31.7	52.1%, >37 U/L
Yang[9] China	41	61.9	40.5/0.7	27.1	36.5%, >89 U/ml
Zhang[29] USA (multicenter)	58	58.0	–	11.5	53.8 U/ml, med
Secondary objective: 24 months DFS: summary report for all patients in the study					
Ahn[35] Korea	–	–	–	–	–
Hu[34] USA (multicenter)	–	–	–	–	–
Luvira[30] Thailand	57	50.0	–	–	
Nickkholgh[32] Germany	63	56.3	–	–	32.0 (U/ml, med, overall)
Nuzzo[31] Italy	–	–	40.0/–	–	–
Saxena[33] Australia	61	53.0	–	–	–

CA19-9, carbohydrate antigen 19-9; *DFS*, disease-free survival; *ER*, early recurrence; *HBV*, hepatitis B virus; *HCC*, hepatocellular carcinoma; *HCV*, hepatitis C virus, any missing or not applicable parts were marked with "–"; *iCCA*, intrahepatic cholangiocarcinoma; med, median

TABLE 3 Postoperative prognostic factors for ER or 2-year DFS after curative-intent iCCA resection

First author (year) country	Tumor size (cm)	Single tumor (%)	Poor tumor differentiation (%)	Microvascular invasion (%)	Macrovascular invasion (%)	LNM (%)	R0 (%)	Adjuvant CT/RT (%)
Primary objective: early recurrence: summary report for patients in the ER recurrence group								
Tsilimigras[8] USA (multicenter)	7.0 (med)	74.7	17.0	33.2	11.7	27.0	83.7	29.8
Wang[10] China	53.3%, >5cm	84.6	–	4.7	7.0	15.5	–	–
Yang[9] China	56.2%, >5cm	76.6	21.4	14.0	–	18.4	–	–
Zhang[29] USA (multicenter)	6.5 (med)	77.8	18.5	28.7	12.0	21.7	87.4	36.5
Secondary objective: 24 months DFS: summary report for all patients in the study								
Ahn[35] Korea	—	–	–	–	–	–	–	–
Hu[34] USA (multicenter)	—	–	–	–	–	–	–	–
Luvira[30] Thailand	6.5 (mean)	86.0	10.0	–	–	64.0	50.0	32.0
Nickkholgh[32] Germany	5.8 (med)	–	–	–	–	–	64.6	30.5
Nuzzo (2010) Italy	—	–	–	–	–	–	–	–
Saxena[33] Australia	—	–	28.0	–	–	28.0	30.0	–

CT, chemotherapy; *DFS*, disease-free survival; *ER*, early recurrence; *iCCA*, intrahepatic cholangiocarcinoma; *LNM*, lymph node metastasis; med, median; *R0*, negative margin resection; *RT*, radiation therapy; any missing or not applicable parts were marked with "–"

analysis, the indications, types, and regimen of adjuvant CT/RT were not reported.[29,30]

Of the prognostic factors analyzed, only microvascular invasion was studied in two almost completely overlapping database studies.[29,34] Because only one of these studies reported the adjusted effect estimate of microvascular invasion, the adjusted effect size was used for pooling, and sensitivity analysis was performed with the study reporting unadjusted effect estimate (Fig. S1). No preoperative prognostic factors such as cirrhosis (HR, 0.89; 95% CI, 0.69–1.16; I^2 = 28%), male sex (HR, 0.90; 95% CI, 0.70–1.14; I^2 = 0%), and HBV status (HR, 0.78; 95% CI, 0.50–1.21; I^2 = 76%), were associated with ER. All but one (HBV) meta-analyzed prognostic factor group were reported as having low heterogeneity ($I^2 < 40\%$). The HBV (I^2 = 76%) group had substantial heterogeneity. A subgroup analysis could not be performed for the HBV group due to a low number of available studies (n = 3).

Reporting Bias

Publication bias could not be assessed due to a low number of studies (having fewer than 10 studies per meta-analyzed prognostic factors).

Sensitivity Analyses

The meta-analysis for microvascular invasion was repeated for sensitivity analysis because two studies (Zhang et al.[29] and Hu et al.[34]) had an overlapping database. The meta-analysis for microvascular invasion was repeated selectively using effect size from the Zhang et al.[29] study only and the Hu et al.[34] study only (Fig. S1). The statistical significance and the effect estimate of the pooled microvascular invasion remained unchanged (HR, 1.56; 95% CI, 1.17–2.10; I^2 = 0% and HR, 1.57; 95% CI, 1.34–1.83; I^2 = 0%, respectively).

DISCUSSION

The current systematic review and meta-analysis summarize the prognostic factors for ER (recurrence within 24 months) and 24-month DFS after curative-intent iCCA resection. Based on the studies included in the review, the definition of ER was defined as recurrence within a range of 12 to 24 months after curative-intent surgery.[8–10,29] After curative-intent iCCA resection, 49.6% (95% CI, 49.2–50.0%) of patients experienced ER.[9,10,29] Of the 10 included studies, 9 were pooled for meta-analysis of the eligible prognostic factors. Of the postoperative prognostic factors, multiple tumors, microvascular invasion, macrovascular invasion, LNM, and R1 were associated

TABLE 4 Risk of bias assessment using Quality in Prognostic factor Studies (QUIPS) tool for the included studies

First author	1. Study participation	2. Study attrition	3. PF measurement	4. Outcome measurement	5. Adjustment for other PF	6. Statistical analysis and reporting	Overall
Tsilimigras et al.	Low	Low	Low	Low	Low	Low	Low
Wang et al.	Low	Mod[a]	Low	Low	Low	Low	Mod
Yang et al.	Low	Low	Low	Mod[b]	Low	Low	Mod
Zhang et al.	Low	Low	Low	Low	Low	Low	Low
Ahn et al.	Low	Mod[a]	Low	Low	Low	Low	Mod
Hu et al.	Low	Low	Low	Low	Low	Low	Low
Luvira et al.	Low	Low	Low	Low	Low	Low	Low
Nickkholgh et al.	Low	Mod[a]	Low	Low	Low	Low	Mod
Nuzzo et al.	Low	Low	Low	Low	Low	Low	Low
Saxena et al.	Low	Low	Low	Low	Low	Low	Low

Mod, moderate; *PF*, prognostic factor

[a]Lacks reporting of exact study attrition rate

[b]Lacks measurement methods for the cancer recurrence.

with an increased hazard for ER or reduced 24-month DFS, whereas receipt of adjuvant chemotherapy/radiation therapy showed the opposite result. Of the preoperative factors, cirrhosis, sex, and HBV status were not associated with ER or 24-month DFS.

This is the first systematic review and meta-analysis to summarize prognostic factors for ER together with 24-month DFS after curative-intent iCCA resection. The ER definition from the four studies ranged from 12 to 24 months, consistent with the studies of other hepatobiliary cancers such as hepatocellular carcinoma or distal cholangiocarcinoma.[8–10,29,36,37] However, the measured prognostic factors differed across the included studies, with varying adjusted and unadjusted analyses. The rare nature of the disease, the relatively novel concept of ER, and the majority of published studies from single-center populations may have been the reasons for such observed heterogenicity.[38]

After pooling of all data for meta-analysis using 2189 patients, we showed how only the postoperative prognostic factors remained associated with ER or 24-month DFS, whereas none of the pooled preoperative factors were associated with ER. All these postoperative prognostic factors were those available from the final surgical pathology report (tumor numbers, microvascular invasion, macrovascular invasion, LNM, R0 resection) and previously shown to be associated with worse 5-year OS after curative-intent iCCA resections.[38] Only adjuvant chemotherapy or radiation therapy was shown to be protective for ER, generally supporting the per protocol findings of the BILCAP study.[39] Our findings of these postoperative prognostic factors may be helpful in two ways: (1) by helping to better identify a population at higher risk of ER after iCCA resection and (2) by providing an opportunity to design trials to explore targeted treatments in the adjuvant settings.[40]

The results from this systematic review and meta-analysis narrowed the knowledge gap by offering some prognostic factors that might play a vital role in the ER of iCCA after resection and highlighted the scarcity of available preoperative prognostic factors. The pooled preoperative prognostic factors of this meta-analysis were limited to only three variables (sex, cirrhosis, HBV). Other preoperative prognostic factors have been previously evaluated, such as serum biomarkers (i.e., neutrophil-to-lymphocyte ratio [NLR]) often sought to augment survival risk stratification tools for patients before undergoing major abdominal liver surgery for iCCA.[15,18] However, these types of serum biomarkers have not been studied in the context of early iCCA recurrence. Furthermore, there are studies using features of radiomics to develop preoperative nomograms to better predict ER of iCCA.[41,42] Building a strong library of preoperative prognostic factors for the ER of iCCA will facilitate the design of future prospective studies that could aid in deciding whether to offer neoadjuvant treatments to improve oncologic outcomes for these patients.

This review had several limitations. A small number of studies ($n = 10$) were included, which might have caused a bias toward the null hypothesis in the quantitative synthesis. To mitigate this, adjusted estimates were used preferentially in the pooling of data. However, when

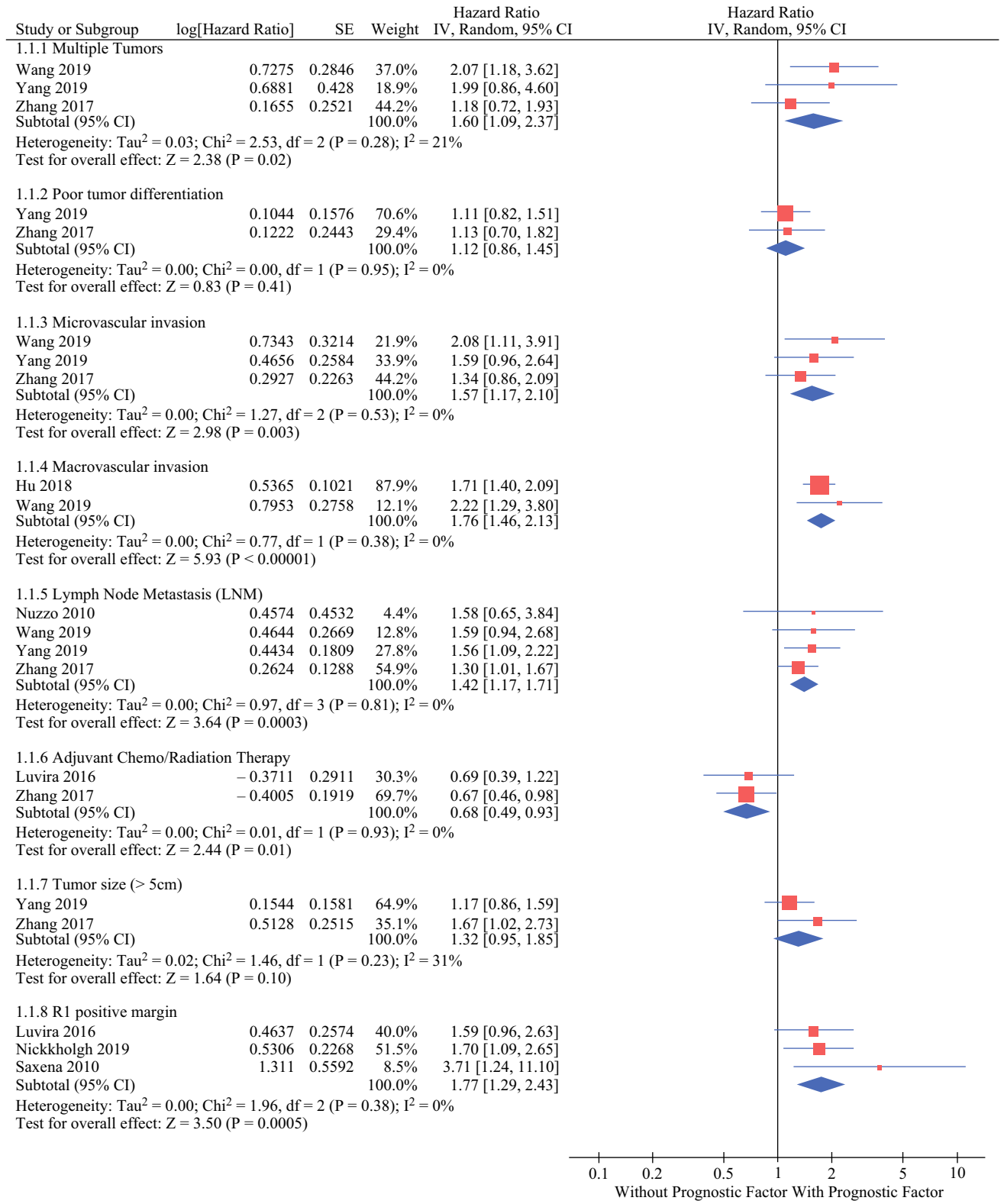

FIG. 2 Forest plots of pooled postoperative prognostic factors from studies reporting early recurrence or 2-year DFS after curative-intent intrahepatic cholangiocarcinoma (iCCA) resection

adjusted estimates are used from multivariable models including both pre- and postoperative factors, a potential bias toward the postoperative factors might occur, resulting in a stronger association with recurrence because the

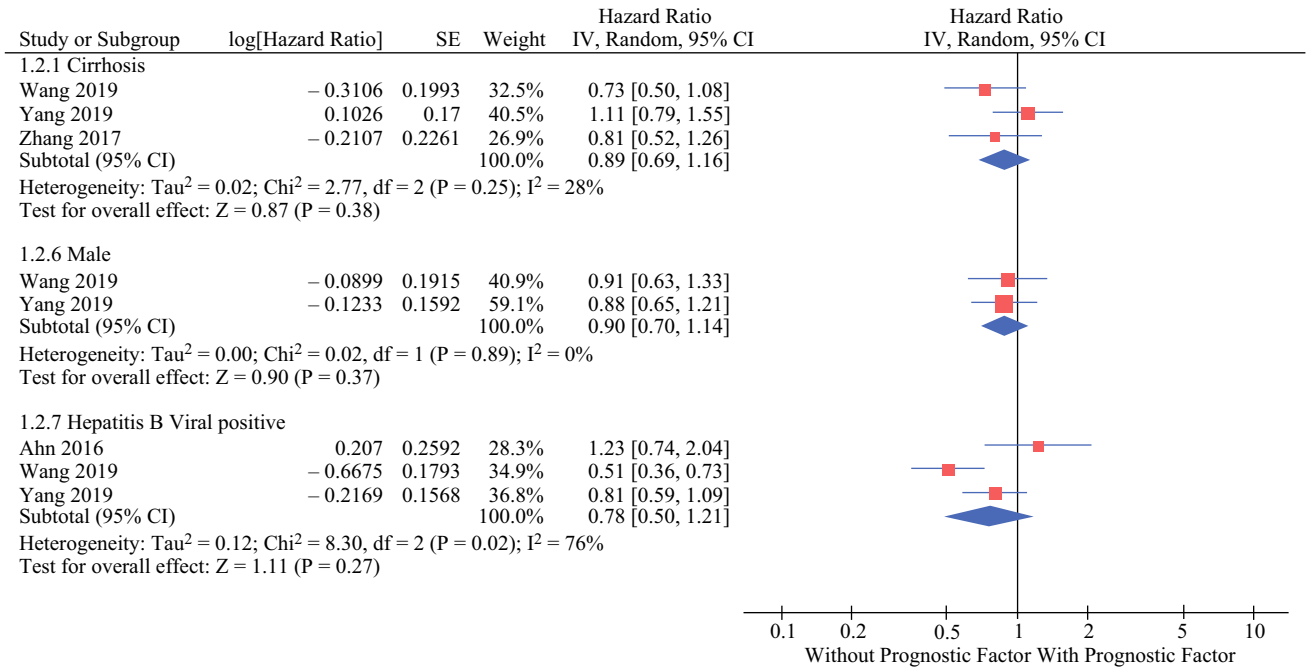

FIG. 3 Forest plots of pooled preoperative prognostic factors from studies reporting early recurrence or 2-year DFS after curative-intent intrahepatic cholangiocarcinoma (iCCA) resection

estimates are derived mostly from a reliable final surgical pathology report. This could be a partial reason why our meta-analysis did not show any preoperative factors to be a significantly associated with ER or 24-month DFS. Thus, future studies should also include models exclusively analyzing the preoperative risk factors.

Several statistical assumptions made for the meta-analysis involved pooling studies reporting in HRs only, combining ER time points for outcomes ranging from 12 to 24 months, using a mix of adjusted and unadjusted estimates for meta-analyses, and pooling ER outcomes with a 24-month DFS. These limitations could have contributed to the substantial heterogeneity observed in the HBV group meta-analysis ($I2^2$ = 76%). Subgroup analysis could not be performed for the HBV group due to a low number of studies (n =3). Meta-analysis was not feasible for other important prognostic factors such as CA19-9 because their effect estimates using the same definition were reported in fewer than two studies. Despite these limitations, pooling evidence from available observational studies enabled us to synthesize relevant and generalizable risk factors.[24]

CONCLUSION

This review provides a synthesized summary of the prognostic factors for ER and 24-month DFS for iCCA after curative-intent surgery. These findings could allow for improved surveillance, prognostication, and treatment decision-making for patients with resectable iCCAs. Further well-designed prospective studies are needed to explore prognostic factors for ER of iCCA focusing on preoperative variables.

APPENDIX 1

SEARCH STRATEGY

Medline-Ovid MEDLINE(R) 1946 to January 14, 2021

#	Searches	Results
1	cholangiocarcinoma/ or klatskin tumor/	9616
2	(Adenoma, Bile Duct/ or Bile Duct Neoplasms/) and Liver Neoplasms/	3518
3	cholangiocarcinom*.mp.	12771
4	cholangiocellular carcinoma*.mp.	796
5	Klatskin*.mp.	927
6	Common Hepatic Duct/ and (Adenocarcinoma/ or Adenoma, Bile Duct/ or Bile Duct Neoplasms/)	825
7	or/1-6 [Cholangiocarcinoma]	15490
8	exp bile ducts, intrahepatic/ or bile canaliculi/	11545
9	intrahepatic*.mp.	35575
10	intra-hepatic*.mp.	962
11	or/8-10 [Intrahepatic]	37008
12	7 and 11 [Cholangiocarcinoma + Intrahepatic]	7493
13	Recurrence/	185969
14	Neoplasm Recurrence, Local/	120657

#	Searches	Results
15	recidiv*.mp.	11368
16	recur*.mp.	651873
17	recur*.kw.	11331
18	recrudescen*.mp,kw.	3241
19	relaps*.mp,kw.	165638
20	Disease-Free Survival/	75806
21	Survival Analysis/	138074
22	Survival Rate/	177115
23	(progress* adj2 surviv*).mp,kw.	42960
24	(diseas* adj2 surviv*).mp,kw.	106691
25	(surviv* adj2 analy*).mp,kw.	170692
26	(rate? adj2 surviv*).mp,kw.	281829
27	"cancer free".mp,kw.	3685
28	exp Neoplasm Metastasis/	206891
29	sc.fs. [secondary]	161616
30	Micrometast*.mp,kw.	6329
31	Micro-metast*.mp,kw.	462
32	metasta*.mp,kw.	506242
33	secondary.mp,kw.	827441
34	metastasectom*.mp,kw.	2302
35	or/13-34 [Recurrence & related terms]	2110846
36	12 and 35 [Cholangiocarcinoma + Intrahepatic + Recurrence]	3552
37	exp Surgical Procedures, Operative/	3199040
38	su.fs.	2017941
39	(surgery or surgeries or surgical* or operat* or laparoscop* or resect* or reresect* or reoperat*).mp.	3428085
40	cholangio*ectom*.mp.	3
41	cholangio*ostom*.mp.	184
42	hepatectom*.mp.	36041
43	hepato*ostom*.mp.	318
44	metastectom*.mp.	78
45	necrosectom*.mp.	836
46	posthepatectom*.mp.	390
47	post-hepatectom*.mp.	405
48	hemihepatectom*.mp.	877
49	hemi-hepatectom*.mp.	103
50	lobectom*.mp.	17503
51	(minimal* adj3 invasiv*).mp.	70591
52	Hepatectomy/	30410
53	(excis* adj8 (liver? or hepat*)).mp.	2664
54	transplant*.mp.	720204
55	graft*.mp.	362724
56	allograft*.mp.	67427
57	or/37-56 [Surgery]	4915416
58	36 and 57 [Cholangiocarcinoma + Intrahepatic + Recurrence + Surgery]	2580
59	(early or earlier or earliest).mp.	1626807
60	(time adj3 recur*).mp.	9111
61	(time adj3 relaps*).mp.	4394
62	timing.mp.	116605
63	Time Factors/	1199216
64	or/59-63 [Early[NA1]]	2760065
65	58 and 64 [Cholangiocarcinoma + Intrahepatic + Recurrence + Surgery + Early]	539
66	(animal or animals or ape or apes or baboon or baboons or bat or bats or bird or birds or boar or boars or bonobo or bonobos or bovine or camel or camels or canine or canines or cat or cats or cattle or chicken or chickens or chimpanzee or chimpanzees or dog or dogs or dromedary or dromedaries or duck or ducks or equine or equines or feline or felines or ferret or ferrets or frog or frogs or fowl or fowls or goat or goats or hare or hares or hen or hens or horse or horses or lamb or lambs or livestock or macaque or macaques or mandrill or mandrills or mice or mink or minks or monkey or monkeys or mouse or murine or ovine or pig or pigs or piglet or piglets or poultry or porcine or orangutan or orangutans or rabbit or rabbits or rat or rats or rodent or rodents or sheep or swine or tamarin or tamarins or tiger or tigers or veterinary or veterinarian or veterinarians or waterfowl or waterfowls or weasel or weasels or veterinar* or (veterinar* or fish or shellfish)).ti,jw.	2553335
67	65 not 66	536
68	(human* or patient? or man or mankind or men or women or woman or adult*).ti,jw.	3466040
69	65 and 68	104
70	limit 65 to humans	534
71	67 or 69 or 70	536
72	remove duplicates from 71	536
73	(adolescence or adolescent or adolescents or babies or baby or boy or boys or child or childhood or children or childrens or children's or fetus or fetal or foetus or foetal or girl or girls or infancy or infant or infants or neonatal or neonatally or neonate or neonates or newborn or newborns or paediatric or paediatrician or paediatricians or paediatrics or pediatric or pediatrician or pediatricians or pediatrics or preschool* or teen or teenage or teenagers or teens or toddler or toddlers or tween* or youth or youths).ti,jw.	1662392
74	72 not 73	533
75	(elder* or senior? or aged or adult* or man or men or woman or women).ti,jw.	847112
76	72 and 75	6
77	limit 72 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)")	21
78	72 not 77	515
79	limit 72 to ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")	422

#	Searches	Results
80	74 or 76 or 78 or 79	536
81	remove duplicates from 80	536

Medline In-Process- Ovid MEDLINE(R) Epub Ahead of Print and In-Process & Other Non-Indexed Citations January 14, 2021

#	Searches	Results
1	cholangiocarcinoma/ or klatskin tumor/	0
2	(Adenoma, Bile Duct/ or Bile Duct Neoplasms/) and Liver Neoplasms/	0
3	cholangiocarcinom*.mp.	3000
4	cholangiocellular carcinoma*.mp.	109
5	Klatskin*.mp.	112
6	Common Hepatic Duct/ and (Adenocarcinoma/ or Adenoma, Bile Duct/ or Bile Duct Neoplasms/)	0
7	or/1-6 [Cholangiocarcinoma]	3101
8	exp bile ducts, intrahepatic/ or bile canaliculi/	0
9	intrahepatic*.mp.	3905
10	intra-hepatic*.mp.	161
11	or/8-10 [Intrahepatic]	4027
12	7 and 11 [Cholangiocarcinoma + Intrahepatic]	1101
13	Recurrence/	0
14	Neoplasm Recurrence, Local/	0
15	recidiv*.mp.	968
16	recur*.mp.	92562
17	recur*.kw.	7338
18	recrudescen*.mp,kw.	266
19	relaps*.mp,kw.	26222
20	Disease-Free Survival/	0
21	Survival Analysis/	0
22	Survival Rate/	0
23	(progress* adj2 surviv*).mp,kw.	11425
24	(diseas* adj2 surviv*).mp,kw.	9092
25	(surviv* adj2 analy*).mp,kw.	10312
26	(rate? adj2 surviv*).mp,kw.	23166
27	“cancer free”.mp,kw.	620
28	exp Neoplasm Metastasis/	0
29	sc.fs. [secondary]	0
30	Micrometast*.mp,kw.	622
31	Micro-metast*.mp,kw.	103
32	metasta*.mp,kw.	91858
33	secondary.mp,kw.	119859
34	metastasectom*.mp,kw.	561
35	or/13-34 [Recurrence & related terms]	328784
36	12 and 35 [Cholangiocarcinoma + Intrahepatic + Recurrence]	569
37	exp Surgical Procedures, Operative/	0
38	su.fs.	0
39	(surgery or surgeries or surgical* or operat* or laparoscop* or resect* or reresect* or reoperat*).mp.	437712
40	cholangio*ectom*.mp.	3
41	cholangio*ostom*.mp.	16
42	hepatectom*.mp.	3023
43	hepato*ostom*.mp.	42
44	metastectom*.mp.	13
45	necrosectom*.mp.	222
46	posthepatectom*.mp.	65
47	post-hepatectom*.mp.	143
48	hemihepatectom*.mp.	151
49	hemi-hepatectom*.mp.	38
50	lobectom*.mp.	3225
51	(minimal* adj3 invasiv*).mp.	16842
52	Hepatectomy/	0
53	(excis* adj8 (liver? or hepat*)).mp.	306
54	transplant*.mp.	52344
55	graft*.mp.	42896
56	allograft*.mp.	6497
57	or/37-56 [Surgery]	505846
58	36 and 57 [Cholangiocarcinoma + Intrahepatic + Recurrence + Surgery]	351
59	(early or earlier or earliest).mp.	250030
60	(time adj3 recur*).mp.	1709
61	(time adj3 relaps*).mp.	547
62	timing.mp.	23076
63	Time Factors/	1
64	or/59-63 [Early]	269508
65	58 and 64 [Cholangiocarcinoma + Intrahepatic + Recurrence + Surgery + Early]	52
66	(animal or animals or ape or apes or baboon or baboons or bat or bats or bird or birds or boar or boars or bonobo or bonobos or bovine or camel or camels or canine or canines or cat or cats or cattle or chicken or chickens or chimpanzee or chimpanzees or dog or dogs or dromedary or dromedaries or duck or ducks or equine or equines or feline or felines or ferret or ferrets or frog or frogs or fowl or fowls or goat or goats or hare or hares or hen or hens or horse or horses or lamb or lambs or livestock or macaque or macaques or mandrill or mandrills or mice or mink or minks or monkey or monkeys or mouse or murine or ovine or pig or pigs or piglet or piglets or poultry or porcine or orangutan or orangutans or rabbit or rabbits or rat or rats or rodent or rodents or sheep or swine or tamarin or tamarins or tiger or tigers or veterinary or veterinarian or veterinarians or waterfowl or waterfowls or weasel or weasels or veterinar* or (veterinar* or fish or shellfish)).ti,jw.	196970
67	65 not 66	52
68	(human* or patient? or man or mankind or men or women or woman or adult*).ti,jw.	451435
69	65 and 68	13

#	Searches	Results
70	limit 65 to humans	0
71	67 or 69 or 70	52
72	(adolescence or adolescent or adolescents or babies or baby or boy or boys or child or childhood or children or childrens or children's or fetus or fetal or foetus or foetal or girl or girls or infancy or infant or infants or neonatal or neonatally or neonate or neonates or newborn or newborns or paediatric or paediatrician or paediatricians or paediatrics or pediatric or pediatrician or pediatricians or pediatrics or preschool* or teen or teenage or teenagers or teens or toddler or toddlers or tween* or youth or youths).ti,jw.	198467
73	71 not 72	52
74	remove duplicates from 73	51

Embase- Embase Classic+Embase 1947 to 2021 January 14

#	Searches	Results
1	exp bile duct carcinoma/ [Embase]	29808
2	cholangiocarcinoma/ or klatskin tumor/	15968
3	(Adenoma, Bile Duct/ or Bile Duct Neoplasms/) and Liver Neoplasms/	367
4	cholangiocarcinom*.mp.	22936
5	cholangiocellular carcinoma*.mp.	1410
6	Klatskin*.mp.	1296
7	Common Hepatic Duct/ and (Adenocarcinoma/ or Adenoma, Bile Duct/ or Bile Duct Neoplasms/)	58
8	or/1-7 [Cholangiocarcinoma]	33529
9	exp intrahepatic bile duct/ [Embase]	9512
10	exp common hepatic duct/ [Embase]	1215
11	exp bile ducts, intrahepatic/ or bile canaliculi/	9512
12	intrahepatic*.mp.	55646
13	intra-hepatic*.mp.	2331
14	or/9-13 [Intrahepatic]	58236
15	8 and 14 [Cholangiocarcinoma + Intrahepatic]	9378
16	cancer recurrence/ [Embase]	198371
17	Recurrence/	162127
18	Neoplasm Recurrence, Local/	32106
19	recidiv*.mp.	17123
20	recur*.mp.	1142400
21	recur*.kw.	56619
22	recrudescen*.mp,kw.	4874
23	relaps*.mp,kw.	389938
24	Disease-Free Survival/	88302
25	Survival Analysis/	25936
26	Survival Rate/	260984
27	(progress* adj2 surviv*).mp,kw.	138109
28	(diseas* adj2 surviv*).mp,kw.	128345
29	(surviv* adj2 analy*).mp,kw.	100629
30	(rate? adj2 surviv*).mp,kw.	379520
31	"cancer free".mp,kw.	6448
32	exp Neoplasm Metastasis/	696854
33	metastasis/ [Embase]	323890
34	Micrometast*.mp,kw.	12148
35	Micro-metast*.mp,kw.	1172
36	metasta*.mp,kw.	970685
37	secondary.mp,kw.	1102064
38	metastasectom*.mp,kw.	4010
39	or/16-38 [Recurrence & related terms]	3505147
40	15 and 39 [Cholangiocarcinoma + Intrahepatic + Recurrence]	5112
41	exp surgery/ [Embase]	5462884
42	exp liver surgery/ [Embase]	182092
43	exp liver resection/ [Embase]	63024
44	hemihepatectomy/ [Embase]	2041
45	liver lobectomy/ or partial hepatectomy/ [Embase]	11095
46	exp Surgical Procedures, Operative/	5462884
47	su.fs.	2218425
48	(surgery or surgeries or surgical* or operat* or laparoscop* or resect* or reresect* or reoperat*).mp.	5528735
49	cholangio*ectom*.mp.	8
50	cholangio*ostom*.mp.	296
51	hepatectom*.mp.	37160
52	hepato*ostom*.mp.	4679
53	metastasectom*.mp.	4010
54	metastectom*.mp.	246
55	necrosectom*.mp.	2249
56	posthepatectom*.mp.	704
57	post-hepatectom*.mp.	931
58	hemihepatectom*.mp.	2561
59	hemi-hepatectom*.mp.	245
60	lobectom*.mp.	48019
61	(minimal* adj3 invasiv*).mp.	136671
62	Hepatectomy/	46903
63	(excis* adj8 (liver? or hepat*)).mp.	3790
64	transplant*.mp.	1017819
65	graft*.mp.	760033
66	allograft*.mp.	124364
67	or/41-66 [Surgery]	7542943
68	40 and 67 [Cholangiocarcinoma + Intrahepatic + Recurrence + Surgery]	3780
69	(early or earlier or earliest).mp.	2652920
70	(time adj3 recur*).mp.	18762
71	(time adj3 relaps*).mp.	10271
72	time factor/ [Embase]	38147
73	Time Factors/	30856
74	or/69-73 [Early]	2709595
75		540

#	Searches	Results
	68 and 74 [Cholangiocarcinoma + Intrahepatic + Recurrence + Prediction + Surgery + Early]	
76	(animal or animals or ape or apes or baboon or baboons or bat or bats or bird or birds or boar or boars or bonobo or bonobos or bovine or camel or camels or canine or canines or cat or cats or cattle or chicken or chickens or chimpanzee or chimpanzees or dog or dogs or dromedary or dromedaries or duck or ducks or equine or equines or feline or felines or ferret or ferrets or frog or frogs or fowl or fowls or goat or goats or hare or hares or hen or hens or horse or horses or lamb or lambs or livestock or macaque or macaques or mandrill or mandrills or mice or mink or minks or monkey or monkeys or mouse or murine or ovine or pig or pigs or piglet or piglets or poultry or porcine or orangutan or orangutans or rabbit or rabbits or rat or rats or rodent or rodents or sheep or swine or tamarin or tamarins or tiger or tigers or veterinary or veterinarian or veterinarians or waterfowl or waterfowls or weasel or weasels or veterinar* or (veterinar* or fish or shellfish)).ti,jw.	3311878
77	75 not 76	536
78	(human* or patient? or man or mankind or men or women or woman or adult*).ti,jw.	5338789
79	75 and 78	100
80	limit 75 to human	516
81	77 or 79 or 80 [Limited to human]	537
82	limit 81 to (conference abstracts or (books or chapter or conference abstract or "conference review") or (book or book series or conference proceeding))	194
83	81 not 82	343
84	81 not (conference abstract or conference review).pt.	345
85	83 or 84	345
86	remove duplicates from 85	336

CCTR-Cochrane Central Register of Controlled Trials 2014 to Present

#	Searches	Results
1	cholangiocarcinoma/ or klatskin tumor/	223
2	(Adenoma, Bile Duct/ or Bile Duct Neoplasms/) and Liver Neoplasms/	34
3	cholangiocarcinom*.mp.	795
4	cholangiocellular carcinoma*.mp.	21
5	Klatskin*.mp.	36
6	or/1-5 [Cholangiocarcinoma]	831
7	Common Hepatic Duct/ and (Adenocarcinoma/ or Adenoma, Bile Duct/ or Bile Duct Neoplasms/)	1
8	exp Bile Ducts, Intrahepatic/ [Embase]	39
9	exp Hepatic Duct, Common/ [Embase]	7
10	exp bile ducts, intrahepatic/ or bile canaliculi/	39
11	intrahepatic*.mp.	1727
12	intra-hepatic*.mp.	116
13	or/7-12 [Intrahepatic]	1834
14	6 and 13 [Intrahepatic Cholangiocarcinoma]	284
15	cancer recurrence/ [Embase]	0
16	Recurrence/	11985
17	Neoplasm Recurrence, Local/	4203
18	recidiv*.mp.	908
19	recur*.mp.	77896
20	recur*.kw.	15913
21	recrudescen*.mp,kw.	514
22	relaps*.mp,kw.	42923
23	Disease-Free Survival/	6895
24	Survival Analysis/	8241
25	Survival Rate/	10321
26	(progress* adj2 surviv*).mp,kw.	27597
27	(diseas* adj2 surviv*).mp,kw.	19179
28	(surviv* adj2 analy*).mp,kw.	17193
29	(rate? adj2 surviv*).mp,kw.	29945
30	"cancer free".mp,kw.	356
31	exp Neoplasm Metastasis/	5231
32	metastasis/ [Embase]	3235
33	Micrometast*.mp,kw.	423
34	Micro-metast*.mp,kw.	81
35	metasta*.mp,kw.	46561
36	secondary.mp,kw.	267998
37	metastasectom*.mp,kw.	201
38	or/15-37 [Recurrence & related terms]	401976
39	14 and 38 [Intrahepatic Cholangiocarcinoma + Recurrence]	221
40	exp General Surgery/ [Embase]	354
41	hemihepatectomy/ [Embase]	0
42	liver lobectomy/ or partial hepatectomy/ [Embase]	0
43	exp Surgical Procedures, Operative/	117422
44	su.fs.	58330
45	(surgery or surgeries or surgical* or operat* or laparoscop* or resect* or reresect* or reoperat*).mp.	290301
46	cholangio*ectom*.mp.	0
47	cholangio*ostom*.mp.	8
48	hepatectom*.mp.	1602
49	hepato*ostom*.mp.	66
50	metastectom*.mp.	11
51	necrosectom*.mp.	102
52	posthepatectom*.mp.	25
53	post-hepatectom*.mp.	35
54	hemihepatectom*.mp.	66
55	hemi-hepatectom*.mp.	9
56	lobectom*.mp.	1595
57	(minimal* adj3 invasiv*).mp.	7047

#	Searches	Results
58	Hepatectomy/	614
59	(excis* adj8 (liver? or hepat*)).mp.	59
60	transplant*.mp.	39642
61	graft*.mp.	32696
62	allograft*.mp.	4754
63	or/40-62 [Surgery]	371428
64	39 and 63 [Intrahepatic Cholangiocarcinoma + Recurrence + Surgery]	143
65	(early or earlier or earliest).mp.	143194
66	(time adj3 recur*).mp.	3139
67	(time adj3 relaps*).mp.	2760
68	time factor/ [Embase]	65250
69	Time Factors/	65250
70	or/65-69 [Early]	204401
71	64 and 70 [Intrahepatic Cholangiocarcinoma + Recurrence + Surgery + Early]	23
72	(animal or animals or ape or apes or baboon or baboons or bat or bats or bird or birds or boar or boars or bonobo or bonobos or bovine or camel or camels or canine or canines or cat or cats or cattle or chicken or chickens or chimpanzee or chimpanzees or dog or dogs or dromedary or dromedaries or duck or ducks or equine or equines or feline or felines or ferret or ferrets or frog or frogs or fowl or fowls or goat or goats or hare or hares or hen or hens or horse or horses or lamb or lambs or livestock or macaque or macaques or mandrill or mandrills or mice or mink or minks or monkey or monkeys or mouse or murine or ovine or pig or pigs or piglet or piglets or poultry or porcine or orangutan or orangutans or rabbit or rabbits or rat or rats or rodent or rodents or sheep or swine or tamarin or tamarins or tiger or tigers or veterinary or veterinarian or veterinarians or waterfowl or waterfowls or weasel or weasels or veterinar* or (veterinar* or fish or shellfish)).ti,jw.	10906
73	71 not 72	23
74	(human* or patient? or man or mankind or men or women or woman or adult*).ti,jw.	517172
75	71 and 74	8
76	73 or 75	23
77	(abstract or book or book article or book book or book note or "book review" or book series article or book series article in press or book series chapter or book series conference paper or book series letter or "book series review" or book series short survey or chapter or conference abstract or conference abstract placebo controlled partly blinded crossover study in 12 sle patients or conference proceeding or "conference review" or journal conference abstract or "journal conference review").pt.	182126
78	76 not 77	17
79	remove duplicates from 78	16

CDSR-Cochrane Database of Systematic Reviews 2005 to Present

#	Searches	Results
1	cholangiocarcinom*.ti,ab.	5
2	cholangiocellular carcinoma*.ti,ab.	0
3	(bile duct? adj2 carcinoma*).ti,ab.	0
4	Klatskin*.ti,ab.	0
5	or/1-4 [Cholangiocarcinoma]	5
6	intrahepatic*.ti,ab.	13
7	intra-hepatic*.ti,ab.	2
8	or/6-7 [Intrahepatic]	15
9	5 and 8 [Cholangiocarcinoma + Intrahepatic]	2
10	recidiv*.ti,ab.	8
11	recur*.ti,ab.	662
12	recur*.kw.	317
13	recrudescen*.ti,ab.	0
14	relaps*.ti,ab.	354
15	(progress* adj2 surviv*).ti,ab.	120
16	(diseas* adj2 surviv*).ti,ab.	64
17	(surviv* adj2 analy*).ti,ab.	23
18	(rate? adj2 surviv*).ti,ab.	79
19	"cancer free".ti,ab.	1
20	Micrometast*.ti,ab.	1
21	Micro-metast*.ti,ab.	1
22	metasta*.ti,ab.	192
23	secondary.ti,ab.	1871
24	metastasectom*.ti,ab.	0
25	or/1-24 [Recurrence]	2871
26	9 and 25 [Intrahepatic Cholangiocarcinoma + Recurrence]	2
27	(surgery or surgeries or surgical* or operat* or laparoscop* or resect* or reresect* or reoperat*).ti,ab.	2047
28	cholangio*ectom*.ti,ab.	0
29	cholangio*ostom*.ti,ab.	0
30	hepatectom*.ti,ab.	3
31	hepato*ostom*.ti,ab.	0
32	metastectom*.ti,ab.	0
33	necrosectom*.ti,ab.	2
34	posthepatectom*.ti,ab.	0
35	post-hepatectom*.ti,ab.	0
36	hemihepatectom*.ti,ab.	0
37	hemi-hepatectom*.ti,ab.	0
38	lobectom*.ti,ab.	5
39	(minimal* adj3 invasiv*).ti,ab.	63
40	(excis* adj8 (liver? or hepat*)).ti,ab.	0
41	transplant*.ti,ab.	314
42	graft*.ti,ab.	167
43	allograft*.ti,ab.	18
44	or/27-43 [Surgery]	2363
45	26 and 44 [Intrahepatic Cholangiocarcinoma + Recurrence + Surgery]	2
46	(early or earlier or earliest).ti,ab.	1195
47	(time adj3 factor*).ti,ab.	4

#	Searches	Results
48	(time adj3 recur*).ti,ab.	31
49	(time adj3 relaps*).ti,ab.	16
50	or/46-49 [Early]	1234
51	45 and 50 [Intrahepatic Cholangiocarcinoma + Recurrence + Surgery + Early]	1

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DECLARATIONS

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