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Complete List of Authors:	Jiang, Jing-Hua; Zhejiang University School of Medicine, Department of Hepatobiliary Fang, Da-Zhang; Zhejiang University School of Medicine, Department of Hepatobiliary Hu, Yi-Ting; Shulan International Medical College, Department of Hepatobiliary and Pancreatic Surgery
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Influence of surgical margin width on survival rate after resection of intrahepatic cholangiocarcinoma: a systematic review and meta-analysis

Authors:

Jing-Hua Jiang [1], Da-Zhang Fang [1], Yi-Ting Hu [2*].

Affiliation:

1. Department of Hepatobiliary and Pancreatic Surgery, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua 321000, China.
2. Department of Hepatobiliary and Pancreatic Surgery, Shulan (Hangzhou) Hospital, Zhejiang Shuren University, Shulan International Medical College, Hangzhou 310022, China.

***Corresponding Author Information:** DR. Yi-Ting Hu. Department of Hepatobiliary and Pancreatic Surgery, Shulan (Hangzhou) Hospital, Zhejiang Shuren University, Shulan International Medical College, Dongxin Road 848#, Hangzhou 310022, China. Tel: +86-13515861057, E-mail: yitingh@yeah.net.

Abstract

Objective: This study attempted to investigate the effect different surgical margin widths on the prognoses of ICC patients after liver resection.

Methods: Published English cohort studies relating to the impact of surgical margin width on ICC patient prognosis in PubMed, Embase and Web of Science databases available by June 2022 were all retrieved and collected. This study analyzed hazard ratio(HR) and confidential interval(95%CI) of overall survival(OS), disease-free survival(DFS), recurrence-free survival(RFS) across the included studies, the quality of the papers was assessed by the Newcastle-Ottawa scale(NOS). The forest plots of hazard ratio and 95%CI were drawn by Stata software. A sensitivity analysis was then adopted to reassure the stability of the results.

Results: In 9 included studies, R0 resection margins were achieved in 2158 out of 2404 patients. Among 2158 patients, there were 770(35.68%) with a wide margin (≥10 mm), and 1388(64.32%) with a narrow margin(<10 mm). With the wide margin group (≥10 mm) as the control, pooled HR of OS in the narrow margin group (<10 mm) was 1.54(95%CI: 1.34-1.77). HR of OS in three subgroups where the margin was less than 5 mm, or ranges from 5 mm to 9 mm, or less than 10 mm in length were 1.88(95%CI: 1.45-2.42), 1.33(95% CI: 1.03-1.72), 1.49(95%CI: 1.20-1.84), respectively. Pooled HR of DFS in the narrow margin group(<10 mm) was 1.51(95%CI: 1.14-2.00). Pooled HR of RFS in the narrow margin group(<10 mm) was 1.35(95% CI: 1.19-1.54). HR of RFS in three subgroups where the margin was less than 5 mm, or ranges from 5 mm to 9 mm, or less than 10 mm in length were 1.38(95%CI: 1.07-1.78), 1.39(95%CI: 1.11-1.74), 1.30(95%CI: 1.06-1.60), respectively.

Conclusion: Among ICC patients who received curative hepatectomy with R0 margin, we found those with margins ≥10 mm had survival advantages over the rest up to a point.

Keywords: intrahepatic cholangiocarcinoma; surgical margin width; prognosis survival rate; meta-analysis

Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary malignancy originating in the liver, which makes up 10%-15% of primary liver cancers. However, without distinct pathogenic factors or clinicopathological features, the diagnosis of ICC tends to be hard[1,2]. Most patients have to receive hepatobiliary resection since they have processed to the advanced stage of ICC[3]. Limited knowledge about its pathological features also adds difficulty to the prognosis of ICC patients. Even after the radical surgery, the recurrence rate remains high and the 5-year survival rate ranges from only 30-35%. The past three decades have seen the incidence and mortality rate of ICC keep elevating while with rather poor prognosis[4].

Since radical hepatic resection remains the best curative treatment for ICC patients[3], efforts should be spared in seeking optimal surgical management and other factors that can enable a better prognosis. Among the incomplete list of factors purposed by current studies to affect the prognosis of ICC patients, the width of the surgical margin is one controversial factor[4,5]. Some research observed that ICC patients with surgical margin width ≥10 mm are likely to have a better prognosis than those with surgical margin width less than 10 mm. Yet contrary research refuted the observation by demonstrating that the surgical margin width did not apply to every ICC patient. Since these studies only include limited samples or only focus on overall survival (OS), their conclusions have not been extensively applied yet[6]. Unlike tumor status, lymph node metastasis and lymph node dissection, surgical margin width is the one and only factor that can be controlled during ICC treatment. Hence, finding an optimal surgical margin width carries great clinical ramifications. Tang *et al.*[7] published a meta-analysis about the influence of surgical margins on the prognoses of ICC patients in 2016. Their research included the hazard ratio (HR) of OS in six retrospective cohort studies, and compares the prognoses of patients with different margin widths with the cutoff value of 10 mm. But still, its absence of disease-free survival (DFS), recurrence-free survival (RFS) and new cohort studies released during the seven years after its publication

renders their research too dated to guide future clinical treatment.

Therefore, this research attempted to update the prior meta-analysis by including studies published in the past seven years that concerns OS, DFS and RFS of ICC patients. Hopefully, the research will provide compelling evidence for the discussion of the optimal surgical margin width.

1. Materials and Methods

1.1 Inclusion Criteria

(1) ICC patients (confirmed by pathological examination) received potentially curative hepatectomy; (2) Patients underwent R0 resection (which was defined as the distance between the nontumorous tissue and cancer cells >1 mm)[2] with clear surgical margin edge; (3) Patients were classified according to the width of the resection margin, defined as the shortest distance from the edge of the tumor to the line of resection[5]. Patients with margin widths shorter than 4 mm or ranging from 5-10 mm were included in the narrow margin group (<10 mm), and those with margin widths equal to 10 mm or above were included in the wide margin group (≥10 mm); (4) With wide margin group as the control, HR and 95% confidential interval (CI) of DFS, RFS, OS in 1-4 mm margin group and 5-9 mm margin group were either available in included studies or can be calculated from HR Excel spreadsheet by using survival curves like Tierney[8].

1.2 Exclusion Criteria

(1) Abstract, literature reviews, pathological reports, editorials and expert reviews; (2) Studies published repeatedly; (3) Study results reached not through calculation; (4) Animal studies; (5) Studies group patients with different cutoff points instead of 5 mm and 10 mm; (6) Repeat resection for recurrence; (7) Patients with extrahepatic metastases.

1.3 Study Search Strategy

Systematic research was completed in PubMed, Embase and Web of Science to collect relevant studies available by June 2022. We searched with a combination of medical research (MeSH) terms and free text terms, including “intrahepatic

cholangiocellular carcinoma", "intrahepatic cholangiocarcinoma", "surgical margin length" and "margins of excision". The reference lists of included studies were manually examined for potential studies that met the inclusion criteria.

1.4 Study Selection

We selected studies by (1) basic information like title, first author, publication year, nation, and the time of research; (2) baseline characteristics like sample size, disease, average age, and sex; (3) key factors that bias hazard ratio evaluation; (4) outcome indicators and measured data.

1.5 Data Extraction

To minimize bias, we had two investigators select studies and extract data in duplicate independently and then adopted cross-validation to measure their accuracy. Disagreement was settled by further discussion or judged by the third investigator. Subsequently, a data extraction sheet designed for this study was used to abstract the following information: (1) basic information about included studies like first author, publication year, nation, type of article, and research period; (2) baseline characteristics about included cohort like number, sex, age, margin width, cutoff points, size of each group, and the longest follow-up time; (3) indicators of surgery like techniques and instruments of liver parenchyma transection; (4) outcome indicators like HR and corresponding 95%CI of DFS, RFS and OS.

1.6 Quality Assessment of Included Studies

Included studies were evaluated by two investigators using the Newcastle-Ottawa Scale (NOS), an assessment scale covering eight items including the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively. Any disagreement in assessment was resolved by the third investigator.

1.7 Statistical Analysis

We used Stata MP16 software to conduct statistical analysis. Between-study heterogeneity was tested by Chi-squared (X^2) test (α=0.1) and further evaluated using I^2. When $I^2 \leq 50\%$, a fixed effect model of the meta-analysis was employed; when $I^2 > 50\%$, a random effect model was used to analyze possible reasons, together with

sub-group and descriptive analysis. If heterogeneity arises from poor research quality, sensitivity analysis ensued to evaluate the stability and certainty of meta-analysis. The publication bias was analyzed by funnel plot. If the funnel plot was symmetrical, there was no publication bias. The inspection level of meta-analysis was set as $\alpha = 0.05$.

2. Results

2.1 Selected Studies and Quality Assessment

Preliminary research returned 73 relevant studies (34 from Pubmed; 28 from Embase; 11 from Web of Science). After screening the title and abstract of these entries identified in the search, 24 studies were retained. Eventually, 9 studies were included after reading their full-text publications. Among these included studies published from 2008 to 2021, 3 were conducted in China, 1 in Austria, 1 in Korea, 1 in France, 2 in USA and 1 in Japan. The PRISMA flow chart for included studies was presented in Figure 1. NOS scores of included studies in Table 1 showed that top-rated retrospective cohort studies were of high quality.

Table 1. Quality assessment of included studies

Study	Selection				Comparability	Outcome			**Score**
	A	B	C	D	E	F	G	H	
Tamandl2008	*	*	*	*	*	*	*	*	**8**
Cho2010	*	*	*	*	*	*	*		**7**
Farges2011	*	*	*	*	*	*	*	*	**8**
Spolverato2015	*	*	*	*	*	*	*	*	**8**
Ma2016	*	*	*	*	*	*	*	*	**8**
Tang2016	*	*	*	*	*	*	*	*	**8**
Watanabe2020	*	*	*	*	**	*	*	**	**10**
Bartsch2020	*	*	*	*	*	*	*		**7**
Zhu2020	*	*	*	*	**	*			**6**
Liu2021	*	*	*	*	*	*	*	*	**8**

* A maximum of 2 stars can be allotted in this category, one for age, and the other for other controlled

factors.

A: Representativeness of the exposed cohort

B: Selection of the non-exposed cohort

C: Ascertainment of exposure

D: Demonstration that outcome of interest was not present at start of study

E: Comparability of cohorts based on the design or analysis

F: Assessment of outcome

G: Was follow-up long enough for outcomes to occur

H: Adequacy of follow-up of cohorts

2.2 Characteristics of Included Studies

2158 out of 2404 reporting ICC patients in included studies underwent R0 resection, and among them, 770 (35.68%) were with wide surgical margin, 1388 (64.32%) with narrow margin. Most involved patients aged around 60. Majority of resections were done with modern technology or dissection devices, such as Cavitron ultrasonic surgical attractor or ultrasonic dissector. The baseline characteristics of narrow (<10 mm) and wide (≥10 mm) margin groups were similar across the 9 included studies. The follow-up length ranges from 1 to 84 months. Detailed information is available in Table 2.

Table 2. Patients' characteristics of 9 cohorts

Author	Year	Nation	No. of Patient	Age, $M(Q_{25}\sim Q_{75})$	Sex, male (%)	Follow-Up, Mouth	Resection width	
							≥10mm	<10mm
Tamandl	2008	Austria	74	63.2（33.3-85.8）	29(39)	1-64	15	38
Cho	2010	Korea	63	61.4(27-82)	41(65)	NA	23	40
Farges	2011	France	212	NA	108(51)	NA	45	116
Spolverato	2015	USA	583	NA	302(52)	NA	174	266
Ma	2016	China	107	61（25-79）	58(54)	1-60	25	50
Zhu	2020	China	126	NA	66(52)	1-54	34	92
Watanab	2020	Japan	635	64.2(32.3-84.4)	388(61)	1-84	237	398

e								
Bartsch	2020	USA	126	NA	NA	0-24	22	109
Liu	2021	China	478	58（49-64）	287(60)	NA	195	283
Total			2404		1279(56)		770	1388

2.3 Meta-analysis Results

2.3.1 OS

9 included studies all related to the influence of surgical margin width on the OS of ICC patients. This meta-analysis synthesized relevant data by categorizing margin width into <10 mm and ≥10 mm groups, and the former was further categorized into three subgroups: <5 mm (1-4 mm, three studies) 5-9 mm (≥5 mm, three studies) and <10 mm (five studies). There was no overall heterogeneity in the included studies (I^2=14.6%, P=0.305). The fixed effect model meta-analysis indicated that, compared with the wide margin group (≥10 mm), pooled HR of the narrow margin group (<10 mm) stood at 1.54 (95%CI: 1.34-1.77). No significant heterogeneity was found across three subgroups, <5 mm (I^2=0.0%, P=0.839), 5-9 mm (I^2=0.0%, P=0.394), and <10 mm (I^2=31.8%, P=0.209) groups. Compared with the wide margin group, pooled HR of three subgroups (<5 mm, 5-9 mm and <10 mm groups) were 1.88 (95%CI: 1.45-2.42), 1.33 (95%CI: 1.03-1.72) and 1.49 (95%CI: 1.20-1.84), respectively, as Figure 2 showed.

2.3.2 DFS

Two included studies relating to the influence of margin width on DFS of ICC patients showed no overall heterogeneity (I^2 =0.0%, P=0.926). According to the result of the fixed effect model in Figure 3, with the wide margin group (≥10 mm) as the control, the overall pooled HR of the narrow margin group (<10 mm) was 1.51 (95%CI: 1.14-2.00) (Figure 3).

2.3.3 RFS

With five included studies concerning the influence of margin width on RFS of

ICC patients, we categorized the outcome variable in the same way as we conducted study on OS. With no heterogeneity across the included studies (I^2=0.0%, P=0.443), the pooled HR was 1.35 (95CI%: 1.19-1.54). The fixed effect model of subgroup analysis found no heterogeneity across <5 mm (I^2=0.0%, P=0.576) and 5-9 mm (I^2=0.0%, P=0.450) groups. Compared with the wide margin group (≥10 mm), pooled HR of <5 mm and 5-9 mm groups were 1.38 (95%CI: 1.07-1.78) and 1.39 (95%CI: 1.11-1.74), respectively. With heterogeneity (I^2=57.7%, P=0.094) in the narrow margin (<10 mm) group, compared with the wide margin (≥10 mm) group, the pooled HR of the narrow margin group was found to be 1.30 (95%CI: 1.06-1.60) in comparison with the wide margin group (≥10 mm) (Figure 4).

2.4 Sensitivity Analysis

By excluding one study at a time, sensitivity analysis of OS and RFS was conducted. Results in Figure 5,6 showed no significant difference between the effect size and the total effect size of OS and RFS, implying that the result reached in this study was relatively stable.

3. Discussion

The incidence and mortality rates of ICC keep climbing across the world. Since neither risk factors nor early-stage clinical features are made clear about ICC, most patients are not diagnosed until ICC reached an advanced stage[1]. Though liver resection is the best potentially curative treatment ICC patients could choose, the five-year survival rate after surgery still ranges from 21% to 35%[9]. With impacts of surgical margin width on the prognoses of patients being noticed recently, surgeons expect a margin width that could optimize prognosis.

R0 is acknowledged to be more effective than R1, yet the effect of margin width in R0 resection on prognoses of ICC patients is still under debate. In 2016, Tang *et al.*[7] carried out a meta-analysis relating to the influence of margin width on the prognoses of ICC patients, indicating that patients with wide margin (≥10 mm) have a survival

advantage over those with narrow margin (<10 mm) (HR: 1.59, 95%CI: 1.09-2.32). Our study further included relevant studies released during 2016-2022 to the 2016 meta-analysis. Two irrelevant studies with a limited sample size in the 2016 meta-analysis were excluded and five eligible retrospective cohort studies published after 2016 were included. Besides, this study also filled the void of RFS (4 included studies) and DFS (2 included studies).

9 included studies all focused on the mass-forming (MF) type of ICC (as it accounts for over 66% of ICC[1]) and categorized the outcome variable into 5 groups: <1 mm, 1-4 mm, 5-9 mm, <10 mm and ≥10 mm. One included study went beyond our research scope as it further categorized wide margin into ≥15 mm group, and relevant data were excluded from the meta-analysis. Pooled HR results indicated that with the wide margin (≥10 mm) group as the control, patients with a margin shorter than 10 mm were prone to poor prognosis (pooled HR of OS: 1.54, 95%CI: 1.34-1.77). It was demonstrated that ICC tumor cells could metastasize by directly infiltrating the adjacent liver parenchyma, accompanied by vascular infiltration and perineural infiltration, and then cause pathological changes of intrahepatic epithelial cells and surrounding tissues[10]. For most metastasis is limited within 10 mm around the primary lesion, a 10 mm or more resection is expected to cure these ICC patients. Ma *et al*.[2] suggested in their study in 2016 that margin width significantly impacts the OS of ICC-MF patients after resection. With the margin width greater than 9 mm, OS increased from 35.7 months to 184.6 months. With the margin width of or greater than 10 mm, DFS increased from 14.1 months to 86 months. The above results were consistent with the conclusion reached in the 2016 meta-analysis that ≥10 mm could be the optimal margin width for prognosis. The conclusion was further confirmed in the single-center research by Zhu *et al.*[11] in 2020. Their research results showed that a resection margin ≥10 mm means favorable OS (HR: 0.403; 95% CI: 0.191-0.854; *P*=0.018) and RFS (HR: 0.470; 95% CI: 0.242-0.914; *P*=0.026). Our study indirectly verified the above conclusions from another perspective. According to OS subgroup analysis results, pooled HR of the <5 mm group and 5-9 mm group were 1.88 (95%CI: 1.45-2.42) and 1.33 (95%CI: 1.03-1.72), respectively. Apparently, the 5-9 mm group has a much lower prognostic risk.

However, such a remarkable difference was observed in the RFS subgroup analysis, where pooled HR of the <5 mm group and 5-9 mm group were 1.38 (95%CI: 1.07-1.78) and 1.39 (95%CI: 1.11-1.74), respectively.

Though sensitivity analysis results indicated no significant difference across studies, the exclusion of 5-9 mm group by Spolverato (2015) in OS analysis and the exclusion of <10 mm group by Tamandl (2008) in RFS analysis led to relatively notable difference. Reviewing the study conducted by Spolverato *et al.* in 2015, we found the 1-year OS rate among 100 patients with 5-9 mm R0 margin (83.9%) was higher than that (79.8%) of 147 patients with ≥10 mm R0 margin. This may be the major factor that impacts the OS rate. As for the study conducted by Tamandl (2008) *et al.*, margin width (1-10 mm, >10 mm) is found to bear little relation to OS or RFS of patients. Such results may be attributed to its study cohort, among whom tumor type, size and lymph node metastasis vary greatly. These explanations were subsequently confirmed in the following studies. The study cohort of the research conducted by Liu *et al.*[12] in 2021 consisted of 478 ICC patients from 13 major Hepato-Biliary and Pancreatic centers in China. They conducted a 1:1 propensity score matching (PSM) analysis to match the prognostic factors like age, type of tumor, and lymph node metastasis, and left margin width as the only outcome variable (cutoff point is 10mm). Results indicated improved OS and DFS in the wide margin group than the narrow margin group. The study also found that in its unpaired subgroup analysis, a wide margin only benefits the American Joint Committee on Cancer (AJCC) stage I ICC patients, not the patients with lymphatic metastasis. Watanabe *et al*. (2020)[6] also observed in their study that wide margin width could impact prognosis. However, a closer review of its patient characteristics found that a higher proportion of single tumor patients and shorter tumor diameter among the wide margin group, while the narrow margin group who suffers from larger and more invasive tumors appear with a greater prevalence of vascular invasion and advanced tumor. These factors are likely to confuse the survival comparison between two groups. The study also pointed out that a wide margin will not bring benefits to patients with lymphatic metastasis, and may increase the risk of adverse complications such as postoperative hemorrhage and liver failure. Taken together above-mentioned analysis,

the surgeon should take tumor type and lymphatic involvement into consideration when completing a margin width of or greater than 10 mm. A margin width greater than 10 mm would benefit MF-ICC patients and patients without lymph node metastasis. Unfortunately, there are several limitations in this study. The type of liver resection (anatomical or non-anatomical), surgical instruments (Cavitron ultrasonic surgical attractor may cause in situ damage to the cutting edge and liver tissue necrosis[6]) and the control of chemotherapy drugs on tumors (some studies show that chemotherapy drugs could control 60-80% of tumor progression[6]) were not analyzed in subgroups. Future studies are required to answer how these above-mentioned factors may influence the prognosis of ICC patients.

In a nutshell, the meta-analysis confirmed that among ICC patients undergoing curative hepatectomy, those with a margin width ≥10 mm had survival advantages over those with a margin width <10 mm. However, surgeons should take individual conditions into consideration in determining the margin width. Margin width <10 mm should not be regarded as a surgical taboo. In sum, while surgeons should try to achieve a surgical margin ≥10 mm, further support from the results of multicenter and high-quality randomized controlled trials is still needed to ensure a better prognosis and longer survival time for patients.

Declarations

Patient and Public Involvement

No patient involved.

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors consent to submit the manuscript for publication.

Availability of data and materials

The data used to support the findings of this study are included within the article.

Competing interest

The authors declare no conflicts of interest.

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Authors' contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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Not applicable.

Reference

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Figure legends

Figure 1 PRISMA flow chart for the included studies

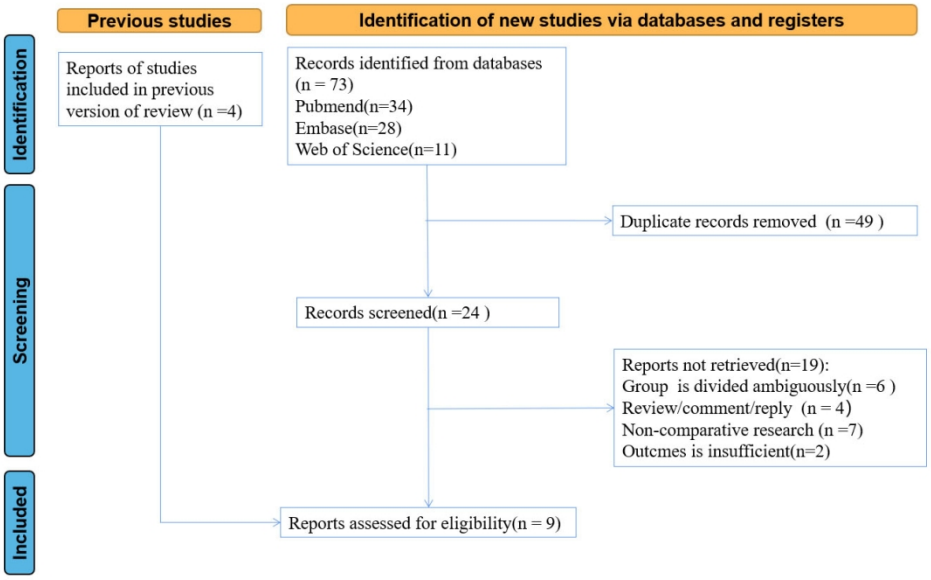
Figure 2 Results of HR pooled analysis of the OS rate of the included studies (with the wide margin group ≥10 mm as the control)

Figure 3 Results of HR pooled analysis of DFS in the included studies (with wide margin group ≥10 mm as the control)

Figure 4 Results of HR pooled analysis of RFS in the included studies (with wide margin group ≥10 mm as the control)

Figure 5 Sensitivity analysis of OS after excluding some studies

Figure 6 Sensitivity analysis of RFS after excluding some studies



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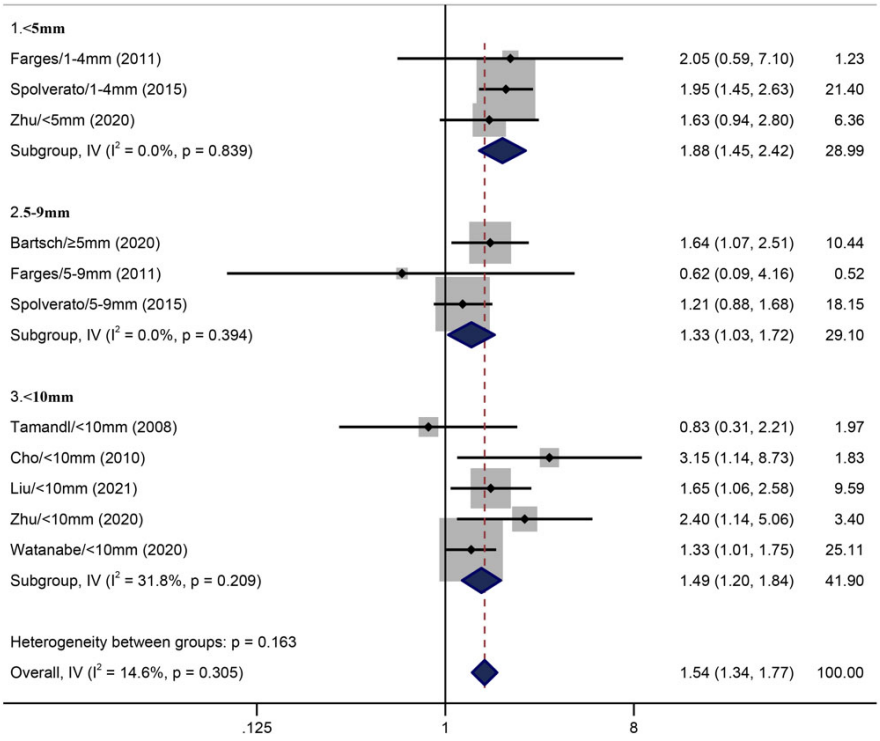

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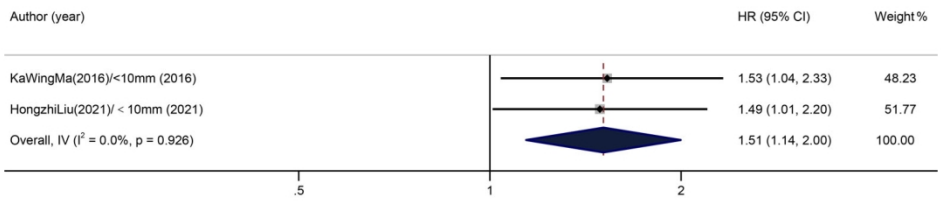

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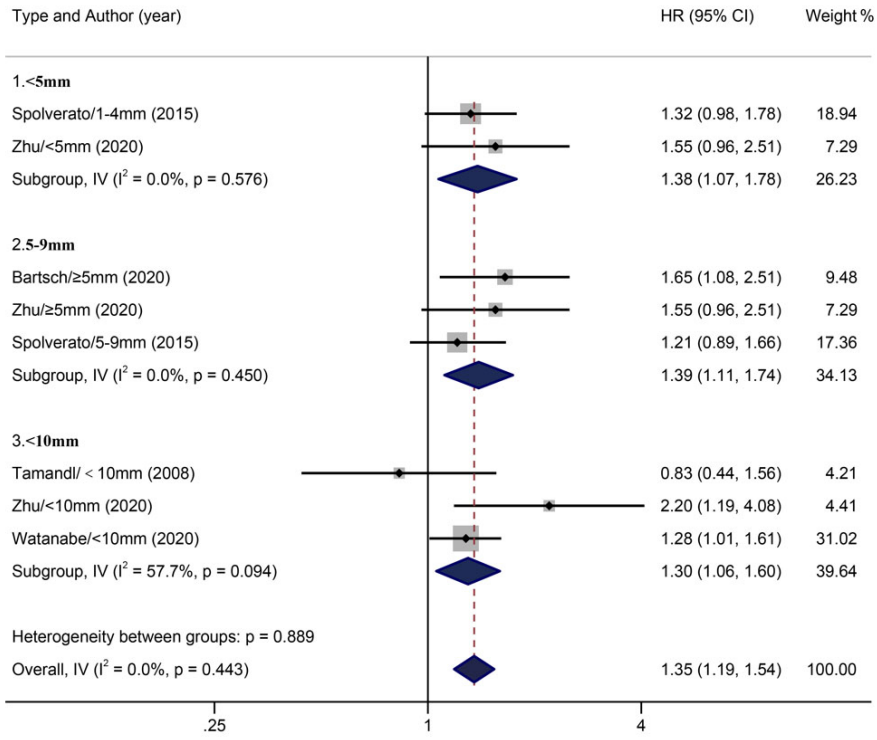

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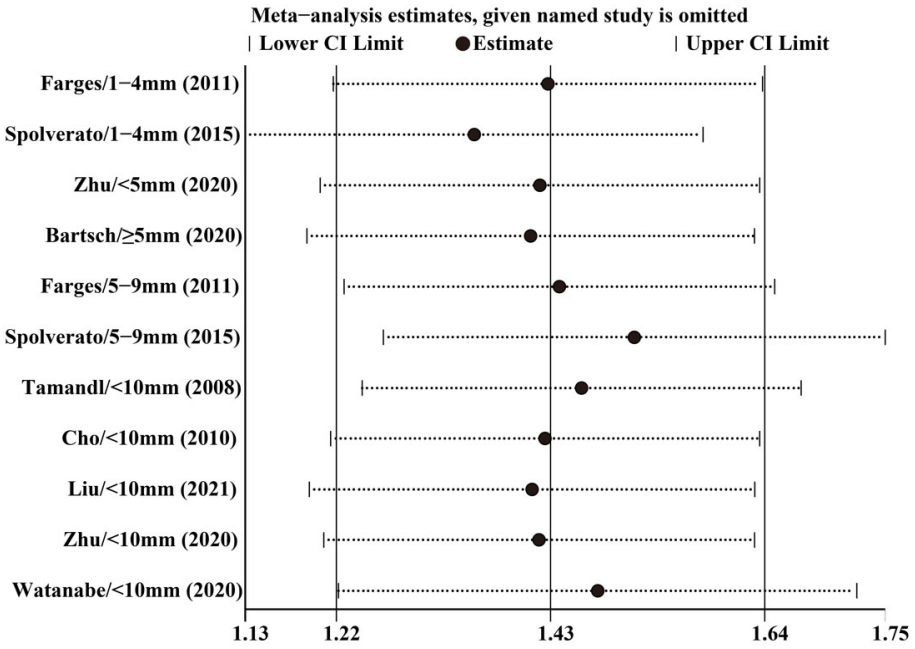

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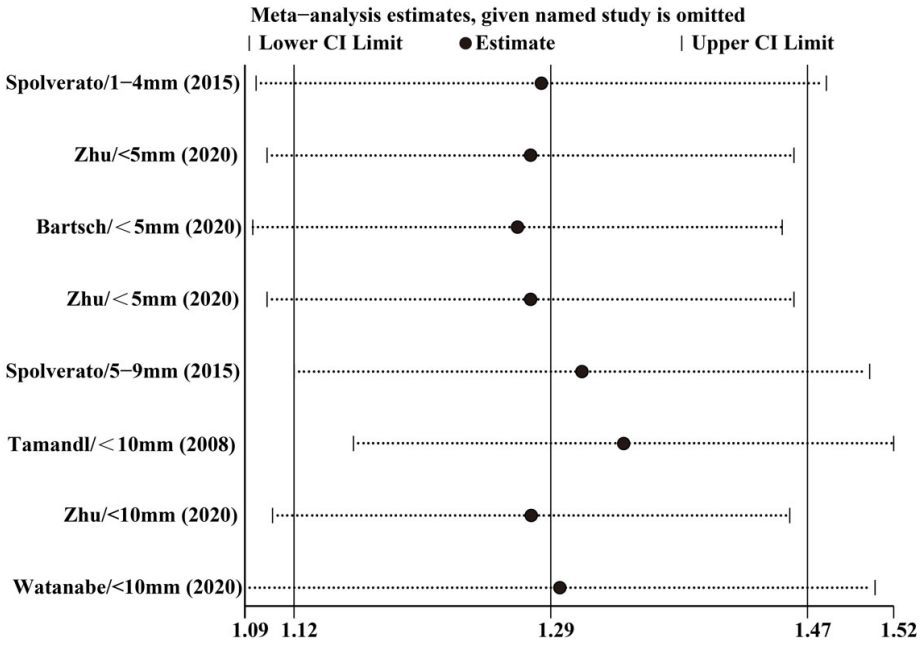

105x78mm (300 x 300 DPI)

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	/
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	/
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	/
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	/
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	5-6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	/
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	/
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	/
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	/
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	/
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	/
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	/

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	6-7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	/
Study characteristics	17	Cite each included study and present its characteristics.	/
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	/
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	7
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	/
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	7-8
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	/
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	/
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	/
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	/
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	8-9
	23b	Discuss any limitations of the evidence included in the review.	9
	23c	Discuss any limitations of the review processes used.	9
	23d	Discuss implications of the results for practice, policy, and future research.	10
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	/
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	/
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	/
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	11
Competing interests	26	Declare any competing interests of review authors.	11
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	11

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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Influence of surgical margin width on survival rate after resection of intrahepatic cholangiocarcinoma: a systematic review and meta-analysis

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Influence of surgical margin width on survival rate after resection of intrahepatic cholangiocarcinoma: a systematic review and meta-analysis

Authors:

Jing-Hua Jiang [1], Da-Zhang Fang [1], Yi-Ting Hu [2*].

Affiliation:

1. Department of Hepatobiliary and Pancreatic Surgery, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua 321000, China.
2. Department of Hepatobiliary and Pancreatic Surgery, Shulan (Hangzhou) Hospital, Zhejiang Shuren University, Shulan International Medical College, Hangzhou 310022, China.

***Corresponding Author Information:** DR. Yi-Ting Hu. Department of Hepatobiliary and Pancreatic Surgery, Shulan (Hangzhou) Hospital, Zhejiang Shuren University, Shulan International Medical College, Dongxin Road 848#, Hangzhou 310022, China. Tel: +86-13515861057, E-mail: yitingh@yeah.net.

Abstract

Objectives: Hepatectomy is the best treatment for patients with intrahepatic cholangiocarcinoma (ICC) at present, but there has been controversy about the width of surgical margins. In this study, we systematically investigated the effects of different surgical margin widths on the prognostic survival of ICC patients undergoing hepatectomy through a meta-analysis.

Design: Systematic evaluation and meta-analysis were performed by using Stata software.

Data sources: PubMed, Embase, and Web of Science databases were systematically searched from inception to June 2022.

Eligibility criteria: Cohort studies published in English were primarily included and patients who underwent negative margin (R0) resection were selected. The effects of surgical margin width on overall survival (OS), disease-free survival (DFS), and recurrence-free survival (RFS) in patients with ICC were assessed.

Data extraction and synthesis: Two investigators independently conducted literature screening and data extraction, while risk of bias was assessed using funnel plots. Literature quality was assessed by the Newcastle-Ottawa Scale (NOS). Forest plots of risk ratios (HR) and their 95% confidence intervals (CI) for outcome indicators were plotted. Heterogeneity was assessed and determined quantitatively using I^2, and the stability of the study results was evaluated using sensitivity analysis.

Results: A total of 9 studies were included. With the wide margin group (≥10 mm) as the control, pooled HR of OS in the narrow margin group (<10 mm) was 1.54 (95%CI: 1.34-1.77). HR of OS in three subgroups where the margin was less than 5 mm, or ranges from 5 mm to 9 mm, or less than 10 mm in length were 1.88 (95%CI: 1.45-2.42), 1.33 (95% CI: 1.03-1.72), 1.49 (95%CI: 1.20-1.84), respectively. Pooled HR of DFS in the narrow margin group (<10 mm) was 1.51 (95%CI: 1.14-2.00). Pooled HR of RFS in the narrow margin group (<10 mm) was 1.35 (95% CI: 1.19-1.54). HR of RFS in three subgroups where the margin was less than 5 mm, or ranges from 5 mm to 9 mm, or less than 10 mm in length were 1.38 (95%CI: 1.07-1.78), 1.39 (95%CI: 1.11-1.74),

1.30 (95%CI: 1.06-1.60), respectively. Neither lymph node lesions (HR: 1.44; 95%CI: 1.22-1.70) nor lymph node invasion (HR: 2.14; 95%CI: 1.39-3.28) were favorable for postoperative OS in ICC patients. Meanwhile, lymph node metastasis (HR: 1.31, 95%CI: 1.09-1.57) was unfavorable for RFS in ICC patients.

Conclusion: ICC Patients who underwent curative hepatectomy with a negative margin ≥10 mm may have a long-term survival advantage, but lymph node dissection also needed to be considered. In addition, tumor-related pathological features needed to be explored to see if they affect the surgical outcome of R0 margins.

Keywords: intrahepatic cholangiocarcinoma; surgical margin width; prognosis survival rate; meta-analysis

Strengths and limitations of this study

1. HRs and their 95% CIs for survival data were available from the literature or can be combined with effect sizes by intercepting survival from survival graphs.
2. The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the literature.
3. Publication bias analysis was performed using Egger test and Begg funnel plot.
4. Sensitivity analysis was used to determine the stability and strength of the combined results.
5. Differences based on the type of study (single-center and multicenter studies) and the limited number of studies may affect the statistical results.

Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary malignancy originating in the liver, which makes up 10%-15% of primary liver cancers. However, without distinct pathogenic factors or clinicopathological features, the diagnosis of ICC tends to be hard[1, 2]. Most patients have to receive hepatobiliary resection since the disease has processed to the advanced stage of ICC[3]. Limited knowledge about its pathological features also adds difficulty to the prognosis of ICC patients. Even after the radical surgery, the recurrence rate remains high and the 5-year survival rate ranges from only 30-35%. The past three decades have seen the incidence

and mortality rate of ICC keep elevating while with a rather poor prognosis[4].

Up to now, radical hepatectomy remains the best option for potentially curative treatment of ICC patients, mainly to achieve negative marginal (R0) resection[5, 6]. But high local recurrence rate after R0 resection may be related to the location and extent of the primary lesion, lymph node involvement, and surgical margin status, leading to a poor prognosis[5, 7]. Additionally, surgical margin width is also of prognostic essence after ICC resection, but the definition of the width remains controversial. A recent multicenter study reported that patients with a margin width ≥10 mm have better long-term prognostic outcomes relative to patients with a surgical margin width <10 mm[8]; however, another study stated that wide margin hepatectomy does not produce a survival benefit in all ICC patients and is more beneficial for patients without lymph node metastases[9]. Hence, it is necessary to evaluate the margin width in patients with ICC undergoing R0 resection.

Li *et al.*[10] evaluated the relationship between surgical margin status and survival benefit in ICC by meta-analysis and found that negative surgical margins are more beneficial for ICC patients' overall survival (OS) and disease-free survival (DFS) after surgical resection, thus emphasizing the importance of R0 resection. In a recent meta-analysis of the effect of surgical margin width on OS in ICC patients, it is similar that ICC patients with R0 ≥10 mm have a longer survival benefit than those with <10 mm[11]. But this analysis did not provide statistical analysis of DFS, recurrence-free survival (RFS), or a more refined stratification of the range of R0 margin width, making the findings lacking reference value for clinical treatment at the present stage. Therefore, this study was updated from the above meta-analysis to investigate the effect of margin width on OS, DFS, and RFS in ICC patients who underwent R0 surgical resection in recent years, as well as a stratification study of margin width (<5 mm, 5-9 mm, <10 mm, and ≥10 mm), to provide more evidence-based medical evidence for the determination of surgical margin width in ICC patients.

1. Methods

1.1 Study Search Strategy

Systematic research was completed in PubMed, Embase and Web of Science to collect relevant studies available by June 2022. The literature search took the form of a combination of medical subject headings (Mesh) and free words, mainly including (((((Cholangiocarcinomas) OR (Cholangiocellular Carcinoma)) OR (Intrahepatic Cholangiocarcinoma)) OR (Cholangiocarcinomas, Intrahepatic)) AND (Surgical margin width)) OR (Length of surgical margin) (Supplementary file). The reference lists of included studies were manually screened for relevant studies that may meet the inclusion requirements.

1.2 Inclusion Criteria

(1) ICC patients (confirmed by pathological examination) received potentially curative hepatectomy; (2) Patients underwent R0 resection (which was defined as the distance between the nontumorous tissue and cancer cells >1 mm)[2] with clear surgical margin edge; (3) Patients were classified according to the width of the resection margin, defined as the shortest distance from the edge of the tumor to the line of resection[12]. Patients with margin widths shorter than 4 mm or ranging from 5-10 mm were included in the narrow margin group (<10 mm), and those with margin widths equal to 10 mm or above were included in the wide margin group (≥10 mm); (4) The correlations of surgical margin width with OS, DFS, and RFS were presented in the included studies., i.e., the Hazard Ratio (HR) and 95% confidence interval (CI) could be obtained directly from the literature or could be calculated indirectly.

1.3 Exclusion Criteria

(1) Abstract, literature reviews, pathological reports, editorials and expert reviews; (2) Studies published repeatedly; (3) Study results reached not through calculation; (4) Animal studies; (5) Studies group patients with different cutoff points instead of 5 mm and 10 mm; (6) Repeat resection for recurrence; (7) Patients with extrahepatic metastases.

1.4 Study Selection

We selected studies by (1) basic information like title, first author, publication year, nation, and the time of research; (2) baseline characteristics like sample size, disease, average age, and sex; (3) key factors that bias hazard ratio evaluation; (4) outcome

indicators and measured data.

1.5 Data Extraction

To minimize bias, we had two investigators select studies and extract data in duplicate independently and then adopted cross-validation to measure their accuracy. Disagreement was settled by further discussion or judged by the third investigator. Subsequently, a data extraction sheet designed for this study was used to abstract the following information: (1) basic information about included studies like the name of the first author, publication year, nation, type of article, and research period; (2) baseline characteristics about included cohort like the number of people receiving R0 resection, sex, age, subgroup threshold, lymph node metastasis, number of people in the narrow margin group of <10 mm and the wide margin group of ≥10 mm, the longest follow-up time, liver parenchymal dissection techniques and instrumentation, tumor subtypes, and adjuvant chemotherapy and radiotherapy; (3) Primary outcome indicator: HR and 95% CI for prognostic OS and DFS for patients in each group. Secondary outcome indicator: HR and 95% CI for RFS and lymph node status. OS was defined as the interval from the date of surgery to the patient's death or last follow-up. DFS was defined as the interval from the date of surgery to the date of first recurrence, secondary malignancy, or death of any disease course. RFS was defined as the interval from the date of surgery to the date of first tumor recurrence, secondary malignancy, or death with evidence of recurrence. Tumor morphology was typologically defined based on preoperative imaging and case reports, and ICC was classified into three categories based on the macroscopic types proposed by the Japanese Liver Cancer Study Group: mass-forming (MF) type, periductal infiltrating (PI) type, and intraductal growth (IG) type[9]. For HR and 95% CI of DFS, RFS and OS, if not directly available from the literature, data such as survival rate can also be intercepted from survival graphs and entered into Excel with information such as follow-up time, and finally combined effect sizes by meta-analysis using RevMan software[13].

1.6 Quality Assessment of Included Studies

Included studies were evaluated by two investigators using the Newcastle-Ottawa Scale (NOS), an assessment scale covering eight items including the selection of the

study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively. Any disagreement in assessment was resolved by the third investigator.

1.7 Statistical Analysis

We used Stata MP16 software to conduct statistical analysis. Between-study heterogeneity was tested by Chi-squared (χ^2) test (α=0.1) and further evaluated using I^2. When $I^2 \leq 50\%$, a fixed effect model of the meta-analysis was employed; when $I^2 > 50\%$, a random effect model was used to analyze possible reasons, together with sub-group and descriptive analysis. If heterogeneity arises from poor research quality, sensitivity analysis ensued to evaluate the stability and certainty of meta-analysis. Publication bias analysis used Egger test and Begg funnel plot. If the funnel plot was symmetrical, indicating a lack of publication bias. The inspection level of meta-analysis was set as α= 0.05.

Patient and Public Involvement

No patient involved.

2. Results

2.1 Selected Studies and Quality Assessment

Preliminary research returned 73 relevant studies (34 from Pubmed; 28 from Embase; 11 from Web of Science). After screening the title and abstract of these entries identified in the search, 24 studies were retained. Eventually, 9 studies were included after reading their full-text publications[2-4, 8, 9, 12, 14-16]. Among these included studies published from 2008 to 2021, 3 were conducted in China, 1 in Austria, 1 in Korea, 1 in France, 2 in USA and 1 in Japan. The PRISMA flow chart for included studies was presented in Figure 1. NOS scores of included studies in Table 1 showed that top-rated retrospective cohort studies were of high quality.

Table 1. Quality assessment of included studies

Study	Selection	Comparability	Outcome	**Score**

	A	B	C	D	E	F	G	H	
Tamandl2008	*	*	*	*	*	*	*	*	**8**
Cho2010	*	*	*	*	*	*	*		**7**
Farges2011	*	*	*	*	*	*	*	*	**8**
Spolverato2015	*	*	*	*	*	*	*	*	**8**
Ma2016	*	*	*	*	*	*	*	*	**8**
Tang2016	*	*	*	*	*	*	*	*	**8**
Watanabe2020	*	*	*	*	**	*	*	**	**10**
Bartsch2020	*	*	*	*	*	*	*		**7**
Zhu2020	*	*	*	*	**	*			**6**
Liu2021	*	*	*	*	*	*	*	*	**8**

Notes: Each study can have up to one "*" for each item on "Selection" and "Outcomes", and up to two "*" for each item on "Comparability".

A: Representativeness of the exposed cohort

B: Selection of the non-exposed cohort

C: Ascertainment of exposure

D: Demonstration that outcome of interest was not present at start of study

E: Comparability of cohorts based on the design or analysis

F: Assessment of outcome

G: Was follow-up long enough for outcomes to occur

H: Adequacy of follow-up of cohorts

2.2 Characteristics of Included Studies

As presented in Table 2, most involved patients aged around 60. The majority of resections were done with modern technology or dissection devices, such as Cavitron ultrasonic surgical attractor or ultrasonic dissector. The baseline characteristics of narrow (<10 mm) and wide (≥10 mm) margin groups were similar across the 9 included studies. The follow-up length ranges from 1 to 84 months. In four studies, several patients were treated with neoadjuvant or adjuvant treatment. Six studies analyzed the tumor morphology, with a predominance of MF type. Only three reported lymph node

metastasis (23.94%-70.5%). Besides, the number of people in the study by Ma *et al.*[2] could not be clearly extracted for the narrow margin group (<10 mm) and the wide margin group (≥10 mm), so the exact number of people in both groups could not be clarified. But some survival data could be extracted from that study, and therefore were also included in our study for survival analysis.

Table 2. Patients' characteristics of 9 cohorts

Year	Nation	No. of Patient	Age, $M(Q_{25}\sim Q_{75})$	Sex, male (%)	Follow-Up, Mouth	Resection width		Lymph node metastasis, n	Adjuvant radiotherapy/ chemotherapy
						≥10 mm	<10 mm		
2008	Austria	53	63.2 (33.3-85.8)	29 (39)	1-64	15	38	NR	NR
2020	Korea	63	61.4 (27-82)	41 (65)	NR	23	40	13	NR
2019	France	161	NR	108 (51)	NR	45	116	47	NC:12 AC: 51
2015	USA	440	NR	302 (52)	NR	174	266	NR	AC: 212 AR: 44
2016	China	95	61 (25-79)	58 (54)	1-60	NR	NR	NR	NR
2020	China	109	NR	66 (52)	1-54	17	92	NR	NC: 1
2020	Japan	635	64.2 (32.3-84.4)	388 (61)	1-84	237	398	152	NR
2020	USA	131	NR	NR	0-24	22	109	NR	PC: 3
2021	China	478	58 (49-64)	287 (60)	NR	195	283	NR	NR

2.3 Meta-analysis Results

2.3.1 OS

9 included studies all related to the influence of surgical margin width on the OS

of ICC patients. This meta-analysis synthesized relevant data by categorizing margin width into <10 mm and ≥10 mm groups, and the former was further categorized into three subgroups: <5 mm (1-4 mm, three studies) 5-9 mm (≥5 mm, three studies) and <10 mm (five studies). There was no overall heterogeneity in the included studies (I^2=14.6%, P=0.305). The fixed effect model meta-analysis indicated that, compared with the wide margin group (≥10 mm), pooled HR of the narrow margin group (<10 mm) stood at 1.54 (95%CI: 1.34-1.77). No significant heterogeneity was found across three subgroups, <5 mm (I^2=0.0%, P=0.839), 5-9 mm (I^2=0.0%, P=0.394), and <10 mm (I^2=31.8%, P=0.209) groups. Compared with the wide margin group, pooled HR of three subgroups (<5 mm, 5-9 mm and <10 mm groups) were 1.88 (95%CI: 1.45-2.42), 1.33 (95%CI: 1.03-1.72) and 1.49 (95%CI: 1.20-1.84), respectively, as Figure 2 showed.

2.3.2 DFS

Two included studies relating to the influence of margin width on DFS of ICC patients showed no overall heterogeneity (I^2 =0.0%, P=0.926). According to the result of the fixed effect model in Figure 3, with the wide margin group (≥10 mm) as the control, the overall pooled HR of the narrow margin group (<10 mm) was 1.51 (95%CI: 1.14-2.00) (Figure 3).

2.3.3 RFS

With five included studies concerning the influence of margin width on RFS of ICC patients, we categorized the outcome variable in the same way as we conducted study on OS. With no heterogeneity across the included studies (I^2=0.0%, P=0.443), the pooled HR was 1.35 (95CI%: 1.19-1.54). The fixed effect model of subgroup analysis found no heterogeneity across <5 mm (I^2=0.0%, P=0.576) and 5-9 mm (I^2=0.0%, P=0.450) groups. Compared with the wide margin group (≥10 mm), pooled HR of <5 mm and 5-9 mm groups were 1.38 (95%CI: 1.07-1.78) and 1.39 (95%CI: 1.11-1.74), respectively. With heterogeneity (I^2=57.7%, P=0.094) in the narrow margin (<10 mm) group, compared with the wide margin (≥10 mm) group, the pooled HR of the narrow margin group was found to be 1.30 (95%CI: 1.06-1.60) in comparison with

the wide margin group (≥10 mm) (Figure 4).

2.3.4 Correlation between lymph node status and prognosis

Subsequently, a subgroup analysis was done on the prognostic impact related to lymph node status. When there was moderate heterogeneity in the effect of lymph node lesions on OS (I^2=57.5%, P=0.051) according to the pooled HR and 95%CI of the multiple analyses of five positive lymph nodes, a random effects model was used for subsequent analysis (Figure 5). The results illustrated that lymph node lesions were detrimental to OS in patients with ICC (HR: 1.44; 95% CI: 1.22-1.70). When there was no significant heterogeneity in the effect of lymph node invasion on OS (I^2=21.2%, P=0.281), a fixed effects model was utilized (Figure 6). The results reported that patients with ICC in the presence of lymph node invasion had markedly shorter OS (HR: 2.14; 95% CI: 1.39-3.28). In addition, the pooled HR of RFS associated with lymph node metastasis was analyzed, and the results showed notable heterogeneity (I^2=85.2%, P=0.009) (Figure 7). The results of the random effects model demonstrated that lymph node metastasis was detrimental to RFS in patients with ICC (HR: 1.31, 95% CI: 1.09-1.57).

2.4 Sensitivity Analysis

By excluding one study at a time, sensitivity analysis of OS and RFS was conducted. Results in Figure 8-9 showed no significant difference between the effect size and the total effect size of OS and RFS, implying that the result reached in this study was relatively stable. Egger test did not detect substantial publication bias in both OS (P=0.508) and RFS (P=0.523), and the Begg funnel plot was symmetrical (Figures 10-11). However, differences based on the type of study (single-center and multicenter studies) and the limited number of studies may affect the above statistical results.

3. Discussion

3.1 Current Status of Surgery for ICC

The incidence and mortality rates of ICC keep climbing across the world, most

patients are not diagnosed until ICC reached an advanced stage[1].

Currently, complete surgical resection with negative histological margins (R0) remains the only curative treatment modality favoring long-term survival outcomes in ICC patients, but only a minority of patients have resectable lesions, resulting in poor postoperative survival[5, 17]. A few studies have shown a better survival benefit for ICC patients undergoing R0 resection compared to R1 resection[2, 12]. But margin status, lymph node status, and the presence of vascular invasion all contribute to the poor prognosis of ICC patients after resection[18-20]. Most patients with ICC usually require adjuvant therapy[21]. In addition, investigators are concerned that in ICC patients undergoing R0 resection, the margin width also affects long-term survival after surgery[8, 15]. However, there has been controversy regarding the effect of R0 margin width on the prognostic survival of ICC patients. Thus, this meta-analysis was done to investigate the effect of margin width on survival outcomes after ICC resection.

3.2 The Impact of Margin Width on ICC Patients' Outcomes

In 2016, Tang *et al.*[11] published the first meta-analysis of the effect of margin width on prognostic survival in ICC patients. This study indicated that patients with wide margin (≥10 mm) have a survival advantage over those with narrow margin (<10 mm) (HR: 1.59, 95%CI: 1.09-2.32). Based on these investigations, we updated the study related to the effect of surgical margin width on the prognosis survival of ICC patients. Two irrelevant studies with a limited sample size in the 2016 meta-analysis were excluded and five eligible retrospective cohort studies published after 2016 were included. Besides, this study also filled the void of RFS (4 included studies) and DFS (2 included studies).

9 included studies all focused on the mass-forming (MF) type of ICC (as it accounts for over 66% of ICC[1]) and categorized the outcome variable into 5 groups: <1 mm, 1-4 mm, 5-9 mm, <10 mm and ≥10 mm. One included study went beyond our research scope as it further categorized wide margin into ≥15 mm group, and relevant data were excluded from the meta-analysis. Pooled HR results indicated that with the wide margin (≥10 mm) group as the control, patients with a margin shorter than 10 mm

were prone to poor prognosis (pooled HR of OS: 1.54, 95%CI: 1.34-1.77). It was demonstrated that ICC tumor cells could metastasize by directly infiltrating the adjacent liver parenchyma, accompanied by vascular infiltration and perineural infiltration, and then cause pathological changes in intrahepatic epithelial cells and surrounding tissues[22]. For most metastasis is limited within 10 mm around the primary lesion, a 10 mm or more resection is expected to cure these ICC patients. Ma *et al*.[2] suggested that margin width significantly impacts the OS of ICC-MF patients after resection. With a margin width greater than 9 mm, OS increased from 35.7 months to 184.6 months. With a margin width of or greater than 10 mm, DFS increased from 14.1 months to 86 months. In a single-center study, patients with a margin width ≥10 mm have longer OS (HR: 0.403, 95%CI: 0.191-0.854, *P*=0.018) and RFS (HR: 0.470, 95%CI: 0.242-0.914, *P*=0.026)[16]. Similarly, in the present study, analysis of the OS subgroup presented that the prognostic risk was substantially lower in patients in the 5-9 mm group (HR: 1.33, 95% CI: 1.03-1.72) than in the group with margin width <5 mm (HR: 1.88, 95% CI: 1.45-2.42). But the difference was not noticeable in the RFS subgroup analysis. Therefore, margin width≥10 mm could be the optimal margin width for prognosis.

3.3 Correlation between Lymph Node Status and Prognosis

A subgroup analysis of lymph node status was done. Several studies have reported that lymph node status, in addition to the margin width, is a pivotal prognostic risk factor affecting ICC patients after surgery[14, 23]. Lymph node lesions, invasion, and metastasis were factors for poor prognosis after undergoing R0 resection. In a national survey by the Japanese Liver Cancer Study Group, surgical margin width has a small impact on the postoperative prognosis of ICC patients, but in patients without lymph node metastasis, wider surgical margins favored postoperative survival outcomes[9]. Additionally, by comparing the basic information of patients in the wide and narrow-margin groups in this study, it was found that the wide-margin group had a higher proportion of patients with single tumors and smaller tumor diameters; in contrast, patients in the narrow-margin group had larger tumor diameters and invasion and a higher proportion of vascular invasion and advanced tumors, which may directly confound the comparison of prognostic survival times between the two groups. Liu

(2021) *et al.*[8] conducted a statistical analysis of the clinical data of 478 ICC patients from 13 hepatobiliary and pancreatic centers and used the propensity score matching (PSM) method for pairwise inclusion at 1:1, matched other factors that may affect prognostic survival such as age, tumor type, and lymph node metastasis-without statistical differences, retaining only the difference in margin width (wide versus narrow margins with a 10-mm threshold) for comparison. The results showed that patients with wide margins had substantially improved OS and DFS compared to patients with narrow margin. But in an unpaired subgroup analysis, wide margins only improved the American Joint Committee on Cancer (AJCC) clinical stage I patients, and patients with lymphatic metastases did not benefit from wide margins. Therefore, we believed that setting the margin width at ≥10 mm may require reference to the patient's tumor type and lymphatic involvement, and 10 mm or larger margins can be achieved as much as possible in ICC patients without lymph node metastasis and single MF type to improve the patient's prognosis for long-term survival benefit.

Adjuvant treatments such as chemotherapy, arterial chemoembolization, and chemoradiotherapy may be beneficial for the survival of postoperative ICC patients with margins as well as positive lymph nodes[21]. Recent meta-analysis results have suggested that lymph node dissection may not have a marked prognostic impact on patients with resectable ICC, but it is associated with postoperative recurrence[24, 25]. Hence, we speculated that adjuvant therapy for ICC patients may also influence the choice of margin width, but in our study, a subgroup analysis of adjuvant therapy was not conducted, as an ongoing study object.

3.4 Sensitivity Analysis

Although the results of the sensitivity analysis did not show substantial differences between studies, the Spolverato (2015) 5-9 mm group in the OS sensitivity analysis[12] and the Tamandl (2008) <10 mm group in the RFS sensitivity analysis were slight prominence[3]. The study by Spolverato (2015) et al. reported that the 1-year OS rate of 100 patients who completed the 5-9 mm R0 margin (83.9%) was higher than the OS of 147 patients who completed the ≥10 mm R0 group (79.8%), which may be a factor influencing the OS comparison.

3.5 Limitations

This study has some limitations. First, all the studies included in this study were published in English, and the exclusion of non-English literature may lead to selection bias. Second, the presence of single-center and multicenter studies in this study may have contributed to some bias in the results. Third, factors such as type of liver resection, surgical instrumentation, and adjuvant treatment were not analyzed in subgroups, and the prognosis of ICC patients by the above factors was inconclusive and warranted further study. Fourth, the size, number, and location of preoperative tumors and their staging also varied, and evaluation of the impact of surgical margins on postoperative survival of ICC patients in terms of tumor pathological characteristics may be required. Finally, since survival data were mostly obtained indirectly through calculations, the conclusions may differ somewhat from clinical trials.

3.6 Conclusion

In conclusion, the meta-analysis revealed that patients undergoing curative hepatectomy for ICC had a survival advantage for a wide margin of ≥10 mm compared with a narrow margin of <10 mm under certain conditions. But surgeons should determine the margin width in relation to the patient's condition and should not consider <10 mm as a contraindication to surgery; in addition, lymph node status should be considered during clinical procedures, as it is also an important factor affecting the patient's postoperative survival outcome. In summary, surgical margins of ≥10 mm should be achieved as much as possible for ICC patients with negative lymph nodes, but further multicenter study results are still warranted to support this view.

Declarations

Patient and Public Involvement

No patient involved.

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors consent to submit the manuscript for publication.

Data availability statement

No additional data available.

Competing interest

The authors declare no conflicts of interest.

Funding

Not applicable.

Authors' contributions

JHJ drafting and revising the article, DZF data analysis, YTH gave final approval of the version to be published, and all authors agreed to be accountable for all aspects of the work.

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Not applicable.

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Figure legends

Figure 1 PRISMA flow chart for the included studies

Figure 2 Results of HR pooled analysis of the OS rate of the included studies (with the wide margin group ≥10 mm as the control)

Figure 3 Results of HR pooled analysis of DFS in the included studies (with wide margin group ≥10 mm as the control)

Figure 4 Results of HR pooled analysis of RFS in the included studies (with wide margin group ≥10 mm as the control)

Figure 5 Results of HR pooled analysis of lymph node lesions on OS in patients with ICC (with wide margin group ≥10 mm as the control).

Figure 6 Results of HR pooled analysis of lymph node invasion on OS in ICC patients (with wide margin group ≥10 mm as the control).

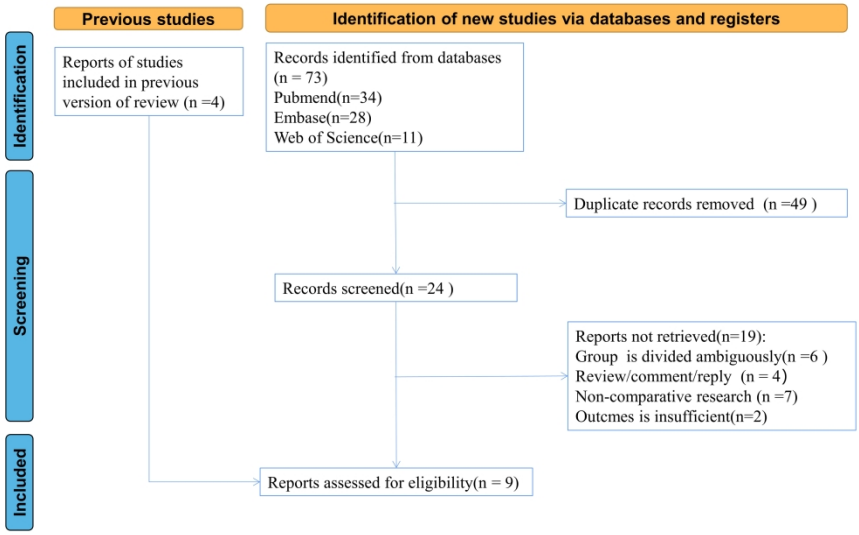
Figure 7 Results of HR pooled analysis of lymph node metastasis on RFS in ICC patients (with wide margin group ≥10 mm as the control).

Figure 8 Sensitivity analysis of OS after leave-out-one analyses

Figure 9 Sensitivity analysis of RFS after leave-out-one analyses

Figure 10 Funnel plot of the relationship between surgical margin width and OS in ICC patients

Figure 11 Funnel plot of the relationship between surgical margin width and RFS in ICC patients



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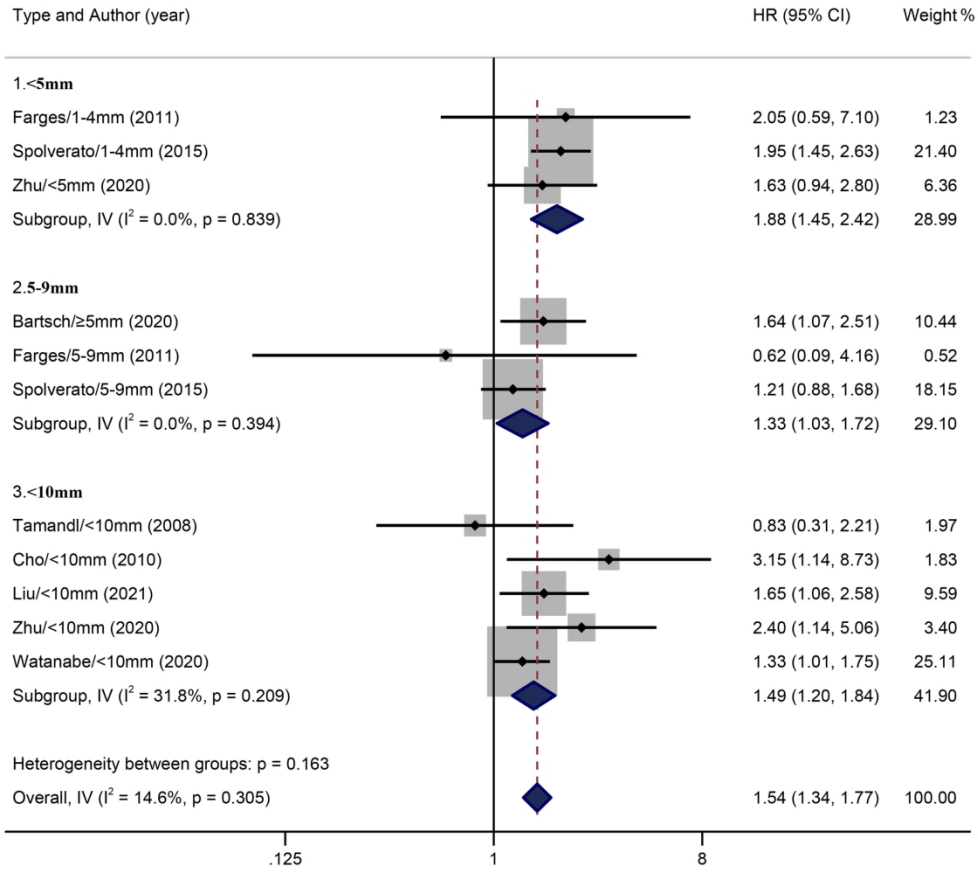

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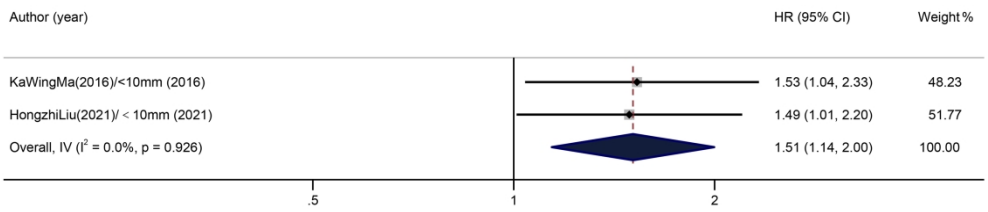

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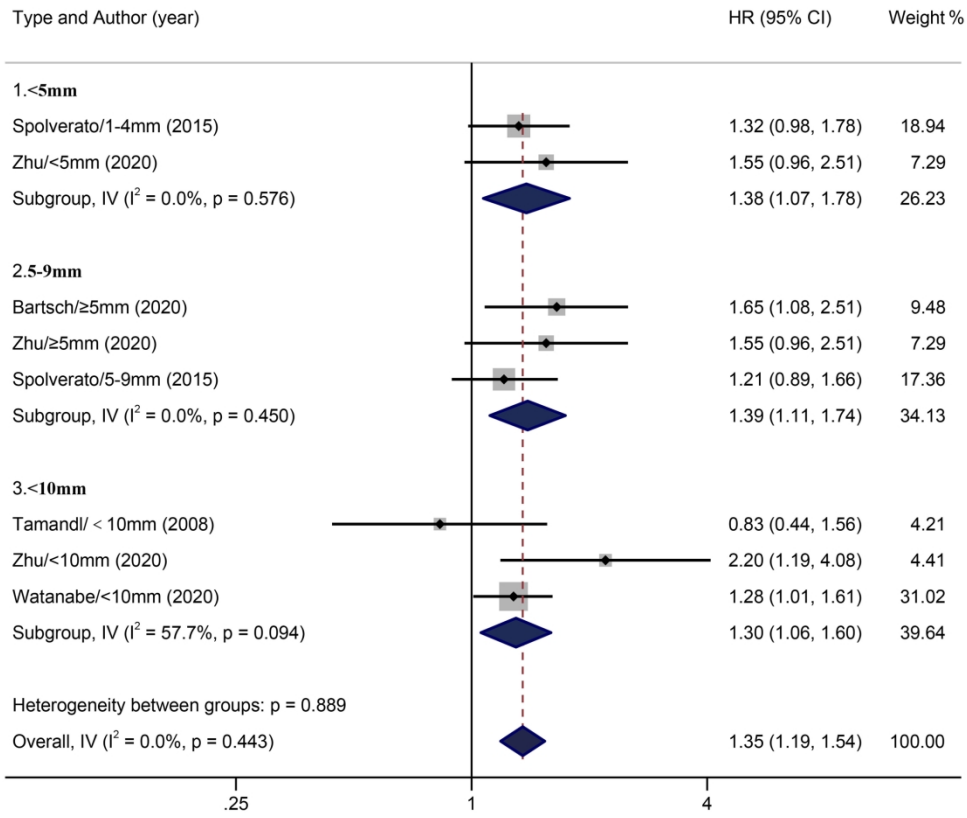

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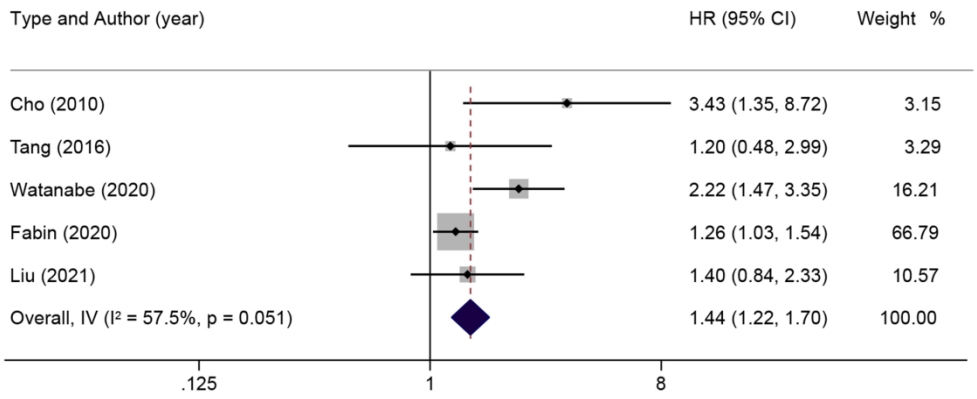

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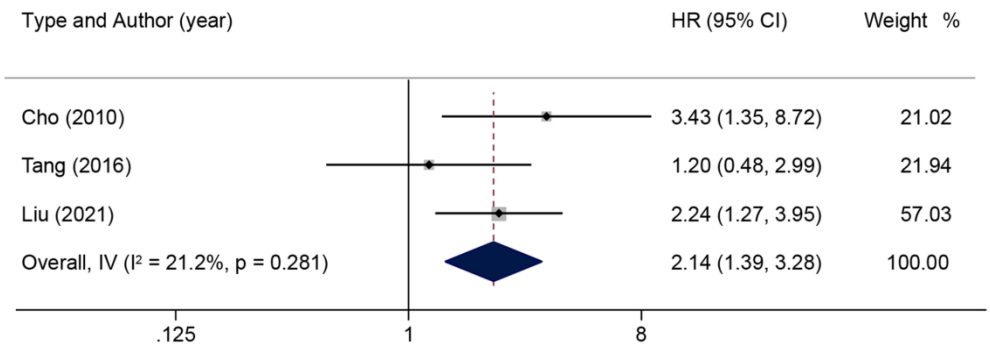

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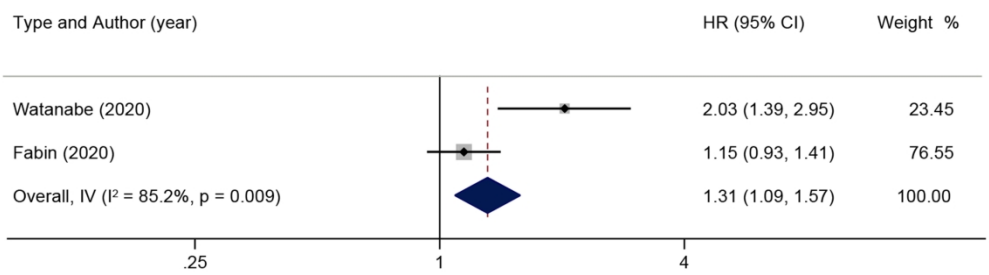

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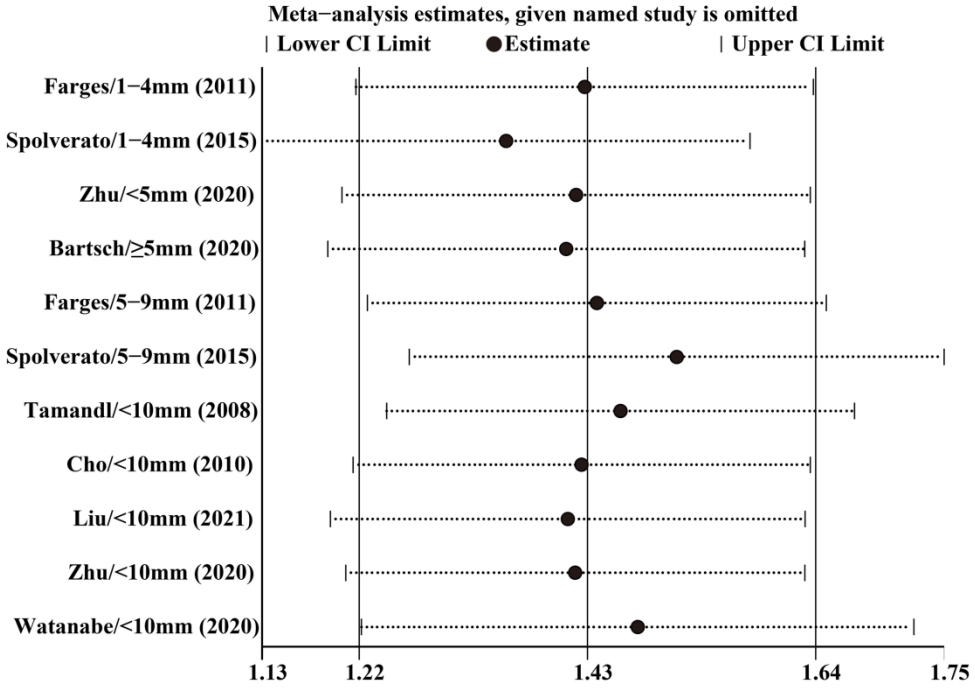

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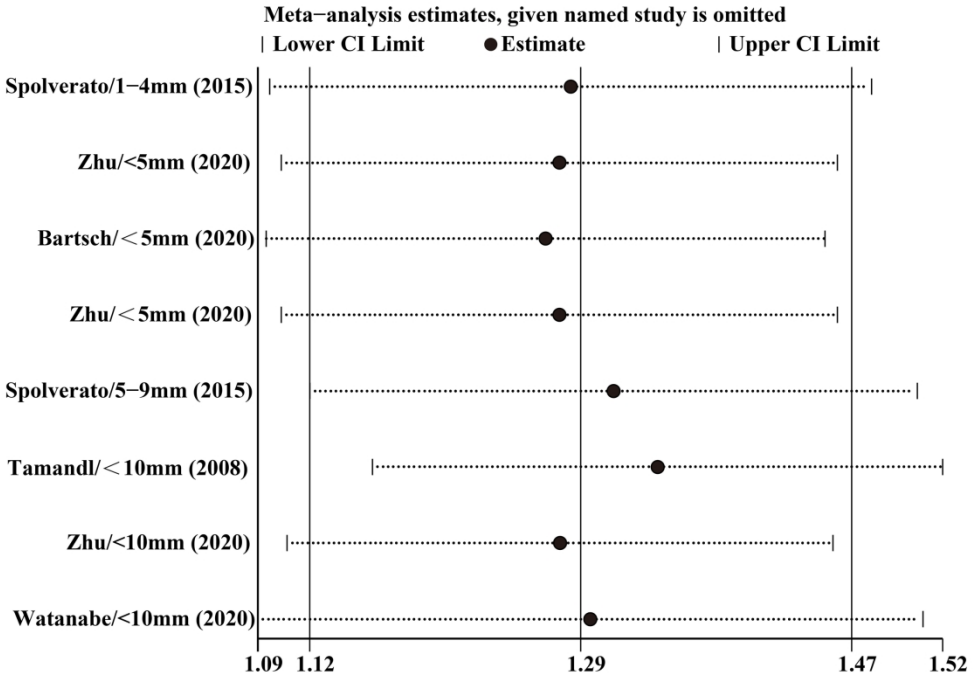

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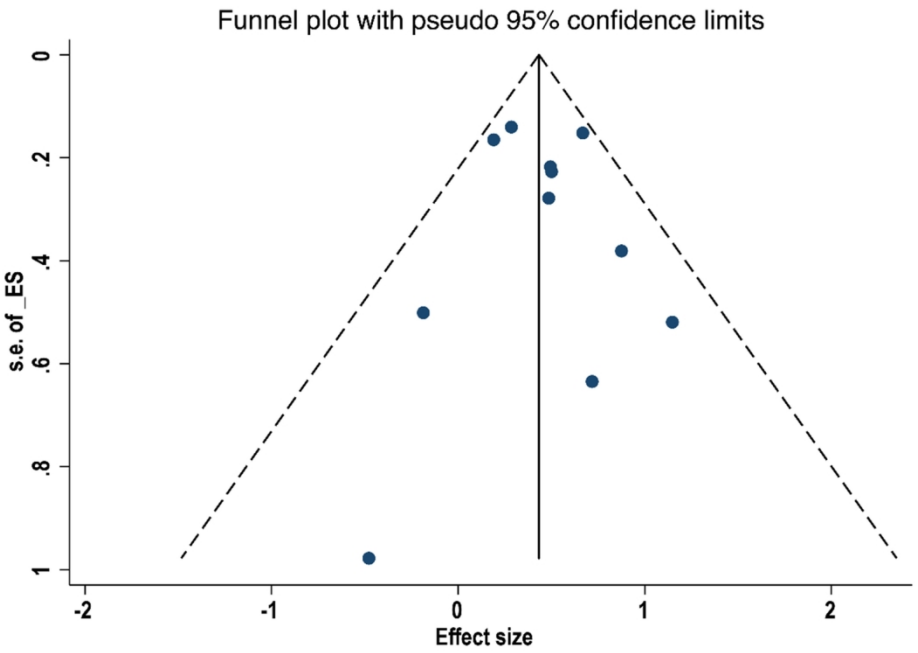

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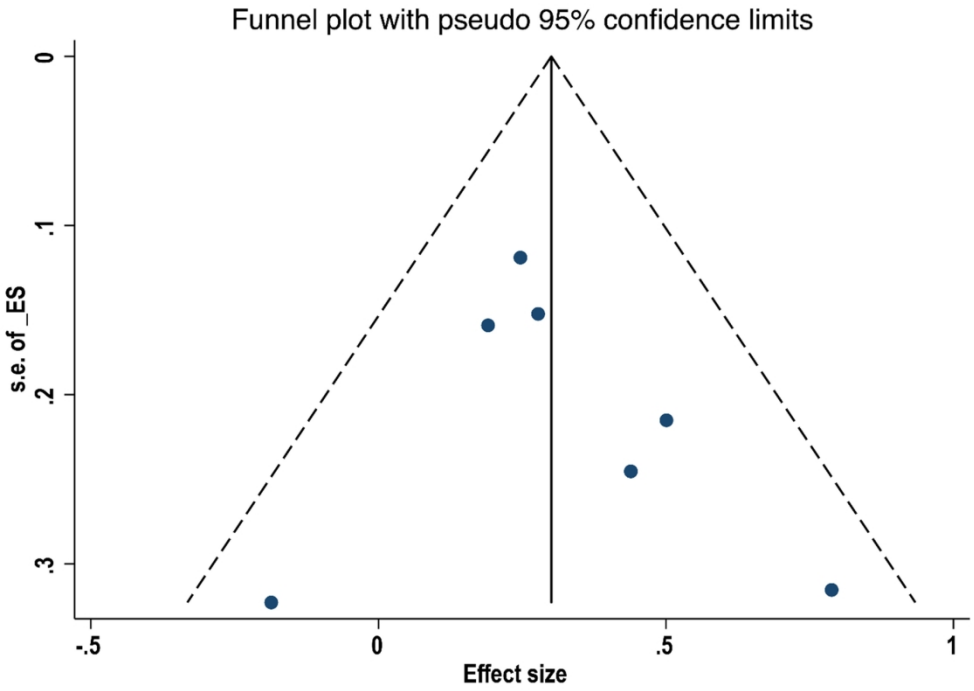

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3-4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6-7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	6-7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	7

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	7-8
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	7-8
Study characteristics	17	Cite each included study and present its characteristics.	8-9
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	7-8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	9-11
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	9-11
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	9-11
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	9-11
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	11
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	9-11
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	9-11
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	11-12
	23b	Discuss any limitations of the evidence included in the review.	15
	23c	Discuss any limitations of the review processes used.	15
	23d	Discuss implications of the results for practice, policy, and future research.	12-14
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	16
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	16
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	16
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	16
Competing interests	26	Declare any competing interests of review authors.	16
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	16

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Surgical margin width – search strategy

Using the MeSH subject heading function in the National Library of Medicine:

1. The subject heading for searching "intrahepatic cholangiocarcinoma" was "Cholangiocarcinoma". The free words were "Cholangiocarcinomas", "Cholangiocellular Carcinoma", "Intrahepatic Cholangiocarcinoma", "Cholangiocarcinomas, Intrahepatic".

2. Search in combination with keywords such as "surgery", "resection margin width", and "resection margin length".

3. Search strategy for Pubmed:

(((((Cholangiocarcinomas) OR (Cholangiocellular Carcinoma)) OR (Intrahepatic Cholangiocarcinoma)) OR (Cholangiocarcinomas, Intrahepatic)) AND (Surgical margin width)) OR (Length of surgical margin)

4. Search strategy for Embase:

Cholangiocarcinomas:ti,ab,kw OR 'Cholangiocellular Carcinoma':ti,ab,kw OR 'Intrahepatic Cholangiocarcinoma':ti,ab,kw OR 'Cholangiocarcinomas, Intrahepatic':ti,ab,kw AND 'Surgical margin width'

5. Search strategy for Web of Science:

(((TS=(Cholangiocarcinomas)) OR TS=(Cholangiocellular Carcinoma)) OR TS=(Intrahepatic Cholangiocarcinoma)) AND TS=(Surgical margin width)

BMJ Open

Influence of surgical margin width on survival rate after resection of intrahepatic cholangiocarcinoma: a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-067222.R2
Article Type:	Original research
Date Submitted by the Author:	17-Mar-2023
Complete List of Authors:	Jiang, Jing-Hua; Zhejiang University School of Medicine, Department of Hepatobiliary Fang, Da-Zhang; Zhejiang University School of Medicine, Department of Hepatobiliary Hu, Yi-Ting; Shulan International Medical College, Department of Hepatobiliary and Pancreatic Surgery
Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Gastroenterology and hepatology
Keywords:	Hepatobiliary disease < GASTROENTEROLOGY, Hepatology < INTERNAL MEDICINE, Hepatobiliary tumours < ONCOLOGY

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Influence of surgical margin width on survival rate after resection of intrahepatic cholangiocarcinoma: a systematic review and meta-analysis

Authors:

Jing-Hua Jiang [1], Da-Zhang Fang [1], Yi-Ting Hu [2*]

Affiliations:

1. Department of Hepatobiliary and Pancreatic Surgery, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua 321000, China.
2. Department of Hepatobiliary and Pancreatic Surgery, Shulan (Hangzhou) Hospital, Zhejiang Shuren University, Shulan International Medical College, Hangzhou 310022, China.

***Correspondence to:**

Dr. Yi-Ting Hu

Department of Hepatobiliary and Pancreatic Surgery, Shulan (Hangzhou) Hospital, Zhejiang Shuren University, Shulan International Medical College, Dongxin Road 848#, Hangzhou 310022, China.

E-mail: yitingh@yeah.net

Abstract

Objectives: Hepatectomy is the best treatment for patients with intrahepatic cholangiocarcinoma (ICC) at present, but there has been controversy about the width of surgical margins. In this study, we systematically investigated the effects of different surgical margin widths on the prognosis of ICC patients undergoing hepatectomy.

Design: Systematic review and meta-analysis.

Data sources: PubMed, Embase, and Web of Science databases were systematically searched from inception to June 2022.

Eligibility criteria: Cohort studies reported in English with patients who underwent negative margin (R0) resection were included. The effects of surgical margin width on overall survival (OS), disease-free survival (DFS), and recurrence-free survival (RFS) in patients with ICC were assessed.

Data extraction and synthesis: Two investigators independently conducted literature screening and data extraction. Risk of bias was assessed using funnel plots and quality was assessed by the Newcastle-Ottawa Scale (NOS). Forest plots of hazard ratios (HRs) and their 95% confidence intervals (CI) for outcome indicators were plotted. Heterogeneity was assessed and determined quantitatively using I^2, and the stability of the study results was evaluated using sensitivity analysis. Analyses were performed using Stata software.

Results: Nine studies were included. With the wide margin group (≥10 mm) as the control, pooled HR of OS in the narrow margin group (<10 mm) was 1.54 (95% CI 1.34-1.77). HR of OS in three subgroups where the margin was less than 5 mm, ranged from 5 mm to 9 mm, or was less than 10 mm in length were 1.88 (1.45-2.42), 1.33 (1.03-1.72), and 1.49 (1.20-1.84), respectively. Pooled HR of DFS in the narrow margin group (<10 mm) was 1.51 (1.14-2.00). Pooled HR of RFS in the narrow margin group (<10 mm) was 1.35 (1.19-1.54). HR of RFS in three subgroups where the margin was less than 5 mm, ranged from 5 mm to 9 mm, or was less than 10 mm in length were 1.38 (1.07-1.78), 1.39 (1.11-1.74), and 1.30 (1.06-1.60), respectively. Neither lymph node lesions (HR 1.44, 95%CI 1.22-1.70) nor lymph node invasion (2.14, 1.39-3.28)

were favorable for postoperative OS in ICC patients. Lymph node metastasis (1.31, 1.09-1.57) was unfavorable for RFS in ICC patients.

Conclusion: ICC Patients who underwent curative hepatectomy with a negative margin ≥10 mm may have a long-term survival advantage, but lymph node dissection also needs to be considered. In addition, tumor-related pathological features need to be explored to see if they affect the surgical outcome of R0 margins.

Keywords: intrahepatic cholangiocarcinoma; surgical margin width; prognosis survival rate; meta-analysis

Strengths and limitations of this study

* The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the included studies.
* Publication bias analysis was performed using Egger test and Begg funnel plot.
* Sensitivity analysis was used to determine the stability and strength of the combined results.
* Differences based on the type of study (eg, single-center and multicenter studies) and the limited number of studies may have impacted the results.

Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary malignancy originating in the liver, which makes up 10%-15% of primary liver cancers. However, without distinct pathogenic factors or clinicopathological features, the diagnosis of ICC tends to be hard[1,2]. Most patients have to receive hepatobiliary resection since the disease has processed to the advanced stage of ICC[3]. Limited knowledge about its pathological features also adds difficulty to the prognosis of ICC patients. Even after the radical surgery, the recurrence rate remains high and the 5-year survival rate ranges from only 30-35%. The past three decades have seen the incidence and mortality rate of ICC keep elevating with a rather poor prognosis[4].

Up to now, radical hepatectomy remains the best option for potentially curative treatment of ICC patients, mainly to achieve negative marginal (R0) resection[5,6]. But high local recurrence rate after R0 resection may be related to the location and extent of the primary lesion, lymph node involvement, and surgical margin status, leading to a poor prognosis[5,7]. Additionally, surgical margin width is also of prognostic essence after ICC resection, but the definition of the width remains controversial. A recent multicenter study reported that patients with a margin width ≥10 mm have better long-term prognostic outcomes relative to patients with a surgical margin width <10 mm[8]; however, another study stated that wide margin hepatectomy does not produce a survival benefit in all ICC patients and is more beneficial for patients without lymph node metastases[9]. Hence, it is necessary to evaluate the margin width in patients with ICC undergoing R0 resection.

Li *et al.*[10] evaluated the relationship between surgical margin status and survival benefit in ICC by meta-analysis and found that negative surgical margins are more beneficial for ICC patients' overall survival (OS) and disease-free survival (DFS) after surgical resection, thus emphasizing the importance of R0 resection. In a recent meta-analysis of the effect of surgical margin width on OS in ICC patients, it is similar that ICC patients with R0 ≥10 mm have a longer survival benefit than those with <10 mm[11]. But this analysis did not provide statistical analysis of DFS, recurrence-free survival (RFS), or a more refined stratification of the range of R0 margin width, making the findings lacking reference value for clinical treatment at the present stage. Therefore, this study was updated from the above meta-analysis to investigate the effect of margin width on OS, DFS, and RFS in ICC patients who underwent R0 surgical resection in recent years, as well as a stratification study of margin width (<5 mm, 5-9 mm, <10 mm, and ≥10 mm), to provide more evidence-based medical evidence for the determination of surgical margin width in ICC patients.

Methods

Search strategy

Systematic searches were done of PubMed, Embase and Web of Science to collect

relevant studies available by June 2022. The literature search took the form of a combination of medical subject headings (Mesh) and free words, mainly including (((((Cholangiocarcinomas) OR (Cholangiocellular Carcinoma)) OR (Intrahepatic Cholangiocarcinoma)) OR (Cholangiocarcinomas, Intrahepatic)) AND (Surgical margin width)) OR (Length of surgical margin) (Supplementary file). The reference lists of included studies were manually screened for relevant studies that may meet the inclusion requirements.

Inclusion criteria

(1) ICC patients (confirmed by pathological examination) received potentially curative hepatectomy; (2) Patients underwent R0 resection (which was defined as the distance between the nontumorous tissue and cancer cells >1 mm)[2] with clear surgical margin edge; (3) Patients were classified according to the width of the resection margin, defined as the shortest distance from the edge of the tumor to the line of resection[12]. Patients with margin widths shorter than 4 mm or ranging from 5-10 mm were included in the narrow margin group (<10 mm), and those with margin widths equal to 10 mm or above were included in the wide margin group (≥10 mm); (4) The correlations of surgical margin width with OS, DFS, and RFS were presented in the included studies., the hazard ratio (HR) and 95% confidence interval (CI) could be obtained directly from the literature or could be calculated indirectly.

Exclusion criteria

(1) Abstract, literature reviews, pathological reports, editorials and expert reviews; (2) Studies published repeatedly; (3) Study results reached not through calculation; (4) Animal studies; (5) Studies group patients with different cutoff points instead of 5 mm and 10 mm; (6) Repeat resection for recurrence; (7) Patients with extrahepatic metastases.

Study selection

We selected studies by (1) basic information like title, first author, publication year, nation, and the time of research; (2) baseline characteristics like sample size, disease, average age, and sex; (3) key factors that bias hazard ratio evaluation; (4) outcome indicators and measured data.

Data extraction

To minimize bias, we had two investigators select studies and extract data in duplicate independently and then adopted cross-validation to measure their accuracy. Disagreement was settled by further discussion or judged by the third investigator. Subsequently, a data extraction sheet designed for this study was used to abstract the following information: (1) basic information about included studies like the name of the first author, publication year, nation, type of article, and research period; (2) baseline characteristics about included cohort like the number of people receiving R0 resection, sex, age, subgroup threshold, lymph node metastasis, number of people in the narrow margin group of <10 mm and the wide margin group of ≥10 mm, the longest follow-up time, liver parenchymal dissection techniques and instrumentation, tumor subtypes, and adjuvant chemotherapy and radiotherapy; (3) Primary outcome indicator: HR and 95% CI for prognostic OS and DFS for patients in each group. Secondary outcome indicator: HR and 95% CI for RFS and lymph node status. OS was defined as the interval from the date of surgery to the patient's death or last follow-up. DFS was defined as the interval from the date of surgery to the date of first recurrence, secondary malignancy, or death of any disease course. RFS was defined as the interval from the date of surgery to the date of first tumor recurrence, secondary malignancy, or death with evidence of recurrence. Tumor morphology was typologically defined based on preoperative imaging and case reports, and ICC was classified into three categories based on the macroscopic types proposed by the Japanese Liver Cancer Study Group: mass-forming (MF) type, periductal infiltrating (PI) type, and intraductal growth (IG) type[9]. For HR and 95% CI of DFS, RFS and OS, if not directly available from the literature, data such as survival rate can also be intercepted from survival graphs and entered into Excel with information such as follow-up time, and finally combined effect sizes by meta-analysis using RevMan software[13].

Quality assessment of included studies

Included studies were evaluated by two investigators using the Newcastle-Ottawa Scale (NOS), an assessment scale covering eight items including the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure

or outcome of interest for case-control or cohort studies respectively. Any disagreement in assessment was resolved by the third investigator.

Statistical analysis

We used Stata MP16 software to conduct statistical analysis. Between-study heterogeneity was tested by Chi-squared (χ^2) test (α=0.1) and further evaluated using I^2. When $I^2 \leq 50\%$, a fixed effect model of the meta-analysis was employed; when $I^2 > 50\%$, a random effect model was used to analyze possible reasons, together with sub-group and descriptive analysis. If heterogeneity arises from poor research quality, sensitivity analysis ensued to evaluate the stability and certainty of meta-analysis. Publication bias analysis used Egger test and Begg funnel plot. If the funnel plot was symmetrical, indicating a lack of publication bias. The inspection level of meta-analysis was set as α= 0.05.

Patient and public involvement

None.

Results

Selected studies and quality assessment

Initial searches returned 73 relevant studies (34 from PubMed; 28 from Embase; 11 from Web of Science). After screening the title and abstract of these entries identified in the search, 24 studies were retained. Eventually, 9 studies were included after reading their full-text publications[2-4,8,9,12,14-16]. Among these included studies published from 2008 to 2021, 3 were conducted in China, 1 in Austria, 1 in Korea, 1 in France, 2 in the USA and 1 in Japan. The PRISMA flowchart for included studies was presented in Figure 1. NOS scores of included studies in Table 1 showed that top-rated retrospective cohort studies were of high quality.

Table 1. Quality assessment of included studies

Study	Selection				Comparability	Outcome			Score
	A	B	C	D	E	F	G	H	
Tamandl2008	*	*	*	*	*	*	*	*	**8**

Cho2010	*	*	*	*	*	*	*		**7**
Farges2011	*	*	*	*	*	*	*	*	**8**
Spolverato2015	*	*	*	*	*	*	*	*	**8**
Ma2016	*	*	*	*	*	*	*	*	**8**
Tang2016	*	*	*	*	*	*	*	*	**8**
Watanabe2020	*	*	*	*	**	*	*	**	**10**
Bartsch2020	*	*	*	*	*	*	*		**7**
Zhu2020	*	*	*	*	**	*			**6**
Liu2021	*	*	*	*	*	*	*	*	**8**

Notes: Each study can have up to one "*" for each item on "Selection" and "Outcomes", and up to two "*" for each item on "Comparability".

A: Representativeness of the exposed cohort

B: Selection of the non-exposed cohort

C: Ascertainment of exposure

D: Demonstration that outcome of interest was not present at the start of the study

E: Comparability of cohorts based on the design or analysis

F: Assessment of outcome

G: Was follow-up long enough for outcomes to occur

H: Adequacy of follow-up of cohorts

Characteristics of included studies

As presented in Table 2, most involved patients aged around 60. The majority of resections were done with modern technology or dissection devices, such as Cavitron ultrasonic surgical attractor or ultrasonic dissector. The baseline characteristics of narrow (<10 mm) and wide (≥10 mm) margin groups were similar across the 9 included studies. The follow-up length ranges from 1 to 84 months. In four studies, several patients were treated with neoadjuvant or adjuvant treatment. Six studies analyzed the tumor morphology, with a predominance of MF type. Only three reported lymph node metastasis (23.94%-70.5%). Besides, the number of people in the study by Ma *et al.*[2] could not be clearly extracted for the narrow margin group (<10 mm) and the wide

margin group (≥10 mm), so the exact number of people in both groups could not be clarified. But some survival data could be extracted from that study, and therefore were also included in our study for survival analysis.

Table 2. Patients' characteristics by study

Year	Nation	No. of Patient	Age, $M(Q_{25}$~$Q_{75})$	Sex, male (%)	Follow-Up, Mouth	Resection width		Lymph node metastasis, n	Adjuvant radiotherapy/ chemotherapy
						≥10 mm	<10 mm		
2008	Austria	53	63.2 (33.3-85.8)	29 (39)	1-64	15	38	NR	NR
2010	Korea	63	61.4 (27-82)	41 (65)	NR	23	40	13	NR
2015	France	161	NR	108 (51)	NR	45	116	47	NC:12 AC: 51
2015	USA	440	NR	302 (52)	NR	174	266	NR	AC: 212 AR: 44
2016	China	95	61 (25-79)	58 (54)	1-60	NR	NR	NR	NR
2020	China	109	NR	66 (52)	1-54	17	92	NR	NC: 1
2020	Japan	635	64.2 (32.3-84.4)	388 (61)	1-84	237	398	152	NR
2020	USA	131	NR	NR	0-24	22	109	NR	PC: 3
2021	China	478	58 (49-64)	287 (60)	NR	195	283	NR	NR

Meta-analysis results

OS

9 included studies all related to the influence of surgical margin width on the OS of ICC patients. This meta-analysis synthesized relevant data by categorizing margin width into <10 mm and ≥10 mm groups, and the former was further categorized into three

subgroups: <5 mm (1-4 mm, three studies) 5-9 mm (≥5 mm, three studies) and <10 mm (five studies). There was no overall heterogeneity in the included studies (I^2=14.6%, P=0.305). The fixed effect model meta-analysis indicated that, compared with the wide margin group (≥10 mm), pooled HR of the narrow margin group (<10 mm) stood at 1.54 (95%CI: 1.34-1.77). No significant heterogeneity was found across three subgroups, <5 mm (I^2=0.0%, P=0.839), 5-9 mm (I^2=0.0%, P=0.394), and <10 mm (I^2=31.8%, P=0.209) groups. Compared with the wide margin group, pooled HR of three subgroups (<5 mm, 5-9 mm and <10 mm groups) were 1.88 (95%CI: 1.45-2.42), 1.33 (95%CI: 1.03-1.72) and 1.49 (95%CI: 1.20-1.84), respectively, as Figure 2 showed.

DFS

Two included studies relating to the influence of margin width on DFS of ICC patients showed no overall heterogeneity (I^2 =0.0%, P=0.926). According to the result of the fixed effect model in Figure 3, with the wide margin group (≥10 mm) as the control, the overall pooled HR of the narrow margin group (<10 mm) was 1.51 (95%CI: 1.14-2.00) (Figure 3).

RFS

With five included studies concerning the influence of margin width on RFS of ICC patients, we categorized the outcome variable in the same way as we conducted study on OS. With no heterogeneity across the included studies (I^2=0.0%, P=0.443), the pooled HR was 1.35 (95CI%: 1.19-1.54). The fixed effect model of subgroup analysis found no heterogeneity across <5 mm (I^2=0.0%, P=0.576) and 5-9 mm (I^2=0.0%, P=0.450) groups. Compared with the wide margin group (≥10 mm), pooled HR of <5 mm and 5-9 mm groups were 1.38 (95%CI: 1.07-1.78) and 1.39 (95%CI: 1.11-1.74), respectively. With heterogeneity (I^2=57.7%, P=0.094) in the narrow margin (<10 mm) group, compared with the wide margin (≥10 mm) group, the pooled HR of the narrow margin group was found to be 1.30 (95%CI: 1.06-1.60) in comparison with the wide margin group (≥10 mm) (Figure 4).

Correlation between lymph node status and prognosis

Subsequently, a subgroup analysis was done on the prognostic impact related to lymph node status. When there was moderate heterogeneity in the effect of lymph node lesions on OS (I^2=57.5%, P=0.051) according to the pooled HR and 95%CI of the multiple analyses of five positive lymph nodes, a random effects model was used for subsequent analysis (Figure 5). The results illustrated that lymph node lesions were detrimental to OS in patients with ICC (HR: 1.44; 95% CI: 1.22-1.70). When there was no significant heterogeneity in the effect of lymph node invasion on OS (I^2=21.2%, P=0.281), a fixed effects model was utilized (Figure 6). The results reported that patients with ICC in the presence of lymph node invasion had markedly shorter OS (HR: 2.14; 95% CI: 1.39-3.28). In addition, the pooled HR of RFS associated with lymph node metastasis was analyzed, and the results showed notable heterogeneity (I^2=85.2%, P=0.009) (Figure 7). The results of the random effects model demonstrated that lymph node metastasis was detrimental to RFS in patients with ICC (HR: 1.31, 95% CI: 1.09-1.57).

Sensitivity analysis

By excluding one study at a time, a sensitivity analysis of OS and RFS was conducted. Results in Figure 8-9 showed no significant difference between the effect size and the total effect size of OS and RFS, implying that the result reached in this study was relatively stable. Egger test did not detect substantial publication bias in both OS (P=0.508) and RFS (P=0.523), and the Begg funnel plot was symmetrical (Figures 10-11). However, differences based on the type of study (single-center and multicenter studies) and the limited number of studies may affect the above statistical results.

Discussion

Current status of surgery for ICC

The incidence and mortality rates of ICC keep climbing across the world, most patients are not diagnosed until ICC reached an advanced stage[1].

Currently, complete surgical resection with negative histological margins (R0)

remains the only curative treatment modality favoring long-term survival outcomes in ICC patients, but only a minority of patients have resectable lesions, resulting in poor postoperative survival[5,17]. A few studies have shown a better survival benefit for ICC patients undergoing R0 resection compared to R1 resection[2,12]. But margin status, lymph node status, and the presence of vascular invasion all contribute to the poor prognosis of ICC patients after resection[18-20]. Most patients with ICC usually require adjuvant therapy[21]. In addition, investigators are concerned that in ICC patients undergoing R0 resection, the margin width also affects long-term survival after surgery[8,15]. However, there has been controversy regarding the effect of R0 margin width on the prognostic survival of ICC patients. Thus, this meta-analysis was done to investigate the effect of margin width on survival outcomes after ICC resection.

The impact of margin width on ICC patients' outcomes

In 2016, Tang *et al.*[11] published the first meta-analysis of the effect of margin width on prognostic survival in ICC patients. This study indicated that patients with wide margin (≥10 mm) have a survival advantage over those with narrow margin (<10 mm) (HR: 1.59, 95%CI: 1.09-2.32). Based on these investigations, we updated the study related to the effect of surgical margin width on the prognosis survival of ICC patients. Two irrelevant studies with a limited sample size in the 2016 meta-analysis were excluded and five eligible retrospective cohort studies published after 2016 were included. Besides, this study also filled the void of RFS (4 included studies) and DFS (2 included studies).

9 included studies all focused on the mass-forming (MF) type of ICC (as it accounts for over 66% of ICC[1]) and categorized the outcome variable into 5 groups: <1 mm, 1-4 mm, 5-9 mm, <10 mm and ≥10 mm. One included study went beyond our research scope as it further categorized wide margin into ≥15 mm group, and relevant data were excluded from the meta-analysis. Pooled HR results indicated that with the wide margin (≥10 mm) group as the control, patients with a margin shorter than 10 mm were prone to poor prognosis (pooled HR of OS: 1.54, 95%CI: 1.34-1.77). It was demonstrated that ICC tumor cells could metastasize by directly infiltrating the adjacent

liver parenchyma, accompanied by vascular infiltration and perineural infiltration, and then cause pathological changes in intrahepatic epithelial cells and surrounding tissues[22]. For most metastasis is limited within 10 mm around the primary lesion, a 10 mm or more resection is expected to cure these ICC patients. Ma *et al*.[2] suggested that margin width significantly impacts the OS of ICC-MF patients after resection. With a margin width greater than 9 mm, OS increased from 35.7 months to 184.6 months. With a margin width of or greater than 10 mm, DFS increased from 14.1 months to 86 months. In a single-center study, patients with a margin width ≥10 mm have longer OS (HR: 0.403, 95%CI: 0.191-0.854, *P*=0.018) and RFS (HR: 0.470, 95%CI: 0.242-0.914, *P*=0.026)[16]. Similarly, in the present study, analysis of the OS subgroup presented that the prognostic risk was substantially lower in patients in the 5-9 mm group (HR: 1.33, 95% CI: 1.03-1.72) than in the group with margin width <5 mm (HR: 1.88, 95% CI: 1.45-2.42). But the difference was not noticeable in the RFS subgroup analysis. Therefore, margin width≥10 mm could be the optimal margin width for prognosis.

Correlation between lymph node status and prognosis

A subgroup analysis of lymph node status was done. Several studies have reported that lymph node status, in addition to the margin width, is a pivotal prognostic risk factor affecting ICC patients after surgery[14,23]. Lymph node lesions, invasion, and metastasis were factors for poor prognosis after undergoing R0 resection. In a national survey by the Japanese Liver Cancer Study Group, surgical margin width has a small impact on the postoperative prognosis of ICC patients, but in patients without lymph node metastasis, wider surgical margins favored postoperative survival outcomes[9]. Additionally, by comparing the basic information of patients in the wide and narrow-margin groups in this study, it was found that the wide-margin group had a higher proportion of patients with single tumors and smaller tumor diameters; in contrast, patients in the narrow-margin group had larger tumor diameters and invasion and a higher proportion of vascular invasion and advanced tumors, which may directly confound the comparison of prognostic survival times between the two groups. Liu (2021) *et al.*[8] conducted a statistical analysis of the clinical data of 478 ICC patients from 13 hepatobiliary and pancreatic centers and used the propensity score matching

(PSM) method for pairwise inclusion at 1:1, matched other factors that may affect prognostic survival such as age, tumor type, and lymph node metastasis-without statistical differences, retaining only the difference in margin width (wide versus narrow margins with a 10-mm threshold) for comparison. The results showed that patients with wide margins had substantially improved OS and DFS compared to patients with narrow margin. But in an unpaired subgroup analysis, wide margins only improved the American Joint Committee on Cancer (AJCC) clinical stage I patients, and patients with lymphatic metastases did not benefit from wide margins. Therefore, we believed that setting the margin width at ≥10 mm may require reference to the patient's tumor type and lymphatic involvement, and 10 mm or larger margins can be achieved as much as possible in ICC patients without lymph node metastasis and single MF type to improve the patient's prognosis for long-term survival benefit.

Adjuvant treatments such as chemotherapy, arterial chemoembolization, and chemoradiotherapy may be beneficial for the survival of postoperative ICC patients with margins as well as positive lymph nodes[21]. Recent meta-analysis results have suggested that lymph node dissection may not have a marked prognostic impact on patients with resectable ICC, but it is associated with postoperative recurrence[24,25]. Hence, we speculated that adjuvant therapy for ICC patients may also influence the choice of margin width, but in our study, a subgroup analysis of adjuvant therapy was not conducted, as an ongoing study object.

Sensitivity analysis

Although the results of the sensitivity analysis did not show substantial differences between studies, the Spolverato (2015) 5-9 mm group in the OS sensitivity analysis[12] and the Tamandl (2008) <10 mm group in the RFS sensitivity analysis were slightly prominent[3]. The study by Spolverato (2015) *et al.*[12] reported that the 1-year OS rate of 100 patients who completed the 5-9 mm R0 margin (83.9%) was higher than the OS of 147 patients who completed the ≥10 mm R0 group (79.8%), which may be a factor influencing the OS comparison.

Limitations

This study has some limitations. First, all the studies included in this study were

published in English, and the exclusion of non-English literature may lead to selection bias. Second, the presence of single-center and multicenter studies in this study may have contributed to some bias in the results. Third, factors such as type of liver resection, surgical instrumentation, and adjuvant treatment were not analyzed in subgroups, and the prognosis of ICC patients by the above factors was inconclusive and warranted further study. Fourth, the size, number, and location of preoperative tumors and their staging also varied, and evaluation of the impact of surgical margins on postoperative survival of ICC patients in terms of tumor pathological characteristics may be required. Finally, since survival data were mostly obtained indirectly through calculations, the conclusions may differ somewhat from clinical trials.

Conclusion

In conclusion, the meta-analysis revealed that patients undergoing curative hepatectomy for ICC had a survival advantage for a wide margin of ≥10 mm compared with a narrow margin of <10 mm under certain conditions. But surgeons should determine the margin width concerning the patient's condition and should not consider <10 mm as a contraindication to surgery; in addition, lymph node status should be considered during clinical procedures, as it is also an important factor affecting the patient's postoperative survival outcome. In summary, surgical margins of ≥10 mm should be achieved as much as possible for ICC patients with negative lymph nodes, but further multicenter study results are still warranted to support this view.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Data availability statement

No additional data available.

Competing interest

The authors declare no competing interests.

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Contributors

JHJ drafting and revising the article, DZF data analysis, YTH gave final approval of the version to be published, and all authors agreed to be accountable for all aspects of the work.

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Figure titles

Figure 1. PRISMA flowchart for the included studies

Figure 2. Results of HR pooled analysis of the OS rate of the included studies (with the wide margin group ≥10 mm as the control)

Figure 3. Results of HR pooled analysis of DFS in the included studies (with the wide margin group ≥10 mm as the control)

Figure 4. Results of HR pooled analysis of RFS in the included studies (with the wide margin group ≥10 mm as the control)

Figure 5. Results of HR pooled analysis of lymph node lesions on OS in patients with ICC (with the wide margin group ≥10 mm as the control)

Figure 6. Results of HR pooled analysis of lymph node invasion on OS in ICC patients (with the wide margin group ≥10 mm as the control)

Figure 7. Results of HR pooled analysis of lymph node metastasis on RFS in ICC patients

(with the wide margin group ≥10 mm as the control)

Figure 8. Sensitivity analysis of OS after leave-out-one analyses

Figure 9. Sensitivity analysis of RFS after leave-out-one analyses

Figure 10. Funnel plot of the relationship between surgical margin width and OS in ICC patients

Figure 11. Funnel plot of the relationship between surgical margin width and RFS in ICC patients

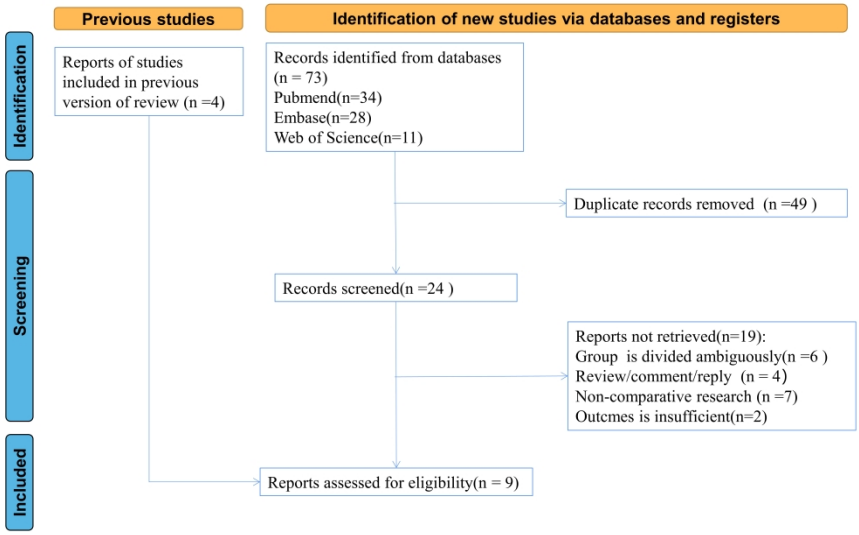

Figure 1. PRISMA flowchart for the included studies

338x190mm (600 x 600 DPI)

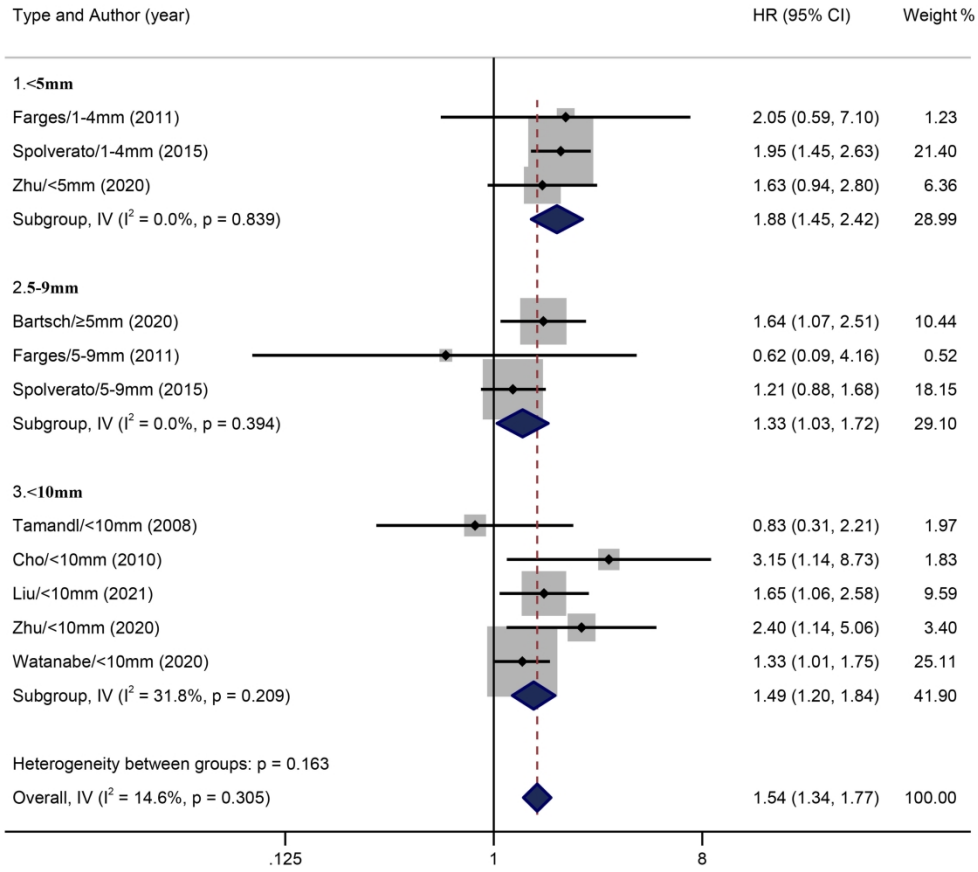

Figure 2. Results of HR pooled analysis of the OS rate of the included studies (with the wide margin group ≥10 mm as the control)

180x160mm (600 x 600 DPI)

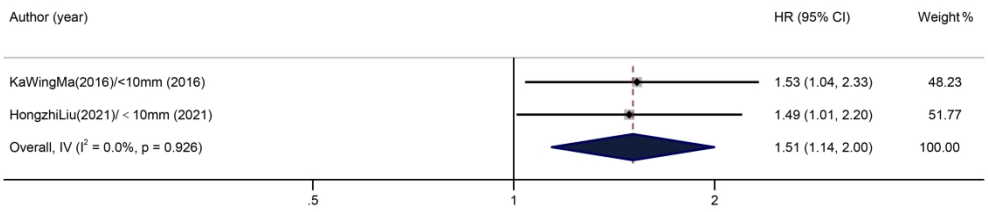

Figure 3. Results of HR pooled analysis of DFS in the included studies (with the wide margin group ≥10 mm as the control)

314x68mm (600 x 600 DPI)

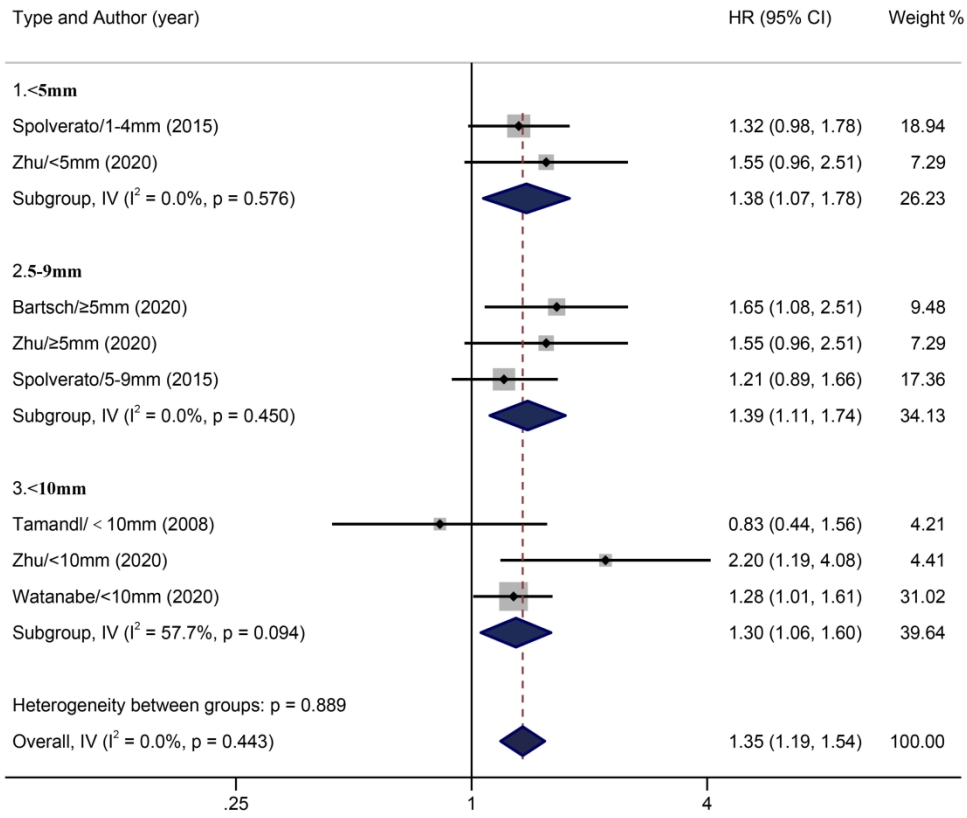

Figure 4. Results of HR pooled analysis of RFS in the included studies (with the wide margin group ≥10 mm as the control)

196x165mm (600 x 600 DPI)

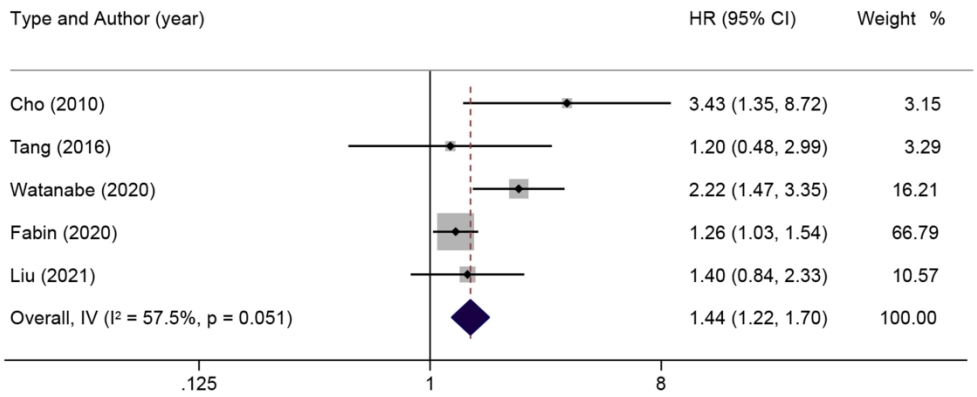

Figure 5. Results of HR pooled analysis of lymph node lesions on OS in patients with ICC (with the wide margin group ≥10 mm as the control)

210x87mm (600 x 600 DPI)

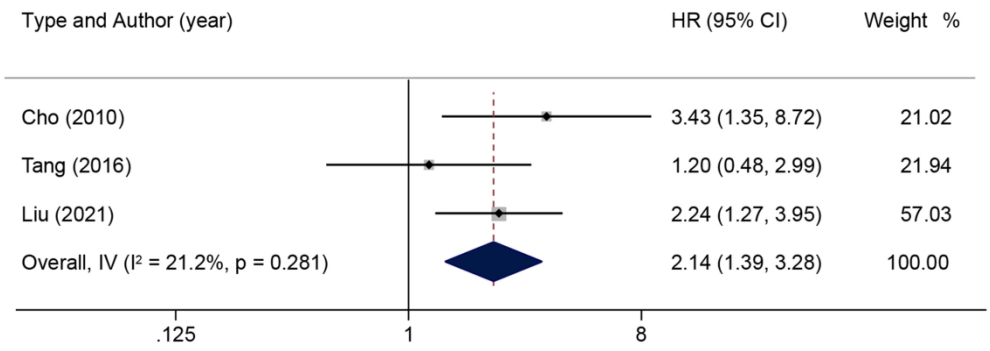

Figure 6. Results of HR pooled analysis of lymph node invasion on OS in ICC patients (with the wide margin group ≥10 mm as the control)

199x77mm (600 x 600 DPI)

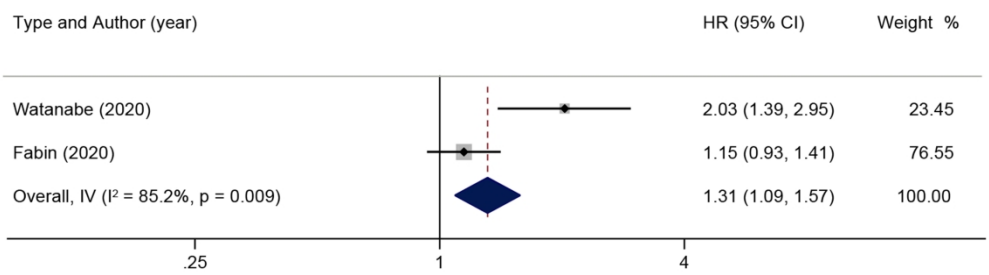

Figure 7. Results of HR pooled analysis of lymph node metastasis on RFS in ICC patients (with the wide margin group ≥10 mm as the control)

231x66mm (600 x 600 DPI)

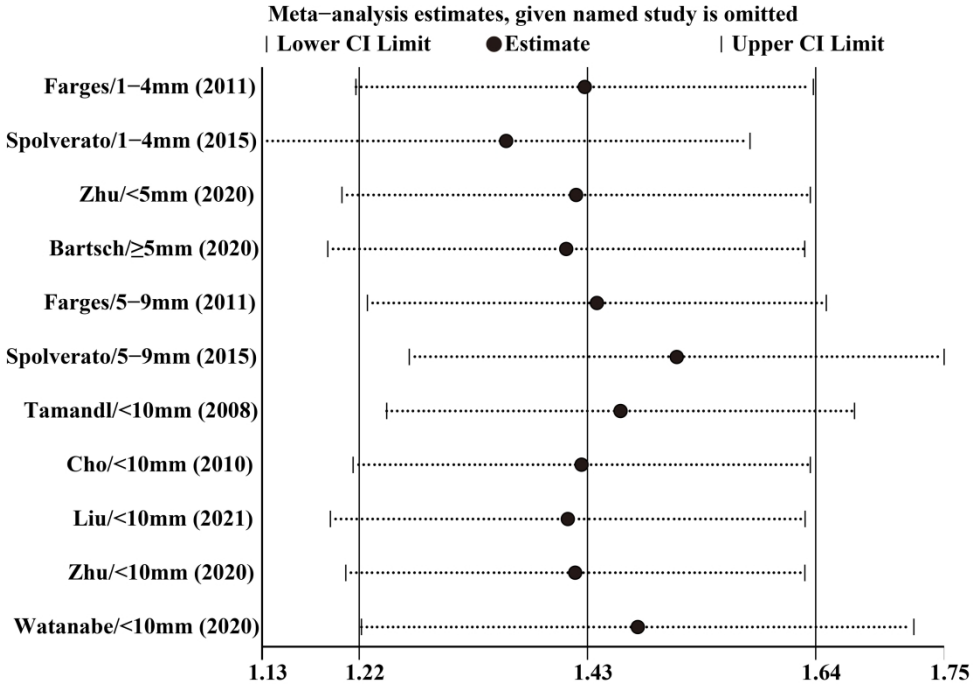

Figure 8. Sensitivity analysis of OS after leave-out-one analyses

221x156mm (600 x 600 DPI)

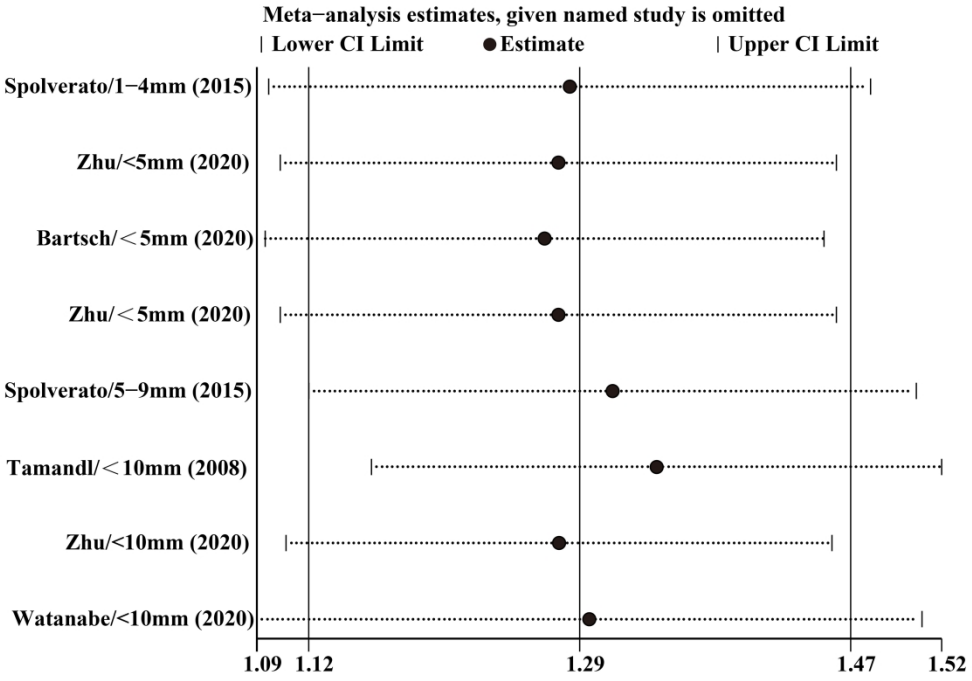

Figure 9. Sensitivity analysis of RFS after leave-out-one analyses

231x164mm (600 x 600 DPI)

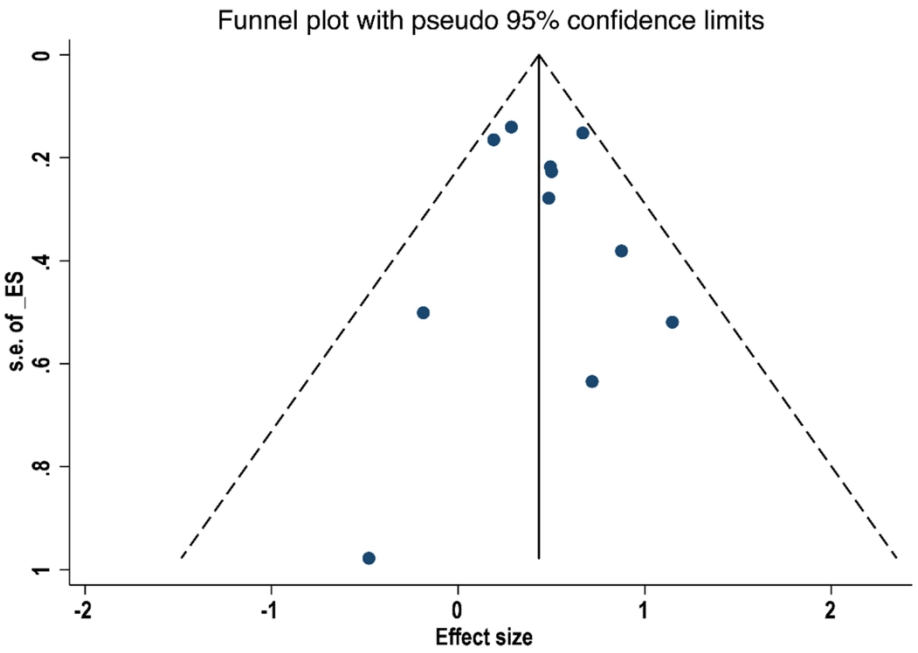

Figure 10. Funnel plot of the relationship between surgical margin width and OS in ICC patients

145x103mm (600 x 600 DPI)

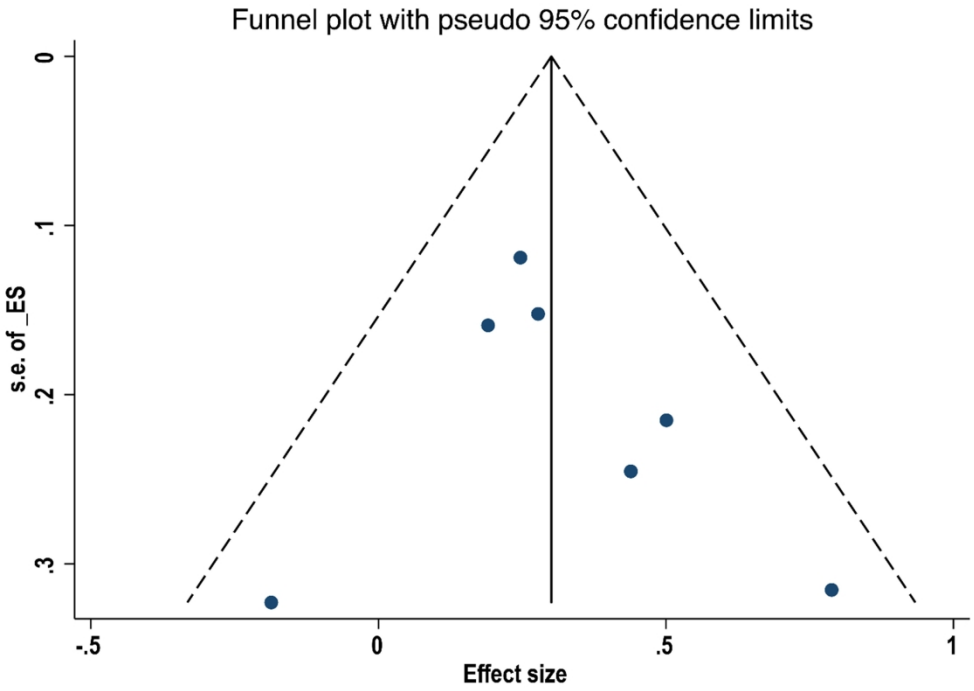

Figure 11. Funnel plot of the relationship between surgical margin width and RFS in ICC patients

167x119mm (600 x 600 DPI)

Surgical margin width – search strategy

Using the MeSH subject heading function in the National Library of Medicine:

1. The subject heading for searching "intrahepatic cholangiocarcinoma" was "Cholangiocarcinoma". The free words were "Cholangiocarcinomas", "Cholangiocellular Carcinoma", "Intrahepatic Cholangiocarcinoma", "Cholangiocarcinomas, Intrahepatic".

2. Search in combination with keywords such as "surgery", "resection margin width", and "resection margin length".

3. Search strategy for Pubmed:

(((((Cholangiocarcinomas) OR (Cholangiocellular Carcinoma)) OR (Intrahepatic Cholangiocarcinoma)) OR (Cholangiocarcinomas, Intrahepatic)) AND (Surgical margin width)) OR (Length of surgical margin)

4. Search strategy for Embase:

Cholangiocarcinomas:ti,ab,kw OR 'Cholangiocellular Carcinoma':ti,ab,kw OR 'Intrahepatic Cholangiocarcinoma':ti,ab,kw OR 'Cholangiocarcinomas, Intrahepatic':ti,ab,kw AND 'Surgical margin width'

5. Search strategy for Web of Science:

(((TS=(Cholangiocarcinomas)) OR TS=(Cholangiocellular Carcinoma)) OR TS=(Intrahepatic Cholangiocarcinoma)) AND TS=(Surgical margin width)

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3-4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6-7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	6-7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	7

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	7-8
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	7-8
Study characteristics	17	Cite each included study and present its characteristics.	8-9
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	7-8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	9-11
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	9-11
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	9-11
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	9-11
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	11
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	9-11
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	9-11
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	11-12
	23b	Discuss any limitations of the evidence included in the review.	15
	23c	Discuss any limitations of the review processes used.	15
	23d	Discuss implications of the results for practice, policy, and future research.	12-14
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	16
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	16
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	16
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	16
Competing interests	26	Declare any competing interests of review authors.	16
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	16

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71