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Meta-analysis

Long-term outcomes of combined hepatocellular-cholangiocarcinoma after hepatectomy or liver transplantation: A systematic review and meta-analysis

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ABSTRACT

Background: Combined hepatocellular-cholangiocarcinoma (cHCC-CC) is a rare primary liver malignancy. We conducted a systematic review and meta-analysis to assess the evidence available on the long-term outcomes of cHCC-CC patients after either hepatectomy or liver transplantation (LT).

Data Sources: Relevant studies published between January 2000 and January 2018 were identified by searching PubMed and Embase and reviewed systematically. Data were pooled using a random-effects model.

Results: A total of 42 observational studies involving 1691 patients (1390 for partial hepatectomy and 301 for LT) were included in the analysis. The median tumor recurrence and 5-year overall survival (OS) rates were 65% (range 38%–100%) and 29% (range 0–63%) after hepatectomy versus 54% (range 14%–93%) and 41% (range 16%–73%) after LT, respectively. Meta-analysis found no significant difference in OS and tumor recurrence between LT and hepatectomy groups.

Conclusion: Hepatectomy rather than LT should be considered as the prior treatment option for cHCC-CC.

Introduction

Combined hepatocellular-cholangiocarcinoma (cHCC-CC) is a rare primary liver malignancy showing unequivocal features of both hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC). Based on a review of 5 cases in 1949, Allen and Lisa classified cHCC-CC into three types: type A is separate masses composed of either HCC or CC; type B is contiguous masses that may mingle; and type C is intimate intermingling of hepatocellular and glandular elements [1]. With the heightened understanding about the pathogenesis of liver malignancies, the 2010 World Health Organization (WHO) guidelines classify cHCC-CC into a classical type similar to Allen and Lisa type C, and several subtypes based on the stem-cell features [2]. Therapeutically, both hepatectomy and liver transplantation (LT) are curative options for the treatment of cHCC-CC. However, most of these previous studies about cHCC-CC were based on small series of patients or even case reports, thus unable to draw definitive conclusions on specific therapeutic guidelines [3–23]. To better define selection of appropriate operative approaches, the present study sought to systematically review the literature available to evaluate and compare the long-term outcomes of cHCC-CC patients after either hepatectomy or LT.

Methods

Systematic search strategy

A literature search was conducted using PubMed and Embase databases to identify all relevant peer-reviewed English-language papers that reported survival after partial hepatectomy or LT of cHCC-CC from January 2000 throughout January 2018. The following MeSH headings and keywords were used: combined hepatocellular-cholangiocarcinoma, mixed hepatocellular-cholangiocarcinoma, hepatectomy, and liver transplantation. The bibliographies of identified articles were further manually searched for additional citations. This study was performed in accordance with the guidelines of preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2009 [24].

Selection criteria

Inclusion criteria were as follows: (1) original articles; (2) patients with cHCC-CC undergoing partial hepatectomy or LT; (3)

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Table 1
Characteristics of the included studies.

References	*n*	Male	Age (yr)	HBsAg(+)	HCV-Ab(+)	AFP ≥ 20 ng/mL	CA 19–9 ≥ 37 U/mL	Cirrhosis	TS >5 cm	MT	ACF	VI	LNM
Hepatectomy													
Jarnagin et al [3]	21	–	–	–	–	–	–	0	–	–	–	33%	5%
Liu et al [4]	12	67%	60	58%	–	–	–	25%	–	–	–	–	–
Yano et al [5]	26	89%	57	27%	38%	69%	–	54%	–	69%	54%	58%	8%
Koh et al [6]	24	67%	55	54%	13%	–	–	54%	–	42%	83%	75%	8%
Sanada et al [7]	11	64%	66	46%	55%	73%	75%	46%	27%	0	27%	46%	–
Aishima et al [8]	40	90%	58	46%	38%	74%	–	28%	40%	50%	–	48%	29%
Bhagat et al [9]	5	40%	71	–	–	–	–	–	–	–	–	–	60%
Lee et al [10]	33[a]	67%	52	49%	12%	–	–	49%	51%	27%	73%	60%	10%
Tang et al [11]	13	92%	57	39%	0	46%	50%	23%	62%	–	46%	23%	8%
Shin et al [12]	12	92%	48	100%	11%	78%	–	80%	–	–	–	–	–
Wakasa et al [13]	18	78%	57	22%	44%	39%	67%	28%	56%	–	–	–	50%
Zuo et al [14]	15	73%	49	73%	20%	–	–	73%	87%	40%	40%	40%	33%
Portolani et al [15]	18	–	–	17%	61%	82%	57%	78%	–	–	–	72%	44%
Kim et al [16]	29[b]	79%	53	76%	3%	69%	48%	59%	55%	35%	69%	28%	7%
Ariizumi et al [17]	44	70%	65	25%	55%	77%	68%	52%	–	–	–	25%	14%
Lee et al [18]	30	87%	61	63%	3%	53%	–	73%	–	–	–	–	–
Park et al [19]	21	71%	59	81%	0	80%	–	62%	48%	24%	–	81%	–
Yu et al [20]	14	86%	54	93%	0	86%	36%	71%	100%	–	–	64%	7%
Yin et al [21]	103	81%	50	73%	1%	58%	–	67%	–	17%	69%	9%	13%
Zhan et al [22]	27[c]	89%	58	30%	15%	37%	–	37%	–	–	–	89%	22%
Groeschl et al [23]	54[d]	67%	62	–	–	–	–	–	60%	26%	–	–	–
Lee et al [26]	27	–	–	–	–	–	–	–	–	–	–	–	–
Park et al [27]	10	80%	52	80%	0	–	–	–	–	–	–	–	–
Song et al [28]	68	75%	56	63%	6%	57%	–	47%	47%	29%	–	77%	–
Yap et al [29]	11	73%	61	54%	18%	–	–	72%	18%	9%	54%	36%	9%
Chu et al [30]	390	84%	49	100%	Excluded	–	30%	74%	67%	39%	–	69%	20%
Kim et al [31]	30	83%	54	67%	8%	50%	–	–	–	13%	–	80%	–
Lee et al [32]	42	71%	54	76%	0	–	21%	71%	48%	5%	69%	12%	33%
Wu et al [33]	32[e]	63%	56	–	–	48%	21%	–	–	–	–	58%	3%
Jung et al [34]	100	75%	54	65%	6%	–	–	–	32%	0	–	35%	0
Zhou et al [35]	144	94%	53	70%	0	54%	36%	63%	–	11%	66%	47%	14%
LT													
Song et al [28]	8	100%	53	100%	0	–	–	100%	0	100%	–	63%	–
Jung et al [34]	32	81%	53	94%	3%	–	13%	–	–	13%	–	19%	0
Chan et al [36]	3	67%	52	100%	0	–	–	–	2%	0	–	33%	0
Maganty et al [37]	3	67%	51	33%	33%	–	–	100%	0	1%	–	–	0
Panjala et al [38]	12	67%	61	17%	42%	75%	25%	83%	–	–	–	25%	0
Park et al [39]	15	87%	59	93%	0	–	–	100%	–	7%	–	–	–
Garancini et al [40]	61	–	–	–	–	–	–	–	–	7%	–	–	–
Abdelfattah et al [41]	3	–	–	–	–	–	–	100%	0	3%	–	–	–
Itoh et al [42]	8	50%	58	38%	63%	–	–	–	–	–	–	50%	–
Wu et al [43]	21	100%	53	95%	19%	62%	57%	86%	81%	76%	–	67%	24%
Serra et al [44]	4	75%	57	0	75%	–	–	100%	–	–	–	25%	–
Vilchez et al [45]	94	75%	57	–	44%	–	–	–	–	–	–	–	–
Magistri et al [46]	3	100%	55	0	100%	–	–	100%	0	–	–	–	–

HBsAg: hepatitis B surface antigen; HCV-Ab: anti-hepatitis C virus antibody; MT: multiple tumor; ACF: absence of capsule formation; VI: vascular invasion; LT: liver transplantation; AFP: a-fetoprotein; CA 19-9: carbohydrate antigen 19-9; TS: tumor size; LNM: lymph node metastasis.

[a] 1 patient underwent liver transplantation;
[b] 4 patients underwent liver transplantation;
[c] 2 patients underwent liver transplantation;
[d] 19 patients underwent liver transplantation;
[e] 8 patients underwent liver transplantation.

Table 2
Outcomes of combined hepatocellular-cholangiocarcinoma following hepatectomy and liver transplantation.

References	*n*	Mortality	MOS (mon)	OS			Recurrence
				1-yr	3-yr	5-yr	
Hepatectomy							
Jarnagin et al [3]	21	10%	32	–	38%	24%	79%
Liu et al [4]	12	0	17	–	–	–	92%
Yano et al [5]	26	12%	23	–	35%	23%	95%
Koh et al [6]	24	–	37	82%	47%	–	58%
Sanada et al [7]	11	9%	18	63%	26%	26%	91%
Aishima et al [8]	40	–	–	79%	49%	35%	73%
Bhagat et al [9]	5	0	23	80%	20%	–	–
Lee et al [10]	33[a]	–	47	69%	60%	0	49%
Tang et al [11]	13	0	60	85%	50%	50%	69%
Shin et al [12]	12	0	30	–	–	–	100%
Wakasa et al [13]	18	–	–	73%	33%	–	50%
Zuo et al [14]	15	0	–	53%	23%	8%	–
Portolani et al [15]	18	–	–	91%	62%	62%	–
Kim et al [16]	29[b]	0	29	78%	37%	–	62%
Ariizumi et al [17]	44	–	15	–	–	24%	57%
Lee et al [18]	30	–	18	63%	36%	8%	87%
Park et al [19]	21	–	10	42%	19%	19%	38%
Yu et al [20]	14	0	8	8%	0	0	58%
Yin et al [21]	103	–	13	74%	41%	36%	65%
Zhan et al [22]	27[c]	4%	22	73%	42%	35%	–
Groeschl et al [23]	35	–	–	71%	46%	–	–
Lee et al [26]	27	–	–	55%	15%	5%	–
Park et al [27]	10	–	23	20%	20%	10%	–
Soon et al [28]	68	–	–	75%	46%	42%	74%
Yap et al [29]	11	0	–	80%	69%	–	46%
Chu et al [30]	390	6%	16	62%	40%	32%	–
Kim et al [31]	30	0	–	69%	51%	37%	–
Lee et al [32]	42	–	–	80%	61%	54%	64%
Wu et al [33]	24	0		–	76%	–	63%
Jung et al [34]	100	0	–	85%	78%	63%	42%
Zhou et al [35]	144	1%	36	84%	50%	41%	72%
LT							
Pooled analysis [28,36,37,41,44,46]	24	0	17	75%	35%	35%	71%
Groeschl et al [23]	19	–	–	89%	48%	–	–
Wu et al [33]	8	–	–	–	75%	–	50%
Jung et al [34]	32	0	–	84%	73%	66%	38%
Panjala et al [38]	12	8%	43	79%	66%	16%	58%
Park et al [39]	15	0	–	67%	60%	60%	47%
Garancini et al [40]	61	–	–	–	–	41%	–
Itoh et al [42]	8	13%	–	88%	73%	73%	14%
Wu et al [43]	21	10%	23	64%	39%	39%	58%
Vilchez et al [45]	94	–	29	82%	47%	40%	93%

MOS: median overall survival; LT: liver transplantation; OS: overall survival.
[a] 1 patient underwent liver transplantation;
[b] 4 patients underwent liver transplantation;
[c] 2 patients underwent liver transplantation.

study populations aged at least 18 years; and (4) studies reporting overall survival (OS). Studies from the same institution covering different time periods were included. Reviews, conference abstracts, nonhuman studies, single case reports, studies focusing on molecular mechanisms of oncogenesis, and studies focusing on patients with Allen and Lisa type A tumors were excluded. The level of evidence of each study was categorized according to the Evidence-Based Medicine Levels of Evidence [25].

Data extraction

Two reviewers independently appraised each article using a predefined form. The first author, publication year, study period, country of origin, trial design, sample size, patient's characteristics, and outcomes of interests were extracted. Differences in opinions between the two investigators were resolved by discussion and consensus.

Statistical analysis

Summary statistics were reported as median values and range for continuous variables, unless otherwise specified. To increase statistical power, a pooled analysis of individual patients undergoing LT was performed to calculate survival probabilities. The statistical analyses were carried out with SPSS version 18 (SPSS, Chicago, Illinois, USA). The meta-analysis was performed using the Review Manager (RevMan) version 5.3 (The Cochrane Collaboration, Software Update, Oxford). Hazard ratios (HR) with 95% confidence interval (CI) were calculated for prognostic factors, and odds ratios (OR) with 95% CI were calculated for OS and tumor recurrence. Random-effects models were utilized due to the inherent between-study heterogeneity of surgical series. Statistical significance was set at $P < 0.05$.

Results

A total of 381 articles were identified by the initial search strategy. Processing according to PRISMA criteria yielded 42 publications containing data of 1691 patients who met the final inclusion criteria (Fig. 1). Of them, 1390 patients underwent partial hepatectomy and the other 301 patients underwent LT. The characteristics of the included patients are summarized in Table 1 [3–23,26–46]. All studies were retrospective

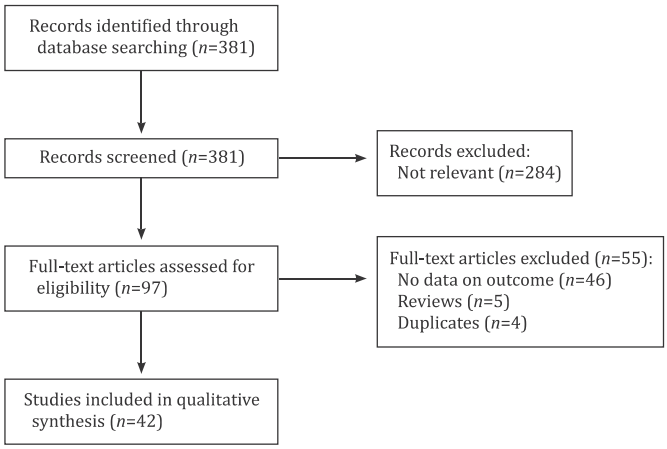

Fig. 1. Flow chart of study screening and selection process.

and classified as level-4 evidence. Most reports originated from Asia (Japan, $n=7$; Korea, $n=14$; China, $n=11$; Saudi Arabia, $n=1$), followed by the United States ($n=6$) and Europe ($n=3$).

Most patients were male (75%, range 40%–100%) with a median age of 56 (range 48–71) years. Seropositivity for HBsAg and anti-HCV Ab was identified in 63% (range 0–100%) and 12% (range 0–100%) patients, respectively. Preoperative alpha fetal protein (AFP) level was above normal (≥20 ng/mL) in 66% (range 37%–86% patients, and CA 19-9 was above normal (≥37 U/mL) in 42% (range 13%–75%) patients. Histopathologic evidence of cirrhosis was present in 69% (range 0–100%) patients. Tumor size > 5 cm, multiple tumors, the absence of capsule formation, vascular invasion, and lymph node metastasis were present in 48% (range 0–100%), 17% (range 0–100%), 66% (range 27%–83%), 48% (range 9%–89%), and 10% (range 0–60%) patients, respectively.

Post-hepatectomy outcomes

The median mortality rate was 0 (range 0–12%). The median 5-year OS rate following hepatectomy was 29% (range 0–63%), with a median survival of 23 (range 8–60) months and a recurrence rate

Study or subgroup	Log [hazard ratio]	SE	Weight	Hazard ratio IV, Random, 95% CI
Vascular invasion				
Koh et al 2005	0.2776	0.1168	39.8%	1.32 [1.05, 1.66]
Aishima et al 2006	2.1780	0.8701	5.3%	8.83 [1.60, 48.59]
Chu et al 2014	0.5002	0.1960	32.6%	1.65 [1.12, 2.42]
Zhou et al 2017	0.9490	0.3198	22.3%	2.58 [1.38, 4.83]
Subtotal (95% CI)			**100.0%**	**1.82 [1.20, 2.76]**
Heterogeneity: Tau² = 0.10; Chi² = 8.47, df = 3 (P = 0.04); I^2 = 65%				
Test for overall effect: Z = 2.83 (P = 0.005)				
Lymph node metastasis				
Aishima et al 2006	1.9337	0.8554	5.6%	6.92 [1.29, 36.98]
Zhan et al 2012	1.7924	0.6795	8.8%	6.00 [1.59, 22.74]
Kim et al 2014	1.2036	0.3689	29.9%	3.33 [1.62, 6.87]
Jung et al 2017	0.8065	0.3446	34.2%	2.24 [1.14, 4.40]
Zhou et al 2017	0.6642	0.4346	21.5%	1.94 [0.83, 4.55]
Subtotal (95% CI)			**100.0%**	**2.84 [1.91, 4.22]**
Heterogeneity: Tau² = 0.00; Chi² = 3.72, df = 4 (P = 0.45); I^2 = 0%				
Test for overall effect: Z = 5.18 (P < 0.00001)				
Tumor size >5 cm				
Soon et al 2013	1.0999	0.3436	48.5%	3.00 [1.53, 5.89]
Kim et al 2014	1.0953	0.5181	21.3%	2.99 [1.08, 8.25]
Zhou et al 2017	0.7491	0.4354	30.2%	2.12 [0.90, 4,97]
Subtotal (95% CI)			**100.0%**	**2.70 [1.69, 4.31]**
Heterogeneity: Tau² = 0.00; Chi² = 0.45, df = 2 (P = 0.80); I^2 = 0%				
Test for overall effect: Z = 4.15 (P < 0.0001)				
Tumor stage ≥ III				
Koh et al 2005	0.8372	0.1446	39.5%	2.31 [1.74, 3.07]
Lee et al 2011	0.9708	0.4902	17.6%	2.64 [1.01, 6.90]
Yin et al 2012	0.2390	0.0827	42.9%	1.27 [1.08, 1.49]
Subtotal (95% CI)			**100.0%**	**1.83 [1.09, 3.07]**
Heterogeneity: Tau² = 0.16; Chi² = 14.29, df = 2 (P = 0.0008); I^2 = 86%				
Test for overall effect: Z = 2.29 (P = 0.02)				

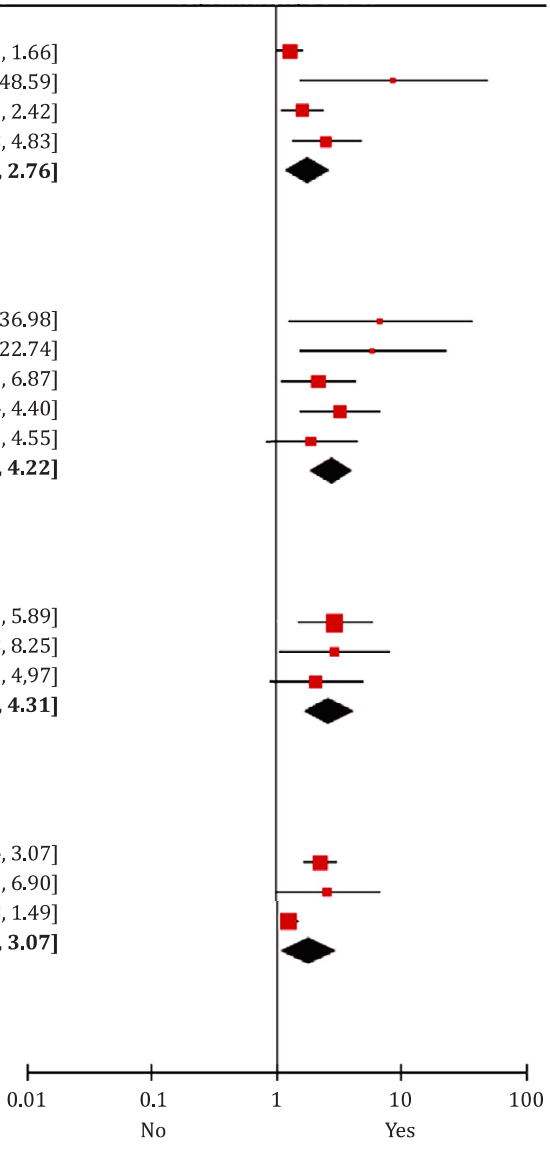

Fig. 2. Forest plots of risk factors associated with overall survival after hepatectomy.

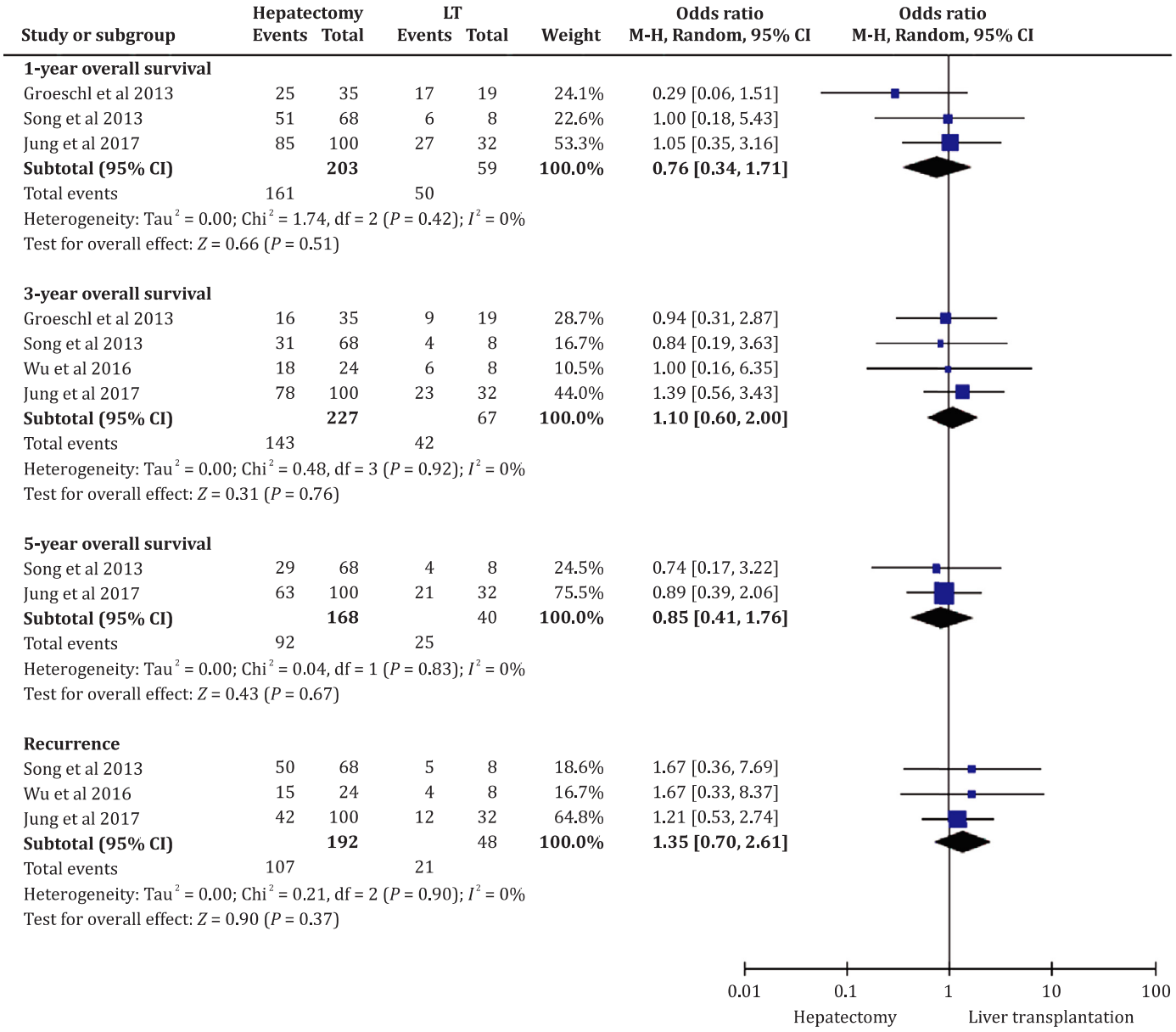

Fig. 3. Forest plots of hepatectomy versus liver transplantation on long-term outcomes. LT: liver transplantation.

of 65% (range 38%–100%) (Table 2). Clinicopathological variables that were evaluated for association with OS by multivariate Cox regression analysis in which at least three papers were included. Vascular invasion (HR = 1.82; 95% CI: 1.20–2.76; $P = 0.005$), lymph node metastasis (HR = 2.84; 95% CI: 1.91–4.22; $P < 0.00001$), tumor size > 5 cm (HR = 2.70; 95% CI: 1.69–4.31; $P < 0.0001$), and tumor stage ≥ III (HR = 1.83, 95% CI: 1.09–3.07; $P = 0.02$) were found to be independently associated with decreased OS (Fig. 2).

Post-LT outcomes

The median mortality rate was 4% (range 0–13%). The median 5-year OS rate following LT was 41% (range 16%–73%), with a median survival of 26 (range 17–43) months and a recurrence rate of 54% (range 14%–93%) (Table 2). Only one study analyzed the independent predictors of poor survival and identified that tumor size > 2.5 cm was statistically significant (HR = 3.22; 95% CI: 0.98–14.3; $P = 0.048$) [34].

Meta-analysis of LT versus hepatectomy

Four studies compared LT ($n = 67$) with partial hepatectomy ($n = 227$) [23,28,33,34]. Meta-analysis found no significant difference in OS and tumor recurrence between LT and hepatectomy groups (Fig. 3).

Discussion

This meta-analysis including 1390 patients showed good short-term outcomes of hepatectomy for cHCC-CC, with a median 90-day mortality of 0. However, the long-term outcome remained unsatisfactory. The 5-year OS reported from each series ranged from 0 to 63% and exceeded 50% only in four series. Vascular invasion, lymph node metastasis, tumor size > 5 cm, and later tumor stage proved to be the independent prognostic factors. Among these, although the nodal status seems the most strongly predictive, the clinical relevance of routine lymphadenectomy is not well established. There are wide practice variations regarding the use of

lymphadenectomy for cHCC-CC across institutions and countries, and nearly 40% of the included studies did not provide quantitative data on the presence or absence of lymph node metastasis. In case of intrahepatic cholangiocarcinoma (ICC), it is generally believed that routine lymphadenectomy did not show survival benefits; however, lymphadenectomy sampling might be useful for nodal staging [47]. The 7th American Joint Committee on cancer tumor-node-metastasis staging system grouped cHCC-CC and ICC into one stage. In this context, routine lymphadenectomy should be considered in patients undergoing resection of cHCC-CC, knowing that it at least enables clinicians to obtain accurate pathologic staging of disease.

Recurrence is a major cause of treatment failure in cHCC-CC after hepatectomy, but no prospective study has been reported to investigate any pre- or postoperative therapies specified in preventing relapse from the primary tumor. In a case report, Hayashi et al. described a 52-year-old man who received adjuvant chemotherapy with cisplatin, 5-fluorouracil and radiation therapy and was alive without any recurrence for 42 months after the operation [48]. Still, series with large numbers of cases are needed and justified. Based on the fact that most cHCC-CC patients, especially those from Asian countries, were affected by HBV and/or HCV infection and antiviral therapy proved to be associated with a lower risk of recurrence among patients with HCC or ICC [49,50], it seems important to commence antiviral therapy after hepatectomy for cHCC-CC related to HBV or HCV, though limited data are currently available.

LT has been universally accepted as a treatment for HCC patients meeting the Milan criteria (1 tumor $\leq$ 5 cm or 2–3 tumors all $\leq$ 3 cm) and offers an excellent >70% probability of 5-year survival to a transplant candidate [51]. In contrast, our analysis clearly demonstrated that LT for cHCC-CC yielded rather poor outcomes, with a median 5-year OS rate of only 41% and a high recurrence rate of 54%. Furthermore, LT showed no significantly improved survival outcomes as compared with hepatectomy. Hence, we think that cHCC-CC is not considered a standard indication for LT, especially in an era of organ shortage. Although Jung et al. reported a significantly favorable 5-year OS of 93% in their patients with 1 or 2 cHCC-CC $\leq$ 2 cm, their study is limited by the small number of patients ($n = 32$) and the absence of comparing these same transplant patients with those who underwent curative-intent resection, which poses a subject to skepticism [34].

Accurate preoperative diagnosis of cHCC-CC based on clinical and imaging findings remains difficult due to that the tumor has the HCC and CC histological features. As a result, cases are often misdiagnosed as HCC or CC, depending on the major component of the tumor and any underlying liver disease. Although the biopsy is still challenging for the diagnosis of cHCC-CC [37], it has a role for suspected patients planned for LT, since cHCC-CC should be excluded from LT because of poor outcome from high recurrence rates.

The current study has some limitations. All the included studies were retrospective studies with a relatively small number of patients involved. Furthermore, in the event of intrahepatic recurrent cHCC-CC, repeated hepatectomy, radiofrequency ablation or transarterial chemoembolization have been considered; however, little attention has been paid to the clinical outcome after different therapeutic strategies in the literature. This makes it difficult to identify the optimal treatment strategies for recurrences.

In conclusion, hepatectomy rather than LT should be considered as the prior treatment option for cHCC-CC.

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Contributors

LDB and ZYM participated in the design and coordination of the study, carried out the critical appraisal of studies and wrote the manuscript. LDB, SXY, and WSJ searched the literature, extracted the data, and assisted in the critical appraisal of included studies. All authors read and approved the final manuscript. ZYM is the guarantor.

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Ethical approval

Not needed.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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