Original Article

The effect of bile duct tumor thrombus on the long-term prognosis of hepatocellular carcinoma patients after liver resection: a systematic review and meta-analysis

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Background: The effect of bile duct tumor thrombus (BDTT) on the postoperative long-term prognosis of hepatocellular carcinoma (HCC) patients is still under debate.

Methods: The PubMed, Embase, Cochrane Library, Web of Science databases were systematically searched to collect the clinicopathologic characteristics, perioperative indices, and postoperative survival outcomes in the BDTT and non-BDTT groups of HCC patients from inception to February 1, 2020. The study outcomes were extracted by two independent investigators.

Results: A total of 15 studies involving 6,484 patients were included. The meta-analysis revealed that the levels of serum total bilirubin and alkaline phosphatase were notably higher in patients with HCC and BDTT than those without BDTT. Meanwhile, HCC patients with BDTT had more aggressive biological characteristics, such as poor tumor differentiation, macrovascular invasion, and lymph node metastasis, as compared to patients without BDTT. The 1-year [odds ratio (OR) 0.39, 95% confidence interval (CI): 0.31–0.48, P<0.01], 3-year (OR 0.33, 95% CI: 0.22–0.51, P<0.01) and 5-year overall survival (OS) rates (OR 0.31, 95% CI: 0.20–0.49, P<0.01) of the BDTT group were significantly worse than those of the non-BDTT group. The hazard ratio of HCC with BDTT was 4.27 (95% CI: 3.47–5.26, P<0.01) within 5 years after hepatectomy.

Conclusions: HCC patients with BDTT had worse OS compared to patients free of BDTT after surgery. BDTT may be a potential prognostic factor for HCC patients.

Keywords: Bile duct tumor thrombus (BDTT); hepatocellular carcinoma (HCC); liver resection; overall survival (OS); prognosis

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy and the fourth leading cause of cancer-related mortality worldwide (1). HCC has a propensity to invade vasculature systems, which leads to intrahepatic metastasis and extrahepatic spread. A series of studies have demonstrated that macrovascular tumor thrombus is a crucial predisposing factor for HCC patients, and liver

resection may provide a survival benefit in select HCC patients with vascular invasion (2,3).

HCC also invades adjacent intra- and extrahepatic biliary tree to form bile duct tumor thrombus (BDTT). BDTT is defined as an intraductal neoplasm, which consists of HCC cells and lining biliary epithelial cells under microscope. BDTT is primarily classified as microscopic and macroscopic tumor thrombus according to its anatomical location in the biliary tract (4). The prevalence of BDTT ranges from 0.5% to 12.9% in surgical specimens obtained from HCC (5). The incidence of BDTT in HCC is relatively low, and it is frequently accompanied by concurrent portal vein or hepatic vein invasion. Therefore, our understanding of BDTT is often limited.

To our knowledge, several studies have demonstrated that BDTT is associated with poor prognosis and should be considered an indicator of worse overall survival (OS) following liver resection for HCC patients (6-8). Nevertheless, some high-quality studies have concluded that HCC patients with BDTT can reach similar long-term outcomes after curative-intent surgery (9-11). Consequently, the survival outcomes for HCC patients with BDTT remain controversial.

Herein, we present the first comprehensive systematic review and meta-analysis, in order to compare the clinicopathologic characteristics, perioperative indices and postoperative OS between HCC patients with and without BDTT, and to further explore the prognostic effect of BDTT on HCC, with the aim to provide relevant guidance for clinical practice. The following article is performed on the basis of the Cochrane Collaboration recommendations. We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/atm-20-4698) (12,13).

Methods

Study protocol and search strategy

The PubMed, Embase, Cochrane Library, and Web of Science databases were systematically searched for relevant articles from inception to February 1, 2020. Other potential records were identified using Scopus and Google Scholar. In addition, the reference lists of the retrieved articles were screened carefully and searched manually to identify more relevant studies. Medical Subject Headings (MeSH) terms and free-text terms were used in combination. The following MeSH terms were used: (carcinoma, hepatocellular AND bile duct thrombus). The following free-text terms were used: ((hepatocellular carcinoma OR liver cancer OR hepatic cancer OR liver neoplasm OR liver tumor OR hepatic tumor OR hepatocarcinoma OR liver cell carcinoma OR HCC OR hepatoma) AND (bile duct tumor thromb* OR bile duct tumour thromb* OR biliary tumor thromb* OR biliary tumour thromb* OR bile duct invasion OR biliary invasion)). The retrieved articles were imported to Endnote X9 software for further screening.

Selection criteria

The inclusion criteria were as follows: (I) clinical studies that compared long-term outcomes between HCC patients with and without BDTT after liver resection; (II) studies with sufficient data available, such as demographics, baseline characteristics, median survival time (MST) and OS outcomes.

The exclusion criteria were as follows: (I) non-HCC; (II) recurrent or secondary HCC; (III) patients underwent adjuvant therapy or liver transplantation; (IV) literature focusing on diagnostic techniques of BDTT; (V) basic experimental studies involving BDTT; (VI) no survival outcomes or curves reported to calculate odds ratio (OR) or hazard ratio (HR); (VII) full-text articles not available; (VIII) case reports, conference abstracts, narrative reviews, comments, letters or other documents unrelated to the topic.

Data extraction

Two independent investigators (JK Feng, YX Wu) screened the titles and abstracts of all the retrieved citations to identify potentially relevant studies. Full-text articles were then obtained for further review. In cases where disagreement occurred, a third author (ZH Chen) was invited to obtain a consensus. A data extraction table was created after repeated discussion and revision. Two authors (JK Feng and YX Wu) extracted the data from original articles into the table. The accuracy and completeness of the data were checked by a third author (ZH Chen).

The contents of the extracted data were composed of the following information: (I) basic information of the enrolled studies, including authors' names, year and country of publication, study design, sample size, gender and age of subjects, and follow-up time; (II) clinicopathologic characteristics, including hepatitis B surface antigen (HBsAg), Child-Pugh classification, the levels of albumin,

total bilirubin, alkaline phosphatase (ALP) and α-fetoprotein (AFP), cirrhosis, tumor size and number, encapsulation, stage and differentiation of the tumor, macrovascular invasion and lymph node metastasis; (III) perioperative indices, including surgical mode (anatomic resection, R0 resection), operating time, intraoperative blood loss, hospital stay, postoperative morbidity and mortality; (IV) long-term survival outcomes, including the 1-, 3-, and 5-year OS rates. Particularly, the following characteristics of the BDTT group were extracted: (I) the number of patients with macroscopic or microscopic BDTT; (II) the number of patients with or without obstructive jaundice; (III) the detailed categorizing protocols of BDTT.

Quality assessment

The Newcastle-Ottawa Scale (NOS) was used to assess the methodologic quality of the included retrospective cohort studies. This scale evaluates studies on the following aspects: (I) selection of the exposed and non-exposed cohorts (4 scores); (II) comparability of different cohorts (2 scores); (III) measurement of outcomes and follow-up (3 scores). If the total score was 7 or greater, the study was of high quality (14). This process was also conducted by two authors (JK Feng, YX Wu). When disagreement in scoring occurred, a third author (ZH Chen) participated in the discussion, and a final decision was made collectively.

Statistical analysis

For binary categorical data, the results are expressed as numbers (percentages), and pooled ORs with corresponding 95% confidence intervals (CIs) were calculated. For continuous variables, the results are presented as mean ± standard deviation (SD), and weighted mean differences (WMDs) with 95% CIs were calculated. When the mean and SD were not available for continuous variables, we used the methods described by Hozo *et al.* (15) to estimate these values. Cumulative meta-analyses were also performed to assess the stability of OR for OS. Moreover, to evaluate the prognostic effect of BDTT on HCC after hepatectomy, pooled HRs with 95% CIs were extracted using the software Engauge Digitizer (Version 10.3, ©2014 Mark Mitchell) from Kaplan-Meier curves using the methods reported by Tierney *et al.* (16).

Chi-square test and I^2 statistic were used to quantify the degree of heterogeneity across different studies, and I^2>50% indicated significant heterogeneity (17). Effect sizes with significant heterogeneity were pooled using a random-effects model. Otherwise, a fixed-effects model was applied. Publication bias of HR was assessed using a funnel plot and Egger's test. Sensitivity analysis was further performed to determine the stability of the overall prognostic effect of HR. Statistical significance was set at a P value less than 0.05 (two-tailed).

All of the above meta-analyses were performed using Stata software (Version 12.0, Stata Corp LP, College Station, TX, USA).

Results

Study selection procedure

The detailed process of the identification of eligible studies is shown in *Figure 1*. A total of 291 studies were identified in our initial broad search. After careful reading of the titles and abstracts of these records, 30 articles were selected for eligibility assessment. Following review of the full text, 15 articles were excluded due to the absence of the non-BDTT group for control (n=8), lack of survival outcomes (n=4) and lack of a full-text article (n=3). Eventually, fifteen studies met our inclusion criteria and were included in this analysis (4-8,10,11,18-25).

Basic characteristics and methodologic quality

The basic characteristics and NOS scores of the included studies are shown in *Table 1*. In total, 6,484 HCC patients were included, of whom 478 (7.4%) had concurrent BDTT and 6,006 (92.6%) did not. The age of the two groups was comparable. Most patients were male, which accounted for 81.2% and 83.0% in the BDTT and non-BDTT groups, respectively. The median follow-up time ranged from 24 to 96 months, with the longest follow-up period exceeding 5 years in all studies.

As shown in *Table 1*, the NOS scores of the included studies ranged from 5 to 9, with a mean score of 6.9 points. Nine of the fifteen articles were categorized as high-quality studies (4-6,11,19-23). The following listed reasons affected the quality: (I) insufficient description of the methods to identify the exposure factor (18); (II) no control for important confounding factors (4,7,8,10,18-21,24,25); (III) not exhibiting appropriate plans to assess outcomes (6-8,18,24,25); (IV) lack of description of lost to follow-up (4-8,10,18-25).

Table S1 displays the details of the BDTT group and

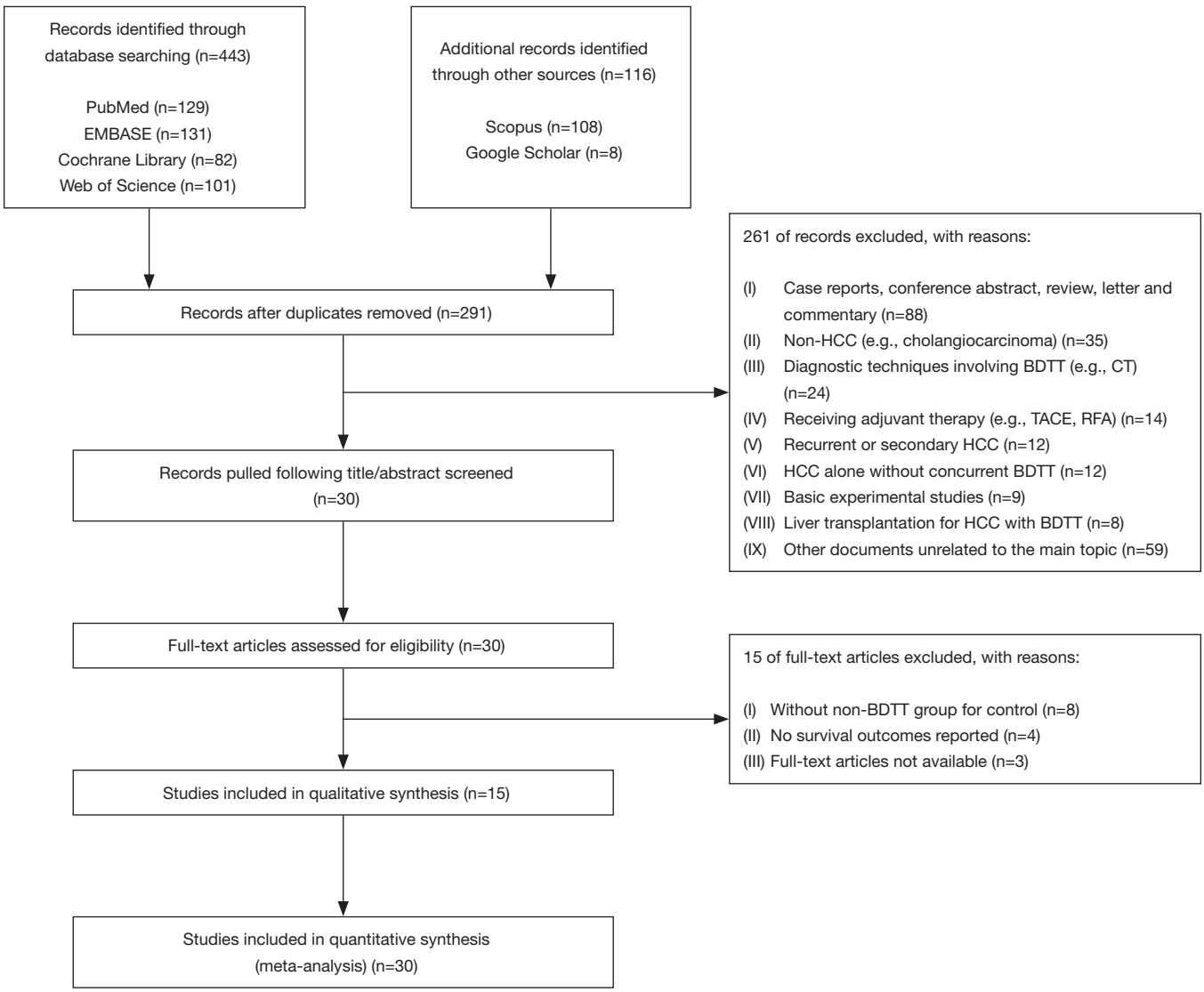

Figure 1 PRISMA flow diagram of the identification process for eligible studies. HCC, hepatocellular carcinoma; BDTT, bile duct tumor thrombus; CT, computed tomography; TACE, transarterial chemoembolization; RFA, radiofrequency ablation.

describes the classification method of BDTT in each of the included studies. As shown in Table S1, four of the fifteen studies contained solely macroscopic BDTT (4,10,18,21), one study only consisted of microscopic BDTT (23), eight studies included both macroscopic and microscopic BDTT (5-8,19,20,24,25), and the remaining studies did not provide the number of patients with macroscopic or microscopic BDTT (11,22). In the BDTT group, 74.8% (305/408) patients had macroscopic BDTT, and 49.1% (201/409) patients were complicated with obstructive jaundice on the first admission to hospital.

Clinicopathologic characteristics

As presented in *Table 2*, no significant differences were found between the BDTT and non-BDTT groups in regard to HBsAg positivity, AFP level, presence of cirrhosis, number and diameter of primary tumor, or encapsulation. The proportions of Child-Pugh class A (OR 0.50, 95% CI: 0.26–0.98, P=0.04), well or moderate tumor differentiation (OR 0.49, 95% CI: 0.37–0.65, P<0.01) and the level of albumin (WMD –1.82, 95% CI: –3.31 to –0.33, P=0.02) were significantly lower in the BDTT group; whereas the levels of total bilirubin (WMD 2.18, 95% CI: 1.56–2.81,

Table 1 Basic characteristics and methodologic quality of the references included in the meta-analysis

References	Published year	Country	Study type*	Number of cases		Age (years)		Gender (male/female)		MFT (months)	NOS score
				BDTT	Non-BDTT	BDTT	Non-BDTT	BDTT	Non-BDTT		
Shiomo *et al.*	2001	Japan	R (1980 to 1999)	17	115	58.8±2.0	60.0±0.8	15/2	96/19	NA	6
Yeh *et al.*	2004	China	R (1986 to 1998)	16	427	52.3±14.7	NA	14/2	NA	25.1	5
Ikenaga *et al.*	2009	Japan	R (1990 to 2006)	15	256	66 (42 to 77)	66 (18 to 83)	12/3	192/64	NA	7
Shao *et al.*	2011	China	R (2000 to 2006)	27	270	47.1±10.5	48.0±11.3	24/3	232/38	NA	7
Yu *et al.*	2011	China	R (2002 to 2008)	20	656	50.6±2.4	50.0±0.6	17/3	565/91	NA	7
Noda *et al.*	2011	Japan	R (1998 to 2007)	22	529	10/12 (≤60/>60)	333/196 (≤60/>60)	21/1	428/101	35	7
Meng *et al.*	2014	China	R (2007 to 2010)	35	378	51.3±2.0	50.2±0.6	24/11	309/69	24	6
Oba *et al.*	2014	Japan	R (1992 to 2012)	13	783	61 (50 to 76)	65 (27 to 85)	12/1	651/132	47	7
Wong *et al.*	2015	China	R (1989 to 2012)	37	222	57 (27 to 86)	56 (19 to 79)	29/8	179/43	NA	9
Rammohan *et al.*	2015	India	R (1997 to 2012)	39	387	52.1±10.9	50.9±18.8	28/11	278/109	64	8
Kim *et al.*	2015	Korea	R (2005 to 2010)	31	62	53 (31 to 73)	56 (20 to 74)	21/10	42/20	30	8
Orimo *et al.*	2016	Japan	R (1996 to 2015)	42	732	61.5 (44 to 80)	64 (18 to 90)	35/7	605/127	45.4	6
Wang *et al.*	2016	China	R (1998 to 2012)	22	110	20/2 (≤65/>65)	86/24 (≤65/>65)	18/4	90/20	NA	8
Pang *et al.*	2016	China	R (2000 to 2012)	35	916	50.1±10.2	51.8±1.4	30/5	824/92	96	6
Yang *et al.*	2018	China	R (2003 to 2011)	107	163	50.6±10.5	49.5±10.6	88/19	140/23	NA	6

In most cells, the continuous variables are presented as mean ± standard deviation or medians (range). The binary categorical variables are displayed as numbers in the corresponding group. *, retrospective study and the time interval of patients included in the cohort study. BDTT, bile duct tumor thrombus; MFT, median follow-up time; NOS, Newcastle-Ottawa Scale; NA, data not available.

Table 2 Summary of meta-analysis comparing HCC patients with and without BDTT

Outcomes of interest (number of studies)	Percentage (%) or mean		Pooled OR/WMD (95% CI)	P	Heterogeneity, χ^2/P/I^2
	BDTT	Non-BDTT			
Clinicopathological characteristics					
HBsAg positive (n=11)	61.9	53.3	1.23 (0.92, 1.64)	0.17	11.80/0.30/15%
Child-Pugh class A (n=10)	76.8	86.7	0.50 (0.26, 0.98)	0.04*	33.18/<0.01/73%
Albumin (g/L) (n=7)†	38.2	40.2	−1.82 (−3.31, −0.33)	0.02*	61.09/<0.01/90%
Total bilirubin (mg/dL) (n=8)†	4.1	1.1	2.18 (1.56, 2.81)	<0.01**	297.31/<0.01/98%
ALP (IU/L) (n=3)†	488.5	302.1	191.54 (147.11, 235.97)	<0.01**	1.98/0.37/0%
AFP ≤400 (ng/mL) (n=5)	43.4	42.9	0.96 (0.56, 1.64)	0.87	9.16/0.05/56%
Presence of liver cirrhosis (n=9)	49.4	48.1	0.78 (0.60, 1.01)	0.06	10.49/0.23/24%
Tumor diameter ≤5 (cm) (n=6)	48.7	53.1	1.18 (0.58, 2.40)	0.66	22.55/<0.01/78%
Solitary tumor (n=6)	66.9	67.9	0.57 (0.26, 1.27)	0.17	21.31/<0.01/77%
Presence of tumor capsule (n=8)	38.4	38.2	0.83 (0.46, 1.50)	0.54	17.64/0.01/60%
Differentiation (well or moderate) (n=10)	57.8	69.9	0.49 (0.37, 0.65)	<0.01**	15.81/0.07/43%
UICC tumor stage I/II (n=6)	33.6	54.9	0.41 (0.17, 1.03)	0.06	24.36/<0.01/80%
Portal vein invasion (n=9)	36.1	26.1	3.01 (1.28, 7.12)	0.01*	55.02/<0.01/85%
Hepatic vein invasion (n=3)	23.3	8.8	2.49 (1.12, 5.51)	0.03*	1.04/0.59/0%
Macrovascular invasion (n=6)	57.6	26.6	3.76 (1.60, 8.83)	<0.01**	20.78/<0.01/76%
Lymph node metastasis (n=4)	8.2	4.0	2.34 (1.10, 5.03)	0.03*	1.39/0.71/0%
Operative and postoperative variables					
Anatomical resection (n=5)	64.5	46.1	2.84 (0.90, 8.97)	0.08	28.26/<0.01/86%
R0 resection (n=5)	75.2	77.1	0.75 (0.35, 1.63)	0.47	9.80/0.04/59%
Operating time (min) (n=2)†	408.0	358.5	48.84 (−18.76, 116.45)	0.16	22.65/<0.01/96%
Intraoperative blood loss (mL) (n=2)†	1054.4	1045.8	15.00 (−0.54, 30.53)	0.06	0.01/0.97/0%
Hospital stay (day) (n=2)†	21.1	19.9	1.04 (0.52, 1.56)	<0.01**	0.23/0.63/0%
Postoperative morbidity (n=4)	23.9	9.9	1.54 (0.71, 3.34)	0.27	11.07/0.01/73%
Postoperative mortality (n=5)	3.1	4.1	1.28 (0.56, 2.89)	0.56	4.60/0.33/13%
Long-term survival outcomes					
1-year OS (n=15)	64.2	81.5	0.39 (0.31, 0.48)	<0.01**	24.01/0.05/42%
3-year OS (n=15)	32.4	59.4	0.33 (0.22, 0.51)	<0.01**	47.33/<0.01/70%
5-year OS (n=15)	21.3	47.0	0.31 (0.20, 0.49)	<0.01**	41.36/<0.01/66%

†, these data were continuous variables and presented as mean; *, P<0.05; **, P<0.01. HCC, hepatocellular carcinoma; BDTT, bile duct tumor thrombus; OR, odds ratio; WMD, weighted mean difference; HBsAg, hepatitis B surface antigen; ALP, alkaline phosphatase; AFP, α-fetoprotein; UICC, Union for International Cancer Control; OS, overall survival.

P<0.01) and ALP (WMD 191.54, 95% CI: 147.11–235.97, P<0.01), and the percentages of portal vein invasion (OR 3.01, 95% CI: 1.28–7.12, P=0.01), hepatic vein invasion (OR 2.49, 95% CI: 1.12–5.51, P=0.03), macrovascular invasion (OR 3.76, 95% CI: 1.60–8.83, P<0.01) and lymph node metastasis (OR 2.34, 95% CI: 1.10–5.03, P=0.03) were significantly higher in the BDTT group. The tumor stage of the BDTT group was more advanced compared to the non-BDTT group, but the difference was not statistically significant (OR 0.41, 95% CI: 0.17–1.03, P=0.06).

Operative and postoperative variables

There were no significant discrepancies in anatomic resection, R0 hepatectomy, time of surgery, intraoperative blood loss or postoperative morbidity and mortality rates between the two groups. Notably, the duration of hospital stay was markedly longer in the BDTT group versus the non-BDTT group (WMD 1.04, 95% CI: 0.52–1.56, P<0.01) (*Table 2*).

OS rates

As shown in *Table 2* and *Figure 2*, the 1-year (64.2% *vs.* 81.5%; OR 0.39, 95% CI: 0.31–0.48, P<0.01; *Figure 2A*), 3-year (32.4% *vs.* 59.4%; OR 0.30, 95% CI: 0.22–0.42, P<0.01; *Figure 2B*) and 5-year OS rates (21.3% *vs.* 47.0%; OR 0.31, 95% CI: 0.20–0.49, P<0.01; *Figure 2C*) of the BDTT group after liver resection were significantly lower compared to the non-BDTT group. *Figure 2D,E,F* shows the forest plots of cumulative meta-analyses of ORs for 1-, 3-, and 5-year OS, respectively. The results showed that the significant differences in favor of the non-BDTT group were initially observed in the studies published in 2009, 2004 and 2004, respectively. Then the 95% CIs developed in a roughly narrowed trend, which suggests that the effect sizes became stable. The detailed survival outcomes of HCC patients with or without BDTT are displayed in Table S2.

Hazard ratio and long-term prognosis

To further evaluate the impact of BDTT on the long-term prognosis of HCC patients, we calculated HRs within 5 years after surgery for every included study and combined the data using forest plots. As shown in *Figure 3*, HCC patients with BDTT had worse long-term prognosis after hepatectomy with a pooled HR of 4.27 (95% CI: 3.47–5.26, P<0.01; I^2=50.3%), which suggests that BDTT may be a potential risk factor for HCC.

Publication bias and sensitivity analysis for HR

As shown in Figure S1, a visual inspection of the funnel plot suggests a symmetric distribution (Figure S1A). Egger's test confirmed that there was no significant publication bias (P=0.955; Figure S1B). Sensitivity analysis (Figure S2) was performed to determine the stability of the overall prognostic effect. The result revealed one study that potentially influenced the pooled HR (11). After exclusion of this study, the heterogeneity between studies was significantly reduced (I^2=3.6%, P=0.41). The pooled HR of 4.58 (95% CI: 3.96–5.28, P<0.01) became more positive compared to the initial value.

Discussion

The present study is the first systematic review and meta-analysis to comprehensively compare the clinicopathologic characteristics, perioperative indices, and survival outcomes between HCC patients with and without BDTT. We first reported the pooled HR of HCC patients with BDTT within 5 years following hepatectomy. In addition, we reviewed 15 well-designed studies of 6,484 HCC patients, including 478 cases with HCC and BDTT, which is the largest sample size to date on this subject.

In the current study, we found that patients with HCC and BDTT had worse liver function, lower levels of albumin, higher levels of total bilirubin and ALP, and a longer duration of hospital stay. HCC with BDTT was associated with more aggressive biological characteristics, such as advanced tumor stage, poor differentiation, macrovascular invasion, and lymph node metastasis, all of which are recognized critical factors that restrict long-term survival. These results are consistent with previous findings (21,26).

HCC patients with BDTT are frequently complicated with obstructive jaundice at first presentation, and the incidence of this combination ranged from 27% to 70% in previous studies (6,20,21,27,28). Generally, when BDTT extends beyond the confluence of the left and right hepatic ducts, the symptoms of obstructive jaundice will appear in patients with HCC and BDTT. The cause of jaundice resulting from BDTT is primarily a tumor thrombus that continuously extends to the extrahepatic bile duct, a dislodged BDTT blocking the common bile duct, or blood clots formed by haemobilia occluding the outflow of biliary

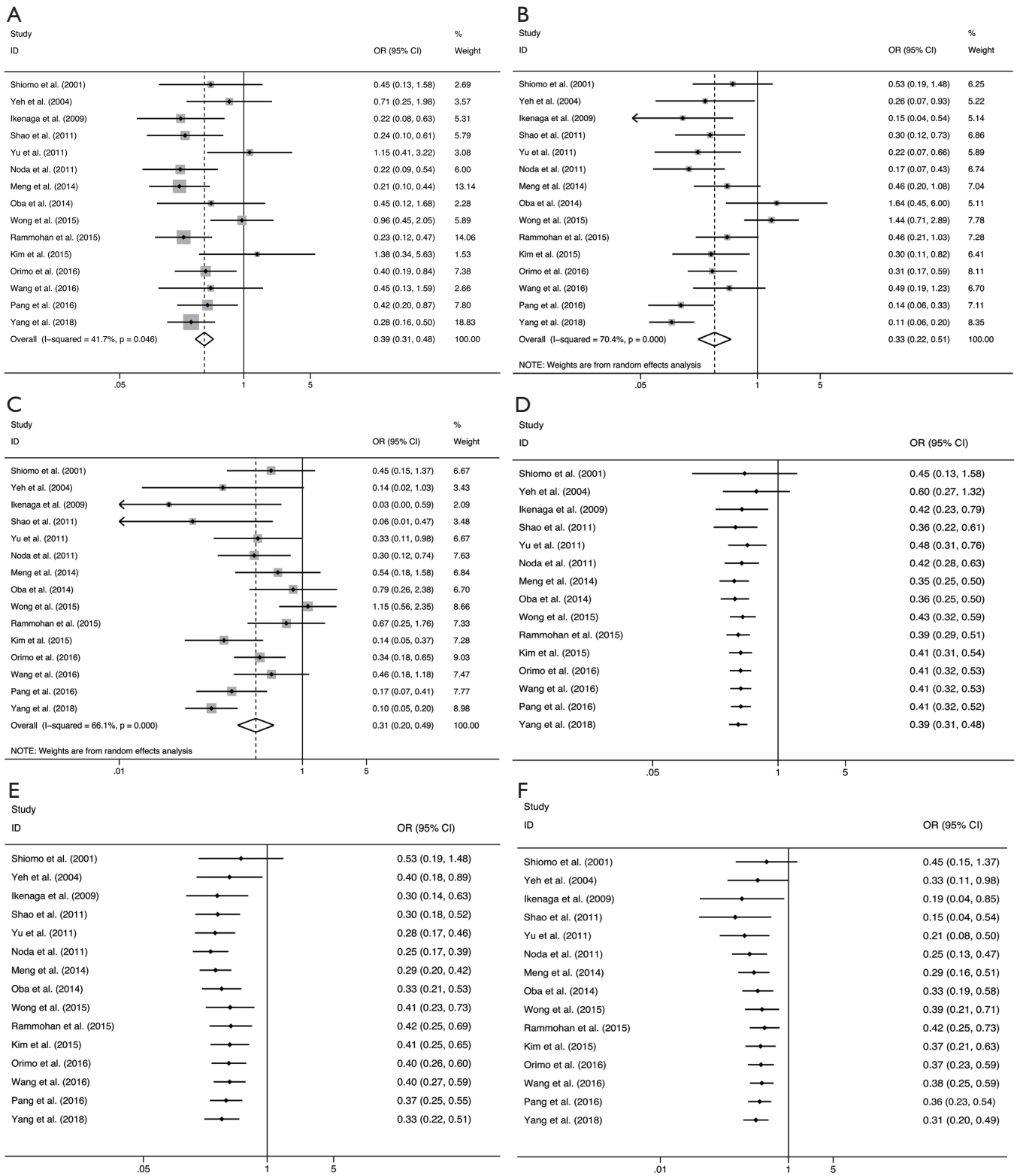

Figure 2 Forest plots of the meta-analysis and cumulative meta-analysis for OS. (A) Forest plot of OR of 1-year OS; (B) forest plot of OR of 3-year OS; (C) forest plot of OR of 5-year OS; (D) cumulative meta-analysis of 1-year OS; (E) cumulative meta-analysis of 3-year OS; (F) cumulative meta-analysis of 5-year OS. OS, overall survival.

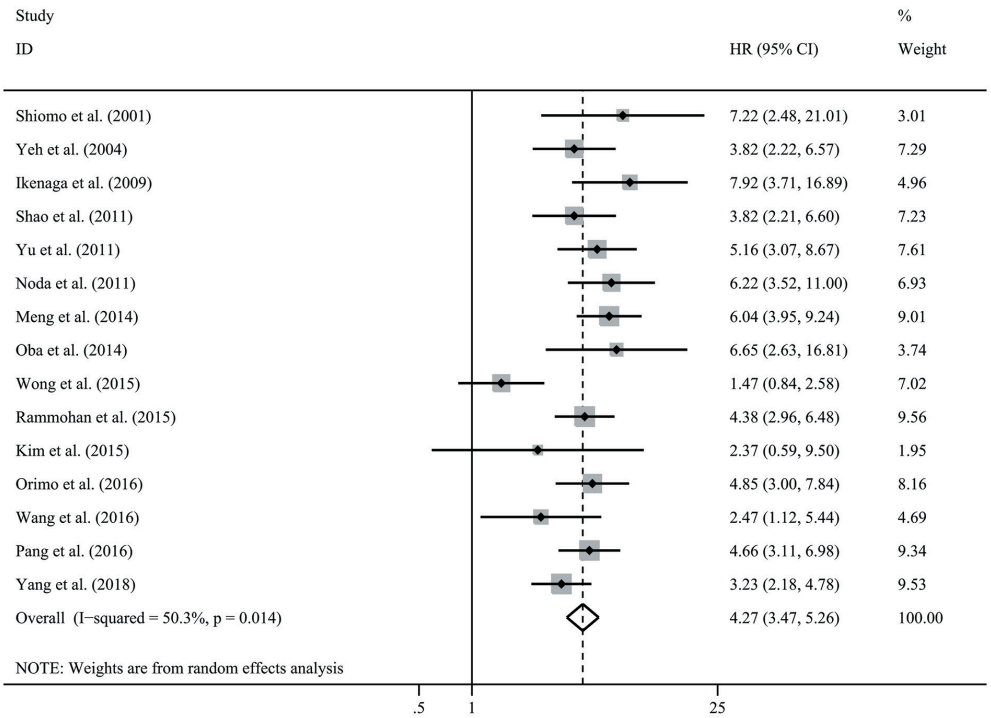

Figure 3 Forest plot of the hazard ratio for OS of HCC patients with BDTT within 5 years after surgery. BDTT, bile duct tumor thrombus; HCC, hepatocellular carcinoma; OS, overall survival.

tract (29-31). Therefore, it is understandable that the levels of total bilirubin and ALP, as indicators of cholestasis, are significantly higher in this subset of patients. As a result, most HCC patients with BDTT undergo preoperative biliary decompression to alleviate jaundice and improve hepatic function (32,33).

Some recent experimental studies have revealed that genetic silencing of the microRNA-200 family, which are molecular regulators inversely associated with epithelial-to-mesenchymal transition (EMT), and overexpression of CCL20, which is a chemokine positively related to the invasion and metastasis of HCC, are much more frequently observed in the samples obtained from HCC patients with BDTT than patients without BDTT (34,35). Besides, since the portal vein, common bile duct and their branches are enclosed together within the Glisson's sheath, tumor cells can invade both structures to form portal vein tumor thrombus (PVTT) and BDTT. All of these factors may partially explain the aggressive biological characteristics that were more commonly encountered in the BDTT group in our study.

As to the outcomes of various treatment modalities, An *et al.* (36) reported that the 1-, 3-, and 5-year OS rates of HCC patients with BDTT undergoing TACE were 20.4%, 6.7% and 1.3%, respectively. Oba *et al.* (4) reported that the 1-, 3-, and 5-year OS rates of the BDTT group receiving non-surgical treatments were 14%, 5% and 0%, respectively. The current study found that the pooled OS rates of patients with HCC and BDTT within 1 year, 3 years and 5 years after surgery were 64.2%, 32.3% and 21.3%, respectively. Therefore, the use of aggressive surgical resection in select HCC patients with BDTT appears reasonable to prolong survival.

However, whether HCC patients with BDTT would reach similar long-term survival after surgical treatment compared to patients without BDTT remains controversial. Oba *et al.* (4) and Wong *et al.* (11) demonstrated that the two groups had comparable 1-, 3-, and 5-year OS rates following hepatectomy, but other researchers concluded that the postoperative OS of HCC patients with BDTT was significantly shorter than patients without BDTT (8,21,25). Our study provided evidence that HCC with BDTT was associated with significantly inferior 1-, 3-, and 5-year OS.

According to earlier studies, the main obstacle to achieving long-term survival in patients with HCC and BDTT is the high incidence of recurrence after surgery.

Yang *et al.* (8) reported that the median recurrence-free survival (RFS) time and cumulative 1-, 3- and 5-year RFS rates in the BDTT group were significantly worse compared to the non-BDTT group. Qin *et al.* (27) and Zeng *et al.* (37) reported that 50% and 43% of HCC patients with BDTT, respectively, suffered tumor recurrence within the first year after hepatectomy. Consequently, adjuvant or neoadjuvant therapy may be administered to these patients to reduce recurrence rates and improve survival outcomes (38).

Vascular invasion is a well-established risk factor for HCC (3,39,40). However, there is no consensus regarding the prognostic effect of BDTT on the long-term survival of HCC. Wong *et al.* (11) demonstrated that the presence of BDTT did not influence the prognosis of HCC patients using multivariate analyses. In contrast, Yang *et al.* (8) noted that macroscopic BDTT was significantly associated with a poor prognosis in HCC patients who underwent liver resection. Our study demonstrated that BDTT was an important predictive factor of a poor prognosis in HCC patients (HR 4.27, 95% CI: 3.47–5.26, P<0.01; I^2=50.3%). However, this result should be further verified because of the many confounding factors existing in the analysis.

Several limitations in the present analysis should be considered. First, all of the studies included in this review were retrospective trials with inherent publication and selection bias. Second, all of the research was performed in Asian countries. Therefore, the applicability of these results must be further validated in Western countries. Third, due to different sample sizes and matched methods across studies, some results of this meta-analysis had relatively great heterogeneity. Lastly, this review did not distinguish different types of BDTT, which may influence the final conclusion.

Conclusions

In conclusion, this systematic review and meta-analysis suggested that the survival outcomes were significantly worse in patients with HCC and BDTT after liver resection than in patients without BDTT. BDTT may be a prognostic factor for HCC patients. Notably, these results must be further validated in more large-scale, well-designed clinical trials.

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