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The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

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META-ANALYSIS

Does size matter for resection of giant versus non-giant hepatocellular carcinoma? A meta-analysis

Aaron JL Lee, Andrew GR Wu, Kuo Chao Yew, Vishal G Shelat

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Abstract

BACKGROUND

Research on long-term survival after resection of giant (≥ 10 cm) and non-giant hepatocellular carcinoma (HCC) (< 10 cm) has produced conflicting results.

AIM

This study aimed to investigate whether oncological outcomes and safety profiles of resection differ between giant and non-giant HCC.

METHODS

PubMed, MEDLINE, EMBASE, and Cochrane databases were searched. Studies designed to investigate the outcomes of giant *vs* non-giant HCC were included. The primary endpoints were overall survival (OS) and disease-free survival (DFS). The secondary endpoints were postoperative complications and mortality rates. All studies were assessed for bias using the Newcastle–Ottawa Scale.

RESULTS

24 retrospective cohort studies involving 23747 patients (giant = 3326; non-giant = 20421) who underwent HCC resection were included. OS was reported in 24 studies, DFS in 17 studies, 30-d mortality rate in 18 studies, postoperative complications in 15 studies, and post-hepatectomy liver failure (PHLF) in six studies. The HR was significantly lower for non-giant HCC in both OS (HR 0.53, 95%CI: 0.50-0.55, $P < 0.001$) and DFS (HR 0.62, 95%CI: 0.58-0.84, $P < 0.001$). No

significant difference was found for 30-d mortality rate (OR 0.73, 95%CI: 0.50-1.08, P = 0.116), postoperative complications (OR 0.81, 95%CI: 0.62-1.06, P = 0.140), and PHLF (OR 0.81, 95%CI: 0.62-1.06, P = 0.140).

CONCLUSION

Resection of giant HCC is associated with poorer long-term outcomes. The safety profile of resection was similar in both groups; however, this may have been confounded by reporting bias. HCC staging systems should account for the size differences.

Key Words: Hepatectomy; Giant hepatocellular carcinoma; Resection; Meta-analysis

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Core Tip: Resection of giant hepatocellular carcinoma (HCC) is associated with poorer long-term outcomes, with a safety profile similar to that of resection of non-giant HCC. The importance of this is that HCC staging systems should account for the size differences.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most prevalent type of primary liver cancer[1]. It is the third most common cause of cancer-related deaths worldwide and has the fifth-highest incidence rate of cancers[2]. Currently, most HCCs develop secondary to underlying liver disease, often due to chronic hepatitis B or C virus infection[3]. Most developed countries have surveillance programs that identify HCC early, resulting in potentially curative treatment for 40%–50% of patients[4,5]. For patients who do not qualify for curative treatment, locoregional or systemic treatments can be used, depending on the stage of the disease[4]. Despite early detection and advances in management, HCC has a 5-year survival rate of 18%[6].

In cancer management, prognostic factors are used in staging systems to help recommend appropriate treatment strategies and counsel patients on recurrence risk and survival estimates[7]. Key predictors of prognosis in patients with HCC include the extent of liver dysfunction, tumor burden, and patient performance status[8]. Tumor size, one of the determinants of tumor burden, has been identified as an independent predictor of overall survival, with larger tumors generally predicting poorer outcomes[9,10]. Despite this, there is currently no consensus on the inclusion of tumor size in HCC staging systems. Some systems, such as the Barcelona Clinic Liver Cancer (BCLC) system[11] and American Joint Committee on Cancer (AJCC) 8th edition staging system[12], include size, while others, such as the Hong Kong Liver Cancer (HKLC) classification[13], do not. Furthermore, the size cut-off may vary in systems that incorporate tumor size, and when used to guide management, such as in the BCLC system, surgical resection remains the primary treatment modality for patients with a single tumor, regardless of tumor size.

Despite being recommended as the first-line treatment for early-stage tumors, resection is still contentious for giant HCC (≥ 10 cm in diameter). Studies on the long-term survival rates after resection of giant and non-giant HCCs have yielded conflicting results. In studies by Noh *et al*[14] and Allemann *et al*[15], no significant difference in survival was found between patients with giant and non-giant HCC. Conversely, studies by Fang *et al*[16] and Lee *et al*[17] found poorer survival outcomes in patients with giant HCC. Furthermore, the prognosis after resection of single large HCCs (≥ 5 cm) has been shown to be closer to intermediate-stage tumors than single tumors of smaller size[18,19]. In light of conflicting evidence, this study aimed to investigate whether oncological outcomes and safety profiles of surgical resection differ between giant and non-giant HCC.

MATERIALS AND METHODS

Search strategy and selection criteria

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic

Reviews and Meta-Analyses guidelines. A search was conducted using PubMed, MEDLINE (via Ovid), EMBASE, and Cochrane Central databases, from inception to 17 December 2021. A combination of search terms such as “HCC" or "liver cancer", "surgical resection" or “hepatectomy” or “liver resection”, “giant” or “huge” or "10 cm" was used. Only English studies were shortlisted for screening purposes. The articles were first screened by their titles and abstracts. Subsequently, full texts of suitable articles were reviewed for inclusion. The search, article review, quality assessment, and data extraction were conducted independently by two authors (Lee AJ and Wu AG). All disagreements were resolved by consensus or by appeal to a senior author. The study protocol was registered with PROSPERO (Number: CRD42022297772).

Inclusion criteria

Cohort and case-control studies were included. Only studies designed to compare the outcomes of resection of giant *vs* non-giant HCC and provided Kaplan-Meier curves for overall survival (OS) or disease-free survival (DFS) were included. In duplicate studies, the most recent study was chosen.

Exclusion criteria

Old studies published before 2000 were excluded from the meta-analysis to ensure that this study was relevant to current practice, as surgical techniques have been refined since then. Studies with a high risk of publication bias such as case reports and series were excluded. Reviews, editorials, conference abstracts, and non-human studies were excluded from the meta-analysis.

Quality assessment

The quality of all the studies was assessed using the Newcastle – Ottawa scale for cohort studies. Studies that scored 7–9 points, 4–6 points, and 3 or fewer points were considered to have a low, moderate, and high risk of bias, respectively.

Data extraction and reconstruction of individual patient data

Two review authors (Lee AJ and Wu AG) independently extracted the publication details (name of the first author, year of publication, and country) and study characteristics (patient demographics, tumor characteristics, Child Pugh score, OS, DFS, hospital mortality, and postoperative complications) from each study. The Child–Pugh score was dichotomized into Child’s A *vs* Child’s B or higher. Individual patient data (IPD) were reconstructed from available Kaplan-Meier survival curves using an iterative algorithm initially proposed by Guyot *et al*[20].

Data Synthesis

The primary endpoints of this study were OS and DFS, while the secondary endpoints were postoperative complications and mortality. Additionally, we investigated whether non-size tumor and liver characteristics such as vascular invasion, multinodularity and presence of Child’s B or higher cirrhosis in non-giant tumors with respect to giant tumors. After extracting the relevant information on OS and DFS from the published survival curves, a one-stage analysis was performed using Cox proportional hazard models based on the shared frailty model. The frailty model was chosen to account for study heterogeneity by incorporating a random-effects term that modelled patients within each study as failure-prone, similar to other individuals in the same study. Stratified Cox models were generated for sensitivity analysis. The stratified Cox models were adjusted for inter-study heterogeneity by allowing patients from a study to share a baseline hazard unique only to the study while constraining partial likelihood estimates of the Cox coefficients to be equal across strata. As the proportional hazard assumption was not upheld at a longer follow-up duration, the restricted mean survival time (RMST) at various time points was also calculated as an alternative measure of treatment effect that does not require model assumptions. Additionally, a two-stage analysis was performed using inverse-variance weighted random-effects meta-analysis.

HR will be presented for the primary endpoints of DFS and OS, and OR for the secondary dichotomous outcomes with their respective 95%CI. Random-effects models were used for all analyses because of the high heterogeneity among the studies.

All analyses were performed using R (version 4.1.2), with statistical significance set at $P < 0.05$.

RESULTS

The search yielded 1682 potentially relevant studies. After duplicate removal and abstract screening, 153 full-text articles were reviewed, of which 24 studies[14-17,21-40] were deemed eligible for meta-analysis. All 24 studies obtained a score of 7 or higher on the Newcastle-Ottawa scale, indicating that they were of high quality. In the overall cohort of 23747 patients, there were 3326 patients in the giant HCC (≥ 10 cm) group and 20421 patients in the non-giant HCC (< 10 cm) group (Figure 1). A summary of the study’s characteristics is provided in Table 1 and 2.

Table 1 Basic characteristics of included studies, hepatocellular carcinoma < 10 cm

Study	Year	Follow-up, mo	No.	Age, yr	Sex (M/F)	Tumour size, cm	Cirrhosis, *n* (%)	Child-Pugh class, *n* (%)	
								A	B + C
Allemann *et al*[15]	2013	25	79	67 (21-85)	NA	4.9 (1-9)	61 (77)	75 (95)	4 (5)
Chang *et al*[21]	2016	72.5	10167	NA	7618/2711	NA	1114 (11)	NA	NA
Choi *et al*[22]	2009	36	447	53.3 (9.7)	344/103	NA	244 (55)	443 (99)	4 (1)
Fang *et al*[16]	2019	20	104	NA	85/19	NA	93 (89)	101 (97)	3 (3)
Giuliante *et al*[23]	2013	NA	28	65.8 (8.8)	22/6	7.9 (7-8.1)	NA	28 (100)	0 (0)
Huang *et al*[24]	2016	26	272	NA	242/30	NA	90 (82)	NA	NA
Jo *et al*[25]	2011	30	40	54.6 (10.5)	36/4	3.81 (2.06)	NA	35 (88)	5 (13)
Lee *et al*[17]	2021	NA	3559	59.1 (12.1)	2716/843	3.36 (2.14)	NA	NA	NA
Lewis *et al*[26]	2019	22	26	NA	NA	NA	NA	NA	NA
Liau *et al*[27]	2005	27	111	63.0 (12.0)	80/31	6.1 (2.5)	40 (36)	104 (94)	7 (6)
Nagano *et al*[28]	2005	NA	143	62.0 (9.0)	112/31	3.25 (1.2-9.5)	81 (57)	101 (71)	NA
Noh *et al*[14]	2016	26.4	73	56.85 (10.7)	56/17	NA	NA	NA	NA
Poon *et al*[29]	2002	56	368	54.1 (12.2)	295/73	5.4 (2.6)	203 (55)	NA	NA
Shah *et al*[30]	2007	34	165	62.0 (14.0)	NA	4.7 (2.2)	NA	145 (88)	14 (8)
Tanaka *et al*[31]	2015	39	291	67 (61-73)	220/71	4 (2.3 – 5)	134 (46)	270 (93)	21 (7)
Taniai *et al*[32]	2008	22.5	291	64.1 (8.7)	225/66	3.71 (1.91)	156 (54)	209 (72)	82 (28)
Thng *et al*[33]	2015	22	63	59 (27-81)	50/13	NA	NA	60 (95)	3 (5)
Wakayama *et al*[34]	2017	57	521	62.8 (10.1)	427/94	4 (2.1)	NA	511 (98)	8 (2)
Yamashita *et al*[35]	2011	NA	412	64.0 (3.0)	328/84	3.8 (2.2)	NA	246 (60)	166 (40)
Yang *et al*[37]	2013	NA	293	47.0 (13.0)	263/57	6.7 (3.8)	201 (69)	231 (79)	62 (21)
Yang *et al*[36]	2014	NA	781	NA	635/146	NA	NA	768 (98)	51 (7)
Yeh *et al*[38]	2003	16.4	985	55.7 (13.11)	776/209	4.5 (2.4)	NA	NA	NA
Zhong *et al*[39]	2017	NA	707	NA	612/95	NA	520 (74)	672 (95)	35 (5)
Zhu *et al*[40]	2015	29.4	495	50.3 (11.2)	436/59	4.8 (2.3)	129 (26)	431 (87)	64 (13)

HCC: Hepatocellular carcinoma; NA: Not available; M: Male; F: Female.

Primary outcomes

Among the included studies, all 24 had extractable data for OS. Non-giant HCC had a lower HR at 0.53 (95%CI: 0.50-0.55, $P < 0.001$; Figure 2) with the one-stage frailty model, and a similarly significant trend was seen with the stratified HR at 0.53 (95%CI: 0.50-0.55, $P < 0.001$; Figure 2). RMST at 1-, 5- and 10-years showed significantly increased hazards for giant HCC. The estimated 1-year OS from the reconstructed IPD was 90.1% for non-giant HCC and 69.5% for giant HCC (RMST 0.91, 95%CI: 0.90-0.92, $P < 0.001$; Figure 2). Two-stage meta-analysis showed that non-giant HCC has a HR of 0.60 (95%CI: 0.50-0.72, $P < 0.01$; Figure 2).

Among the included studies, 17 studies[14-17,22,25-27,29-32,34,35,37,40] had extractable data for DFS. Non-giant HCC had a lower HR at 0.62 (95%CI: 0.58-0.84, $P < 0.001$; Figure 3) in the one-stage frailty model, and a similarly significant trend was seen with the stratified HR at 0.61 (95%CI: 0.57-0.65, $P < 0.001$; Figure 3). RMST at 1-, 5- and 10-years all shown significantly increased hazards for giant HCC. The estimated 1-year DFS from the reconstructed IPD was 58.9% for non-giant HCC and 35.7% for giant HCC (RMST 0.82, 95%CI: 0.80-0.84, $P < 0.001$; Figure 3). Two-stage meta-analysis showed that non-giant HCC has a HR of 0.63 (95%CI: 0.52-0.76, $P < 0.01$; Figure 3).

Secondary outcomes

Among the included studies, 18 studies[15,17,22,24,25,27-32,34-40] reported 30-d mortality rates whereas only two studies[36,39] reported 90-d mortality rates (Figure 4). While resection of non-giant HCC had lower odds of death within the first 30 d after surgery, the difference was not statistically

Table 2 Basic characteristics of included studies, hepatocellular carcinoma ≥ 10 cm

Study	Year	Follow-up, mo	No.	Age, yr	Sex (M/F)	Tumour size, cm	Cirrhosis, *n* (%)	Child-Pugh class, *n* (%)	
								A	B + C
Allemann *et al*[15]	2013	25	22	72 (36-88)	NA	13.5 (10-21)	9 (41)	22 (100)	0 (0)
Chang *et al*[21]	2016	72.5	912	NA	740/162	NA	166 (18)	NA	NA
Choi *et al*[22]	2009	36	50	50.8 (12.5)	34/16	NA	13 (26)	48 (96)	2 (4)
Fang *et al*[16]	2019	20	84	NA	76/8	NA	72 (86)	77 (92)	7 (8)
Giuliante *et al*[23]	2013	NA	37	62.2 (11)	28/9	12 (11-15)	NA	36 (97)	1 (3)
Huang *et al*[24]	2016	26	127	NA	114/13	NA	90 (71)	NA	NA
Jo *et al*[25]	2011	30	11	52.4 (8.4)	6/5	14.5 (4.11)	NA	11 (100)	0 (0)
Lee *et al*[17]	2021	NA	426	55.7 (14.3)	345/81	13.14 (4.95)	NA	NA	NA
Lewis *et al*[26]	2019	22	16	NA	NA	NA	NA	NA	NA
Liau *et al*[27]	2005	27	82	62.0 (14.0)	48/34	14.7 (4.1)	8 (10)	73 (89)	5 (6)
Nagano *et al*[28]	2005	NA	26	56.2 (12.2)	19/7	14.8 (10-30)	5 (19)	22 (85)	NA
Noh *et al*[14]	2016	26.4	41	55.1 (10.8)	33/8	NA	NA	NA	NA
Poon *et al*[29]	2002	56	120	50.9 (12.8)	99/21	13.8 (3)	32 (27)	NA	NA
Shah *et al*[30]	2007	34	24	57.0 (15.0)	NA	13.1 (2.9)	NA	24 (100)	0 (0)
Tanaka *et al*[31]	2015	39	24	64.5 (54-71)	20/4	13 (11.2-14.1)	7 (29)	20 (83)	1 (4)
Taniai *et al*[32]	2008	22.5	29	62.0 (9.4)	26/3	13.45 (2.77)	12 (41)	23 (79)	6 (21)
Thng *et al*[33]	2015	22	23	63 (34-84)	20/3	NA	NA	20 (87)	3 (13)
Wakayama *et al*[34]	2017	57	54	63.9 (12.7)	43/10	12.4 (3.7)	NA	49 (92)	4 (8)
Yamashita *et al*[35]	2011	NA	53	60.0 (2.0)	48/5	13.2 (0.4)	NA	38 (72)	15 (28)
Yang *et al*[37]	2013	NA	258	45.0 (12)	212/46	13.2 (4.1)	171 (66)	217 (84)	41 (16)
Yang *et al*[36]	2014	NA	304	NA	242/62	NA	NA	250 (83)	16 (5)
Yeh *et al*[38]	2003	16.4	211	47.8 (13.4)	164/74	13.9 (3.4)	NA	NA	NA
Zhong *et al*[39]	2017	NA	150	47.3 (10.9)	123/27	12.4 (2.5)	88 (59)	142 (95)	8 (5)
Zhu *et al*[40]	2015	29.4	244	46.8 (11.3)	209/35	12 (2.3)	67 (27)	210 (86)	34 (14)

HCC: Hepatocellular carcinoma; NA: Not available; M: Male; F: Female.

significant (OR 0.73, 95%CI: 0.50-1.08, $P = 0.116$). No significant heterogeneity was observed ($I^2 = 0\%$, $P = 0.60$). In the two studies that reported the 90-d mortality rate, the 90-d mortality rate was higher than the 30-d mortality rate; however, no significant difference was found between the different tumor size groups.

Among the studies included, 15 studies[15,22,25,27-32,35-40] reported major postoperative complications (Figure 4). While resection of non-giant HCC had lower odds of major postoperative complications, the difference was not statistically significant (OR 0.81, 95%CI: 0.62-1.06, $P = 0.140$). Substantial heterogeneity was observed among the included studies ($I^2 = 71\%$, $P < 0.01$).

Among the included studies, six studies[22,27,30,31,34,37] reported post-hepatectomy liver failure (PHLF) (Figure 4). While resection of non-giant HCC had lower odds of PHLF, the difference was not statistically significant (OR 0.59, 95%CI: 0.17-2.05, $P = 0.41$). No significant heterogeneity was observed ($I^2 = 45\%$, $P = 0.10$).

Among the included studies, 20 studies[14-16,21-25,27-34,36-38,40] reported on vascular invasion, 13 studies[15,16,21,22,24,27-29,31,32,37,39,40] on cirrhosis, 16 studies[15,16,22,23,25,27,28,30-37,39,40] on Child Pugh's score and 9 studies[21,22,24,27,29,32,34,37,40] on tumor number (Table 3). While non-giant HCC was found to have significantly lower odds of vascular invasion (OR 0.367, 95%CI: 0.236-0.572, $P < 0.0001$) and multinodular tumors (OR 0.592, 95%CI: 0.376-0.939, $P < 0.0259$), it was found to have significantly higher odds of cirrhosis (OR 1.955, 95%CI: 1.317-2.903, $P = 0.0009$). No significant difference was found between the different tumor size groups for presence of Child-Pugh B and above (OR 1.008, 95%CI: 0.745-1.364, $P = 0.9592$).

Table 3 Comparison of tumor characteristics and liver function

Factor	OR	95%CI	*P* value
Vascular invasion	0.367	0.236-0.572	< 0.0001
Multinodular	0.592	0.374-0.939	0.0259
Child-Pugh score	1.008	0.745-1.364	0.9592
Cirrhosis	1.955	1.317-2.903	0.0009

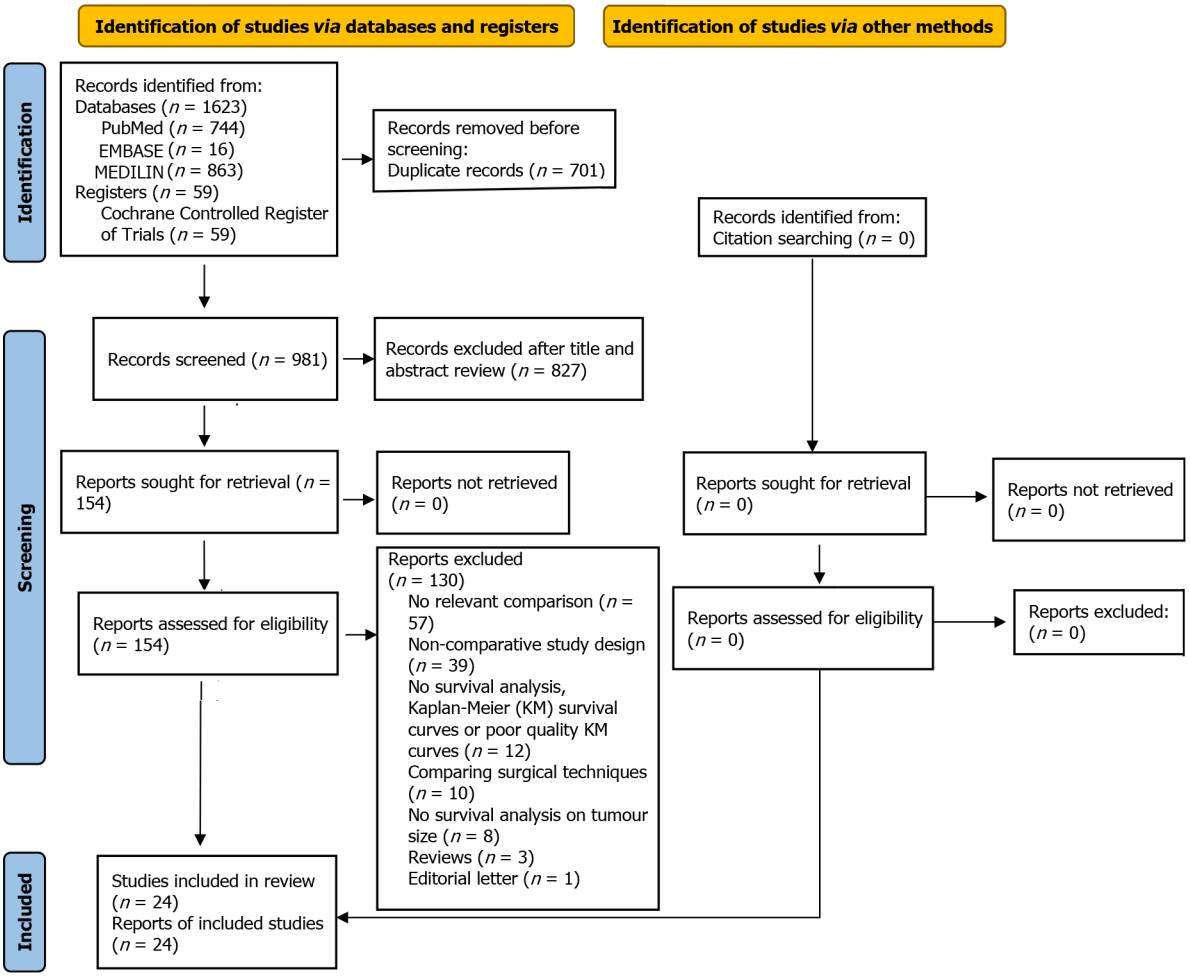

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Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram.

DISCUSSION

In this meta-analysis of 23747 patients, surgical resection of non-giant HCC was associated with approximately half the rate of death from any cause and a lower rate of disease recurrence than surgical resection of giant HCC. These pooled associations showed a significant disparity in long-term outcomes between the two groups despite the use of the same treatment modality. Furthermore, giant HCC is shown to be associated with higher odds of vascular invasion and multinodular tumors, factors that have been shown to be associated with poorer outcomes[41,42]. In contrast, the short-term perioperative outcomes and safety profiles, measured by 30-d mortality and postoperative complications, respectively, did not differ significantly between the two groups. Hence, while HCC size may not affect the safety and efficacy of surgical resection in the short term, this study illustrates not only a possible correlation between a larger tumor size and poorer outcomes, but also demonstrates that giant HCC have different tumor characteristics from non-giant HCC. Therefore, giant HCC should be staged differently because they are associated with poorer outcomes and prognostically poorer tumor characteristics.

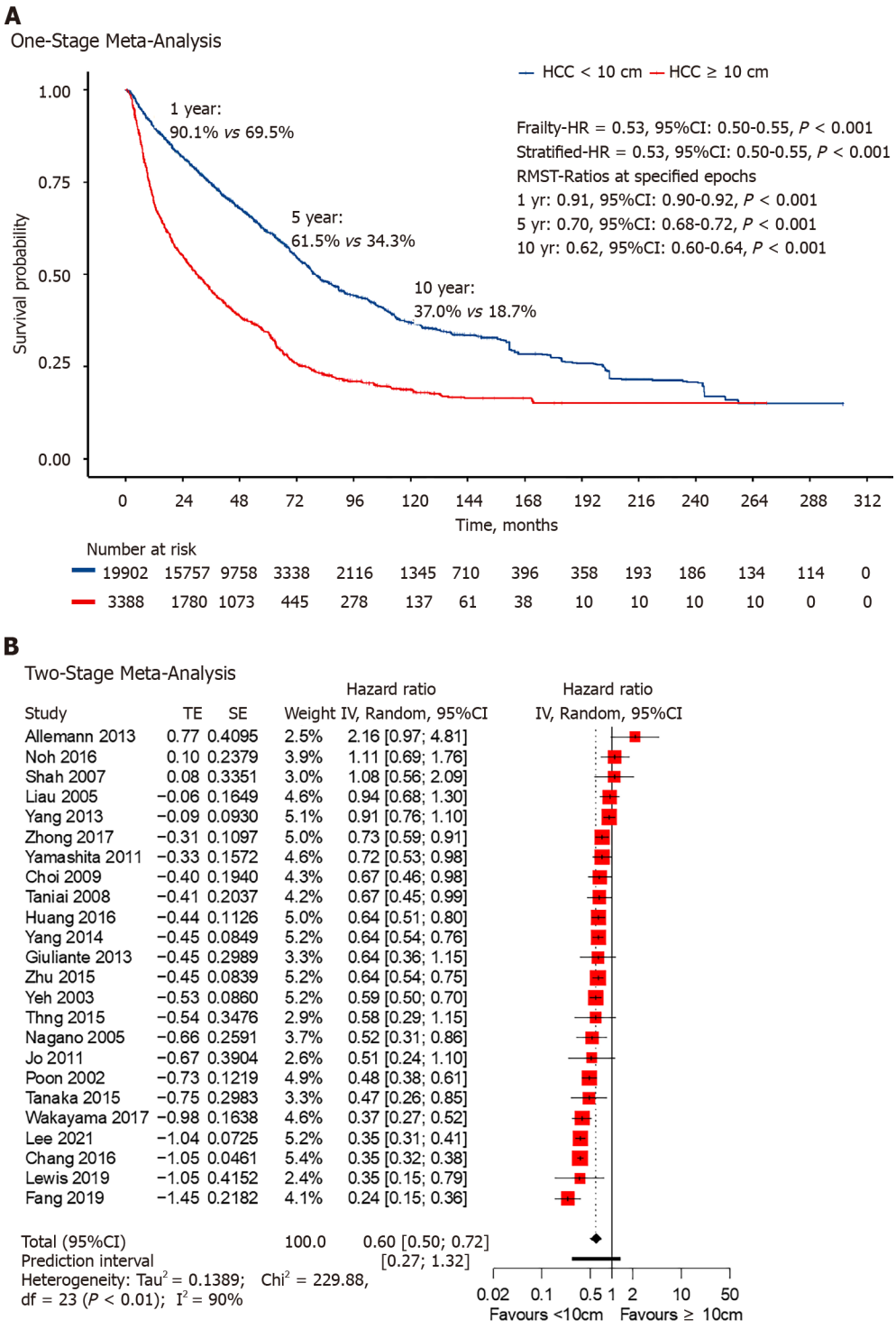

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Figure 2 Overall survival curves, numbers-at-risk table and Forest plot. A: Overall survival (OS) curves and numbers-at-risk table for giant *vs* non-giant hepatocellular carcinoma from reconstructed individual patient data; B: OS forest plot. HCC: Hepatocellular carcinoma; HR: Hazard ratio; RMST: Restricted mean survival time.

Despite being a major risk factor for the development of HCC[43], cirrhosis and cirrhotic severity were not found to be associated with larger tumor size. In this study, non-giant HCC were found to have a higher risk of developing cirrhosis. A possible explanation for this is that cirrhotic patients are more likely receiving 6 moly ultrasound scan surveillance[44]. Therefore, tumors are likely to be detected before they reach larger sizes. Similarly, no association was found between the presence of Child-Pugh B cirrhosis and higher and larger tumor sizes. This shows that larger tumor size may not be correlated with greater odds of cirrhosis or more severe cirrhosis.

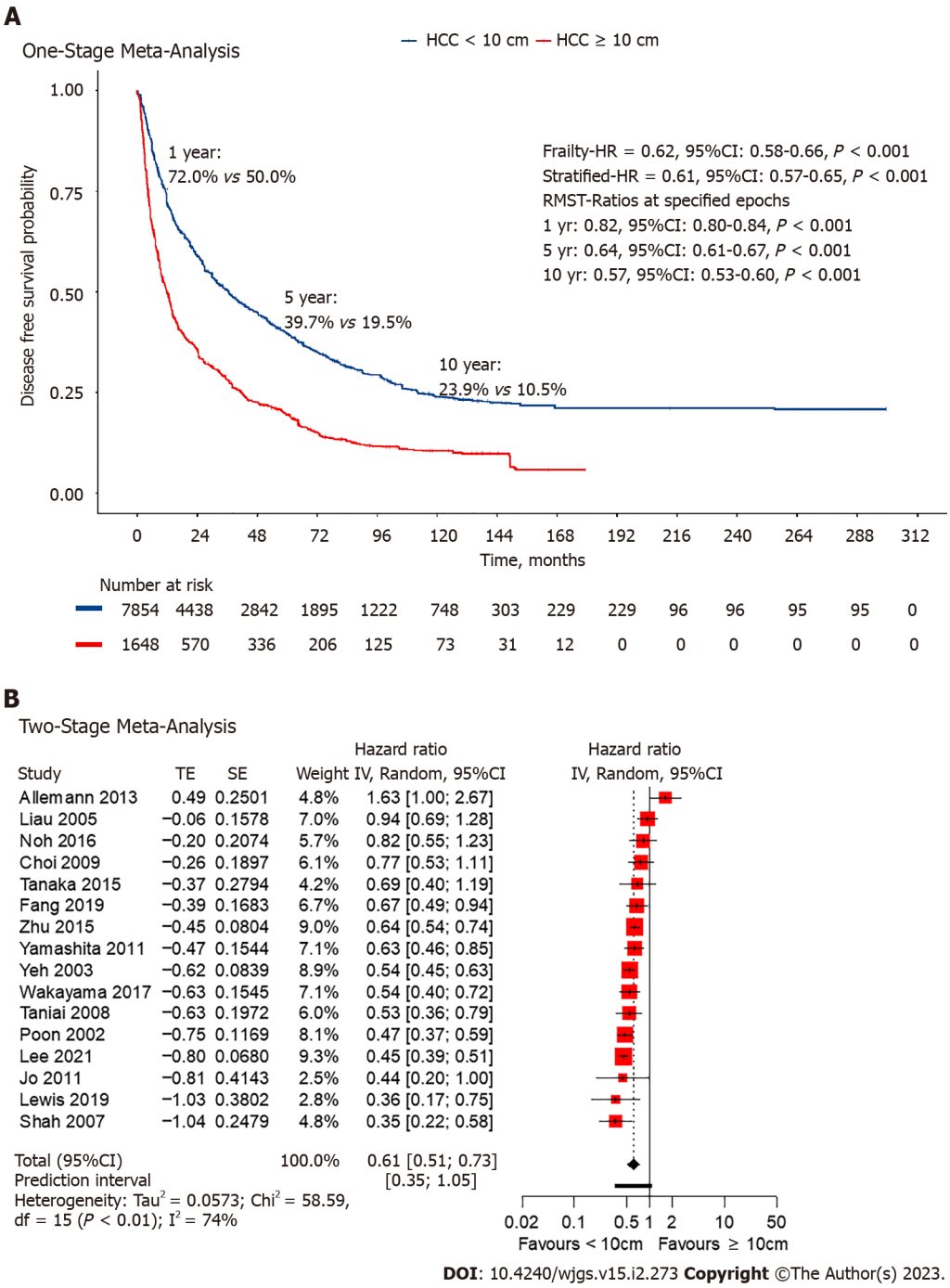

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Figure 3 Disease-free survival curve, numbers-at-risk table and Forest plot. A: Disease-free survival (DFS) curves and numbers-at-risk table for giant *vs* non-giant hepatocellular carcinoma from reconstructed individual patient data; B: DFS forest plot. HCC: Hepatocellular carcinoma; HR: Hazard ratio; RMST: Restricted mean survival time.

The myriad of HCC staging systems testifies that no single system is 'ideal'. The BCLC staging system is widely accepted in clinical practice and classifies patients into stages based on their performance status (PS) and Child-Pugh score[11]. The BCLC staging system does not place sufficient importance on tumor size when stratifying patients. Tumor size only plays a role in sorting patients with a single tumor, PS 0, and Child-Pugh A into very early stage (0) and early-stage (A), for which < 2 cm is the cut-off set for being classified as stage 0. However, this classification into stages 0 and A seems inconsequential for patients with single tumors, since the final determinant of management options in this group of patients is portal pressure and bilirubin levels, with no consideration given to size. This is evident because surgical resection is the first option for patients with normal total bilirubin levels and no evidence of clinically significant portal hypertension. Given the findings of this study, BCLC stage A patients with single tumors should be further classified, based on tumor size, into giant and non-giant subgroups since survival after surgical resection differs significantly between these two groups. As a cut-off size of 10 cm was used, this study was unable to determine the exact size beyond which the

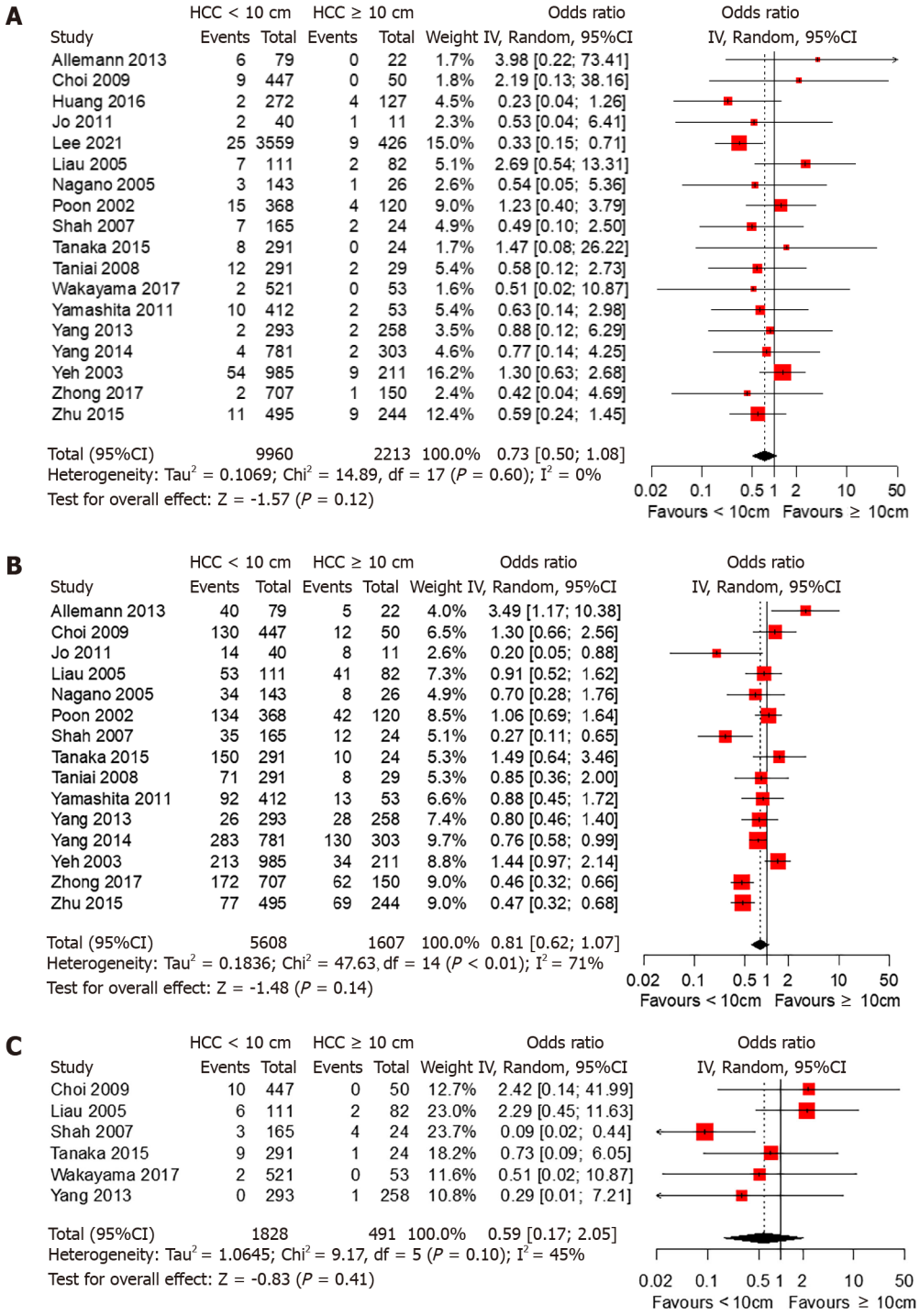

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Figure 4 Forest plots for morbidity and 30-d mortality. A: Forest plot of the 30-d mortality rate; B: Forest plot of the postoperative complication rate; C: Forest plot of post-hepatic liver failure rate. HCC: Hepatocellular carcinoma.

oncological prognosis was inferior.

Similarly, in other staging systems, other prognostic factors have taken precedence over tumor size. In the latest AJCC 8th edition staging system[12], solitary tumors ≤ 2 cm are now staged as T1a regardless of microvascular invasion, which differs from the 7th edition, where microvascular invasion determines whether the tumor is T1 or T2. However, for tumors > 2 cm in diameter, vascular invasion and multifocality play a larger role in staging; the absence of these factors would place the tumor in T1b, regardless of tumor size. In both the Cancer of the Liver Italian Program score[45,46] and Okuda staging system[47], the criteria for tumor size are ambiguous, using relative tumor size compared to the liver (tumor burden) as the cut-off. In contrast, the HKLC classification was constructed solely based on PS, Child-Pugh score, liver tumor status, and the presence of extrahepatic vascular invasion or metastasis, without considering size[13]. Hence, many of the current staging systems ignore tumor size, and even in

those that include size, size plays a limited role in staging the tumors. However, as giant HCC has been shown to be associated with vascular invasion and multinodular tumors, these factors should not be treated as mutually exclusive. From a technical perspective, the surgical resection of giant HCC is challenging. A large tumor size limits the surgical working space, increases the risk of tumor seeding from surgical manipulation, and distorts liver anatomy, thus potentially increasing operative difficulty. Further, it is likely that resection of large tumor entails dissection zone in proximity to hilum or major vessels, thus increasing the likelihood of bleeding or bile leak. In addition, surgical resection of giant HCC is in general entails major hepatectomy with small future liver remnant and associated risk of PHLF.

Although both groups had similar 30-d postoperative mortality and major complication rates, these may not accurately reflect the safety profile of surgical resection in each group. As the 90-d postoperative mortality rate has rarely been reported, only the 30-d mortality rate could be used as an indicator of postoperative mortality. However, a review by Egger *et al*[48] found that most studies reported an approximate doubling of mortality rates between 30 and 90 d following surgery. As the findings of this study were based on 30-d mortality rates, they may not accurately reflect the safety profile of surgical resection. Additionally, many studies did not specify which postoperative complications the patients experienced, and only 6 of the 24 studies[22,27,30,31,34,37] specified if the patients developed PHLF. Since PHLF has been found to be an independent predictor of mortality[2], the development of PHLF after HCC resection may be more indicative of the safety profile than complication rates alone. Thus, to improve the safety profile assessment of surgical resection, more precise reporting of major postoperative complications, particularly PHLF, and reporting of the 90-d mortality rate are required.

Although long-term outcomes for giant HCCs are significantly worse than those for non-giant HCCs, surgery continues to be the preferred treatment option. There is consensus that non-surgical treatment options for single giant HCC are associated with poorer outcomes than surgical resection, although many studies supporting surgical resection in the management of giant HCC have used transarterial chemoembolization (TACE) as a comparison[49-51]. In a recent meta-analysis of 1892 patients, Gui *et al*[52] found that TACE + radiofrequency ablation offers oncological outcomes comparable to surgical resection with lower morbidity. Although the meta-analysis was not specific to the treatment of giant HCC, it opens up the possibility of exploring the multimodal and combination approaches in patients with giant HCC. While surgical resection remains the current preferred treatment option for patients with giant HCC, future prospective studies should investigate different modalities of intervention for single or multiple giant HCC to determine whether these treatments can provide better quality of life outcomes with low therapy-associated morbidity. In addition, with scientific progress and innovation, radiation therapies including external beam radiation and selective internal radiation therapy, have a complementary role in the multidisciplinary care of patients with HCC[53].

This study has several limitations that should be considered. First, all included studies were retrospective studies with a risk of selection bias. As such, the favorable safety profile of giant HCC resection and the similar liver function in both giant and non-giant HCC may in part be due to the selection of younger and fitter patients with well-preserved liver function, or a publication bias. Second, there was a high degree of heterogeneity among studies. Hence, caution should be exercised when interpreting the results. Third, survival data, such as OS and DFS, were manually extracted from the survival curves. Hence, the possibility of errors during the data extraction cannot be eliminated. Fourth, although the algorithm used allows for a close approximation of the original IPD, it does not provide further details, such as patient-level covariates, which may provide greater insight. Lastly, this study was not able to assess whether total tumor volume (calculated by the equation $(4\pi \times r1 \times r2 \times r3)/3$; where r1, r2, and r3 are half of the largest, intermediate, and shortest tumor dimensions respectively) could be a prognosticator of oncological outcomes.

CONCLUSION

In summary, the results of this study show that surgical resection of giant HCC is associated with poorer long-term survival outcomes and should therefore be treated as a separate disease entity. While it was found that surgical resection of both giant and non-giant HCC had similar safety profiles, this may be confounded by poor reporting of the 90-d mortality rate. HCC staging systems should account for these size differences.

ARTICLE HIGHLIGHTS

Research background

There is currently no consensus on the inclusion of tumor size in hepatocellular carcinoma (HCC) staging systems. Furthermore, the size cut-off may vary in systems that incorporate tumor size, and a

consensus is warranted for inclusion of size into the staging criteria with cut-off to be determined by multi-center collaborative clinical studies.

Research motivation

Research on long-term survival after resection of giant (≥ 10 cm) and non-giant HCC (< 10 cm) has produced conflicting results.

Research objectives

This study aimed to investigate whether oncological outcomes and safety profiles of resection differ between giant and non-giant HCC.

Research methods

PubMed, MEDLINE, EMBASE, and Cochrane databases were searched. Studies designed to investigate the outcomes of giant *vs* non-giant HCC were included. The primary endpoints were overall survival (OS) and disease-free survival (DFS). The secondary endpoints were postoperative complications and mortality rates. All studies were assessed for bias using the Newcastle–Ottawa Scale.

Research results

24 retrospective cohort studies involving 23747 patients (giant = 3326; non-giant = 20421) who underwent HCC resection were included. OS was reported in 24 studies, DFS in 17 studies, 30-d mortality rate in 18 studies, postoperative complications in 15 studies, and post-hepatectomy liver failure (PHLF) in six studies. The HR was significantly lower for non-giant HCC in both OS (HR 0.53, 95%CI: 0.50-0.55, $P < 0.001$) and DFS (HR 0.62, 95%CI: 0.58-0.84, $P < 0.001$). No significant difference was found for 30-d mortality rate (OR 0.73, 95%CI: 0.50-1.08, $P = 0.116$), postoperative complications (OR 0.81, 95%CI: 0.62-1.06, $P = 0.140$), and PHLF (OR 0.81, 95%CI: 0.62-1.06, $P = 0.140$).

Research conclusions

Resection of giant HCC is associated with poorer long-term outcomes. The safety profile of resection was similar in both groups; however, this may have been confounded by reporting bias. HCC staging systems should account for the size differences.

Research perspectives

Future prospective studies should investigate different modalities of intervention for giant HCC to determine whether these treatments can provide better quality of life outcomes with low therapy-associated morbidity.

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FOOTNOTES

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