Systematic Review and/or Meta-analysis

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Anatomic versus nonanatomic resection for intrahepatic cholangiocarcinoma: a systematic review and meta-analysis

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Background: The value of anatomic resection (AR) in intrahepatic cholangiocarcinoma (ICC) remains controversial. This study compares the perioperative safety and long-term outcomes of AR versus nonanatomic resection (NAR) in ICC patients.

Methods: A systematic search was conducted in PubMed, Medline, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), and Wanfang database for prospective or retrospective studies comparing the efficacy of AR and NAR in, ICC published to 1 June 2024. Meta-analyses were performed on surgical factors, perioperative outcomes, and long-term prognosis for both the entire cohort and the propensity score-matched (PSM) cohort. The primary outcome measures were overall survival (OS) and disease-free survival (DFS).

Results: Seven studies, including 1801 ICC patients, were analyzed. In both the entire and the PSM cohort, the AR group demonstrated superior OS (HR = 0.71, 95% CI = 0.57–0.88, $P = 0.002$ and HR = 0.70, 95% CI = 0.59–0.83, $P < 0.0001$, respectively) and DFS (HR = 0.75, 95% CI = 0.62–0.91, $P = 0.004$ and HR = 0.68, 95% CI = 0.58–0.79, $P < 0.00001$, respectively) compared to the NAR group. AR significantly improves 1-year, 3-year, 5-year DFS, and 5-year OS(all $P < 0.05$). In the PSM cohort, AR and NAR groups showed comparable blood loss, operative times, overall complications, and major complications (all $P > 0.05$). Subgroup analysis revealed that among patients with tumor > 5 cm, AR achieved better OS and DFS, whereas patients with tumors ≤ 5 cm did not experience survival benefits from AR.

Conclusion: This study suggests that AR, compared to NAR, can improve OS and DFS without increasing perioperative risks, particularly in ICC patients with tumors larger than 5 cm.

Keywords: anatomic resections, intrahepatic cholangiocarcinoma, prognosis, survival

Introduction

Primary liver cancer is the sixth most common cancer and the third leading cause of cancer-related death worldwide, encompassing hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) and combined hepatocellular-cholangiocarcinoma (cHCC-CC) [1–3]. ICC is the second most common primary liver malignancy, and its incidence is on the rise globally[4,5]. Currently, radical resection remains the only potentially curative treatment for ICC.

In recent years, systemic therapy for liver cancer is promising[6]. However, it cannot be ignored that hepatectomy has been widely utilized in the management of malignant liver tumors. The purpose of hepatectomy is to completely remove the tumor while ensuring an adequate resection margin to minimize the risk of recurrence[7–9]. Liver resections are categorized into nonanatomic resections (NAR), which involve the removal of liver parenchyma surrounding the tumor with sufficient margins, and anatomic resections (AR), which involve the removal of

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entire anatomical liver segments[10,11]. On the one hand, with the further understanding of the functional anatomy of the liver, AR has been shown to allow for the complete remove the liver segments within the Glisson sheath's blood supply and corresponding hepatic venous drainage, potentially reducing the risks of postoperative bleeding, bile leakage, and liver failure[12]. Additionally, as the portal vein system is the primary route for intrahepatic metastasis of liver cancer (especially HCC). For example, the transfer of blood flow between the portal vein and the tumor supplying artery is one of the mechanisms of tumor metastasis in HCC[13]. Complete resection of liver segments is conducive to the eradication of local micrometastases, and this advantage of AR is considered beneficial to prevent recurrence[14]. The long-term prognostic benefits of AR in HCC treatment has been well-documented[12,15]. However, given the distinct molecular characteristics and malignant behavior of ICC, whether AR offers a long-term survival advantage in ICC remains uncertain[16–19]. Currently, there is no systematic review addressing this issue.

To address these unresolved questions, we conducted a meta-analysis evaluating the efficacy of AR versus NAR in the treatment of ICC.

Method

The meta-analysis was registered with PROSPERO and follows the guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, Supplemental Digital Content 12, http://links.lww.com/JS9/D550) and the A MeaSurement Tool to Assess systematic Reviews (AMSTAR) checklist(Supplemental Digital Content 1, http://links.lww.com/JS9/D539)[20,21].

Search strategy

A comprehensive and systematic search of PubMed, Embase, Medline, Cochrane Library, Wanfang database, and CNKI database was conducted to identify studies comparing the safety and efficacy of AR and NAR in ICC patients. The search included studies published up to 1 June 2024. The search strategy is a combination of the following keywords: 'ICC' or 'iCCA' or 'intrahepatic cholangiocarcinoma' or 'intrahepatic bile duct carcinoma' or 'intrahepatic bile duct cancer' or 'intrahepatic cholangiocellular carcinoma' or 'intrahepatic bile duct tumor' or 'intrahepatic cholangiocyte carcinoma'; 'resection'; 'anatomical' or 'anatomic'; 'nonanatomic' or 'non anatomic' or 'non-anatomic' or 'nonanatomical' or 'non-anatomical' or 'non anatomical'. Both Chinese and English articles were included in the search.

Inclusion and exclusion criteria

Inclusion criteria: (1) ICC diagnosis confirmed by histopathology; (2)Studies comparing the therapeutic effects of AR and NAR; (3) Prospective or retrospective studies; (4) Reported at least one outcome of interest, such as OS, DFS, and complications; and (5) Full-text available in English or Chinese.

Exclusion criteria: (1) Nonhuman clinical studies; (2) Studies where prognostic data could not be extracted; (3) Duplicate publication of article; (4) Noncomparative studies: letters, case reports, reviews, editorials, guidelines, and abstracts.

HIGHLIGHTS

- There is controversy regarding the efficacy of AR versus NAR in ICC. This is the first meta-analysis comparing AR and NAR in ICC patients for perioperative safety and long-term survival outcomes.
- Compared to NAR, AR is associated with better OS and DFS in ICC patients without increasing perioperative risks.
- AR provides a survival benefit for tumors larger than 5 cm; however, for tumor size ≤ 5 cm, the long-term outcomes of AR and NAR are comparable.

Data extraction and quality assessment

Two reviewers independently extracted data using a standardized data extraction form and summarized the results. Initially, titles and abstracts were reviewed to exclude duplicates and unrelated studies. Full texts were then thoroughly reviewed to confirm eligibility, and the following data were extracted: year of publication, country, study type, study design, sample size, and patient characteristics. Outcomes of interest included: surgery-related indicators (operative blood loss and operation time), postoperative hospital stay, perioperative complications, OS, and DFS. For PSM studies, data were extracted separately for before and after matching. Any disagreement between the two reviewers were resolved through discussion, with a third reviewer involved to reach a consensus.

The quality of the included studies was assessed independently by two reviewers using the Newcastle–Ottawa Scale (NOS)[22]. Each study was scored on a scale of 0–9, with a score of ≥ 6 considered qualified for inclusion in the meta-analysis.

Statistical analysis

Mean differences (MD) with 95% CI were used to assess continuous variables, while risk ratios (RR) with 95% CI were used to evaluate categorical variables. Hazard ratios (HR) with 95% CI were extracted to evaluate combined effects. If survival data were not directly available in the articles, we utilized Engauge Digitizer software to extract data from Kaplan–Meier curves. Log hazard ratios (logHR) were calculated using the methodology outlined by Tierney *et al*.[23] Cochrane's Q and I^2 statistics were used to assess heterogeneity among the included studies. The value of I^2 in the range of 0% to 25% indicates that the heterogeneity is not significant, 25–50%, 50–75%, and $>75\%$ indicates low, medium, and high heterogeneity, respectively[24]. If heterogeneity was acceptable ($P \geq 0.1$, $I^2 < 50\%$), a fixed-effects model (FEM) was used for the meta-analysis; otherwise, a random-effects model (REM) was employed. High heterogeneity was addressed through subgroup analysis or sensitivity analysis. If excluding a particular study significantly reduced heterogeneity, that study was considered a primary source of heterogeneity. Publication bias was comprehensively evaluated using funnel plots, Begg's test, and Egger's test[25–27]. Statistical significance was set at $P < 0.05$.

Results

Study selection and quality evaluation

The study selection process is illustrated in the PRISMA flowchart (Fig. 1). A total of 1375 studies were initially identified. After removing 547 duplicates through a combination of automatic

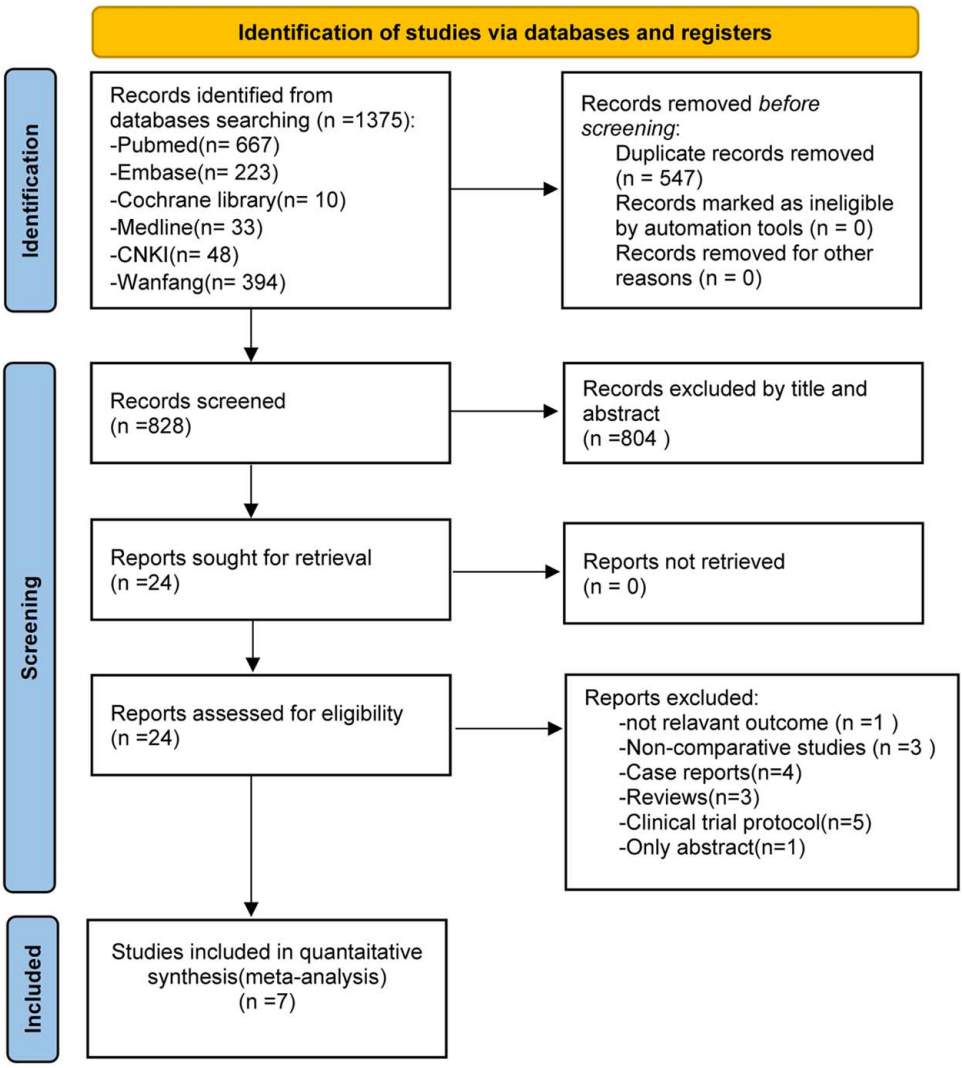

Figure 1. Flowchart of study identification and selection.

and manual methods, 804 studies were excluded based on title and abstract screening due to clear irrelevance. Following a full-text review, seven studies that compared AR and NAR in ICC patients were included in this study[11,16–18,28–30]. All included studies were retrospective, with five PSM studies[11,16–18,28], including two multicenter studies[11,18]. A total of 1801 ICC patients (890 in the AR group and 911 in the NAR group) who underwent surgery were included. All studies had NOS scores above 7, indicating good quality (Supplemental Table S1,Supplemental Digital Content 2, http://links.lww.com/JS9/D540). The risk of bias was assessed using the Cochrane risk of bias tool (Supplemental Figure S1,Supplemental Digital Content 3, http://links.lww.com/JS9/D541). The basic characteristics of the included studies was shown in Table 1. The number of patients per study ranged from 145 to 671, with the proportion of patients in the AR group ranging from 45.3 to 69.4%. Most studies reported a higher proportion of male patients (49.7–64.4%). HBV infection was reported in four studies[16–18,28], with HBV patient proportions of 46.8%, 50.7%, 31.3%, and 26.8%, respectively. Two studies[16,18] reported on HCV infection, with proportions ranging from 2.1 to 3.4%. Meta-analysis for the baseline data for the entire cohort showed that the AR group had a significantly lower proportion of patients with cirrhosis (RR: 0.69; 95% CI: 0.59–0.81; $P < 0.00001$) and multiple tumors (RR: 0.71; 95% CI: 0.58–0.86; $P = 0.0006$) (Supplemental Figure S2a,c, Supplemental Digital Content 4, http://links.lww.com/JS9/D542). These differences were eliminated after PSM (Supplemental Figure S2b,d, Supplemental Digital Content 4, http://links.lww.com/JS9/D542). The PSM cohort's basic characteristics are detailed in Table 2. All key outcome results from this meta-analysis are presented in Table 3.

Operative outcomes

Operative time

Six studies reported the operative time[16–18,28–30], involving a total of 1523 patients. The operative time was longer in the AR group (MD: 25.35 min; 95% CI: 4.97–45.74; $P = 0.01$). The heterogeneity was high ($I^2 = 94\%$), and data were pooled using random-effects model (REM) (Supplemental

Table 1

Characteristics of the entire cohort

References	Country	Design type	Center	Group	NP	Age	Sex(M/F)	Tumor size(cm)	Solotary/ Multiple	Child-Pugh (A/B/C)	Tumor differentiation (well-moderate/ poor)	Adjuvant treatment	HBV	HCV	Cirrhosis	Hepatolithiasis	Nodal metastasis	NOS score
Si A.[16]	China	PSM	Single	AR	305	52.9 (46.0–60.0)	192/113	5.0 (3.4–7.0)	234/71	305/0/0	278/27	74	143	7	55	44	55	8
				NAR	366	55.4 (47.0–65.0)	236/130	5.7 (4.0–8.0)	223/113	366/0/0	519/47	81	171	7	102	56	64	
Ke Q.[11]	China	PSM	Multi	AR	126	61 (≥60 years)	68/58	44 (≤5 cm)	126/0	86/40/0	94/32	26	NA	NA	31	NA	NA	8
				NAR	152	53 (≥60 years)	111/41	72 (≤5 cm)	152/0	80/72/0	121/31	24	NA	NA	68	NA	NA	
Li B.[17]	China	PSM	Single	AR	85	59 (27–87)	49/36	4.5 (1–13)	85/0	81/4/0	62/23	22	37	NA	40	11	11	8
				NAR	65	54 (27–76)	44/21	6 (2–13)	65/0	62/3/0	36/29	21	39	NA	43	3	8	
Wu J.[18]	China	PSM	Multi	AR	80	24 (>65 years)	43/37	35 (≤5 cm)	65/15	NA	58/22	31	23	2	21	80	28	8
				NAR	67	19 (>65 years)	30/37	23 (≤5 cm)	50/17	NA	50/17	23	23	3	28	67	27	
Wu X.[30]	China	Retrospective study	Single	AR	68	57 (≤70 years)	33/35	5.89 ± 2.65	54/14	NA	37/31	NA	NA	NA	9	26	24	8
				NAR	30	25 (≤70 years)	22/8	6.62 ± 3.40	26/4	NA	18/12	NA	NA	NA	5	6	10	
Wang C.[28]	China	PSM	Single	AR	139	49 (≥60 years)	85/54	69 (≤5 cm)	112/27	117/22/0	81/58	NA	38	NA	33	NA	49	9
				NAR	137	43 (≥60 years)	82/55	78 (≤5 cm)	85/52	126/11/0	78/59	NA	36	NA	28	NA	28	
Han X.[29]	China	Retrospective study	Single	AR	87	71.4 ± 5.2	54/33	4.5 ± 1.5	NA	NA	NA	NA	NA	NA	NA	NA	NA	8
				NAR	94	70.8 ± 4.8	49/45	4.6 ± 1.4	NA	NA	NA	NA	NA	NA	NA	NA	NA	

AR, anatomic resections; M/F, male/female; NA, not available; NAR, nonanatomic resections; NOS, Newcastle–Ottawa Scale; PSM, propensity score matching;

Table 2
The basic characteristics of the PSM cohort

References	Group	NP	Age	Sex (M/F)	Tumor size(cm)	Solotary/ Multiple	Child-Pugh (A/B/C)	Tumor differentiation (well-moderate/poor)	Adjuvant treatment	HBV	HCV	Cirrhosis	Hepatolithiasis	Nodal metastasis
Si A.[16]	AR	229	54.0 (46.0–61.5)	149/80	5.1 (3.6–7.3)	61/168	229/0/0	206/23	55	108	5	48	30	40
	NAR	229	54.0 (48.0–60.0)	133/96	5.2 (3.8–7.9)	59/170	229/0/0	199/30	51	104	2	49	36	40
Ke Q.[11]	AR	58	22 (≥ 60 years)	38/20	24 (≤ 5 cm)	58/0	76/51/0	42/16	6	NA	NA	22	NA	NA
	NAR	58	23 (≥ 60 years)	39/19	27(≤ 5cm)	58/0	84/61/0	40/18	9	NA	NA	21	NA	NA
Li B.[17]	AR	29	61 (27–87)	16/13	5 (2–13)	29/0	25/4/0	18/11	7	16	NA	16	1	4
	NAR	29	57 (36–72)	16/13	4.5 (1–12)	29/0	27/2/0	20/9	8	14	NA	17	2	1
Wu J.[18]	AR	50	38 (> 65 years)	26/24	19 (≤ 5 cm)	39/11	NA	38/12	22	14	2	14	50	23
	NAR	50	34 (> 65 years)	24/26	21 (≤ 5 cm)	41/9	NA	37/13	17	17	2	15	50	20
Wang C.[28]	AR	99	36 (≥ 60 years)	58/41	50 (≤ 5 cm)	80/19	89/10/0	58/41	NA	23	NA	16	NA	18
	NAR	99	29 (≥ 60 years)	59/40	60 (≤ 5 cm)	74/25	88/11/0	57/42	NA	20	NA	19	NA	27

AR, anatomic resections; M/F, male/female; NA, not available; NAR, nonanatomic resections; PSM, propensity score matching.

Figure S3a,Supplemental Digital Content 5, http://links.lww.com/JS9/D543). After PSM, four studies[16–18,28], involving a total of 814 patients, reported operative time. The pooled data using REM showed that the difference in operative time between the two groups was no longer significant ($P = 0.11$) (Fig. 2A).

Operative blood loss

Before PSM, six studies reported operative blood loss[16–18,28–30]. As shown in Supplemental Figure S3b (Supplemental Digital Content 5, http://links.lww.com/JS9/D543), there was no significant difference in operative blood loss between the AR group and the NAR group (MD: −11.13 ml; 95% CI: −103.88 to 81.62; $P = 0.81$). After PSM, four studies[16–18,28]reported operative blood loss. The heterogeneity was not significant ($I^2 = 4\%$), and data were pooled by FEM. The blood loss between the two groups was comparable (MD: 21.32 ml; 95% CI: −12.33 to 54.97; $P = 0.21$) (Fig. 2B).

Postoperative outcomes

Postoperative hospital stay

Before PSM, six studies reported postoperative hospital stay[16–18,28–30], showing no significant difference between the two groups (MD: 0.53 days; 95% CI: −0.34 to 1.41; $P = 0.23$) (Supplemental Figure S3c, Supplemental Digital Content 5, http://links.lww.com/JS9/D543). After PSM, four studies reported postoperative hospital stay[16–18,28]. With moderate heterogeneity ($I^2 = 68\%$), REM was used for pooling the data, which also showed no significant difference in postoperative hospital stay between the AR and NAR groups (MD: 0.59 days; 95% CI: −1.40 to 2.58; $P = 0.56$) (Fig. 2C).

Complications

Six studies[11,16–18,29,30], involving 1525 patients (751 in the AR group and 774 in the NAR group), reported on postoperative complications. The studies showed low heterogeneity ($I^2 = 23\%$). Pooled data using REM indicated no significant difference in complication rates between the AR and NAR groups (RR: 1.05; 95% CI: 0.91–1.21; $P = 0.52$) (Supplemental Figure S3d, Supplemental Digital Content 5, http://links.lww.com/JS9/D543). After PSM, four studies[11,16,18,28], involving 415 patients in each group, reported on postoperative complications with $I^2 = 37\%$. FEM was used to pool the data, again showing no significant difference between the AR and NAR groups (RR: 1.13; 95% CI: 0.92–1.39; $P = 0.23$) (Fig. 2D).

Major complications

Six studies reported major complications[11,16–18,29,30], involving 1525 patients. There was low heterogeneity ($I^2 = 35\%$), and pooled data using REM indicated a higher rate of major complications in the AR group (RR: 1.44; 95% CI: 1.01–2.05; $P = 0.04$) (Supplemental Figure S3e, Supplemental Digital Content 5, http://links.lww.com/JS9/D543). After PSM, four studies[11,16,18,28] reported major complications, among which Wang *et al*.'s study showed no major complications in both the AR and NAR group. The heterogeneity was low ($I^2 = 0\%$), and data were pooled using FEM. The difference in major complications between the two groups was no longer significant (RR: 1.28; 95% CI: 0.78–2.10; $P = 0.33$) (Fig. 2E).

Table 3

Summary results of the meta-analyses

	Entire cohort							PSM cohort						
						Heterogeneity							Heterogeneity	
Outcomes	**Studies, *n***	**AR**	**NAR**	**HR/RR (95%CI)**	***P***	**I^2,%**	***P***	**Studies, *n***	**AR**	**NAR**	**HR/RR (95%CI)**	***P***	**I^2,%**	***P***
Operative outcomes														
Operative time (min)	6	764	759	25.35 (4.97–45.74)	0.01	94	< 0.00001	4	407	407	24.84 (–5.32 to 55.00)	0.11	78	0.004
Operative blood loss (ml)	6	764	759	–11.13 (–103.88 to 81.62)	0.81	94	< 0.00001	4	407	407	21.32 (–12.33 to 54.97)	0.21	4	0.37
Postoperative outcomes														
Postoperative hospital stay	6	764	759	0.53 (–0.34 to 1.41)	0.23	69	0.007	4	407	407	0.59 (–1.40 to 2.58)	0.56	68	0.03
Overall complications	6	751	774	1.05 (0.91–1.21)	0.52	23	0.26	4	415	415	1.13 (0.92–1.39)	0.23	37	0.19
Major complications	6	751	774	1.44 (1.01–2.05)	0.04	35	0.17	4	415	415	1.28 (0.78–2.10)	0.33	0	0.87
Oncological outcomes														
Overall survival	7	890	911	0.71 (0.57–0.88)	0.002	56	0.03	5	465	465	0.70 (0.59–0.83)	< 0.0001	0	0.59
1-year OS	6	803	817	0.88 (0.66–1.17)	0.38	71	0.004	5	465	465	0.77 (0.64–0.92)	0.005	0	0.69
3-year OS	6	803	817	0.84 (0.71–0.99)	0.04	74	0.002	5	465	465	0.82 (0.66–1.00)	0.06	67	0.02
5-year OS	6	803	817	0.87 (0.78–0.97)	0.01	67	0.01	5	465	465	0.86 (0.80–0.94)	0.0006	48	0.10
Disease-free survival	5	735	787	0.75 (0.62–0.91)	0.004	52	0.08	5	465	465	0.68 (0.58–0.79)	< 0.00001	0	0.78
1-year DFS	5	735	787	0.79 (0.71–0.88)	< 0.0001	26	0.25	5	465	465	0.77 (0.68–0.89)	0.0002	0	0.64
3-year DFS	5	735	787	0.88 (0.80–0.98)	0.02	60	0.04	5	465	465	0.88 (0.81–0.95)	0.001	18	0.30
5-year DFS	5	735	787	0.91 (0.84–0.98)	0.02	58	0.05	5	465	465	0.90 (0.84–0.96)	0.001	35	0.19
Univariate analysis of OS	4	579	615	0.67 (0.48–0.95)	0.02	76	0.006	3	386	386	0.78 (0.59–1.04)	0.09	58	0.09
Univariate analysis of DFS	3	511	585	0.66 (0.51–0.87)	0.003	62	0.07	3	386	386	0.75 (0.64–0.87)	0.0002	0	0.52
Multivariate analysis of OS	5	666	709	0.67 (0.49–0.91)	0.01	72	0.007	4	436	436	0.72 (0.47–1.12)	0.15	88	< 0.0001
Multivariate analysis of DFS	3	511	585	0.72 (0.51–1.02)	0.06	77	0.01	4	436	436	0.68 (0.59–0.79)	< 0.00001	37	0.19

AR, anatomic resections; DFS, disease-free survival; HR, hazard ratio; RR, relative risk; NAR, non-anatomic resections; OS, overall survival; PSM, propensity score matching.

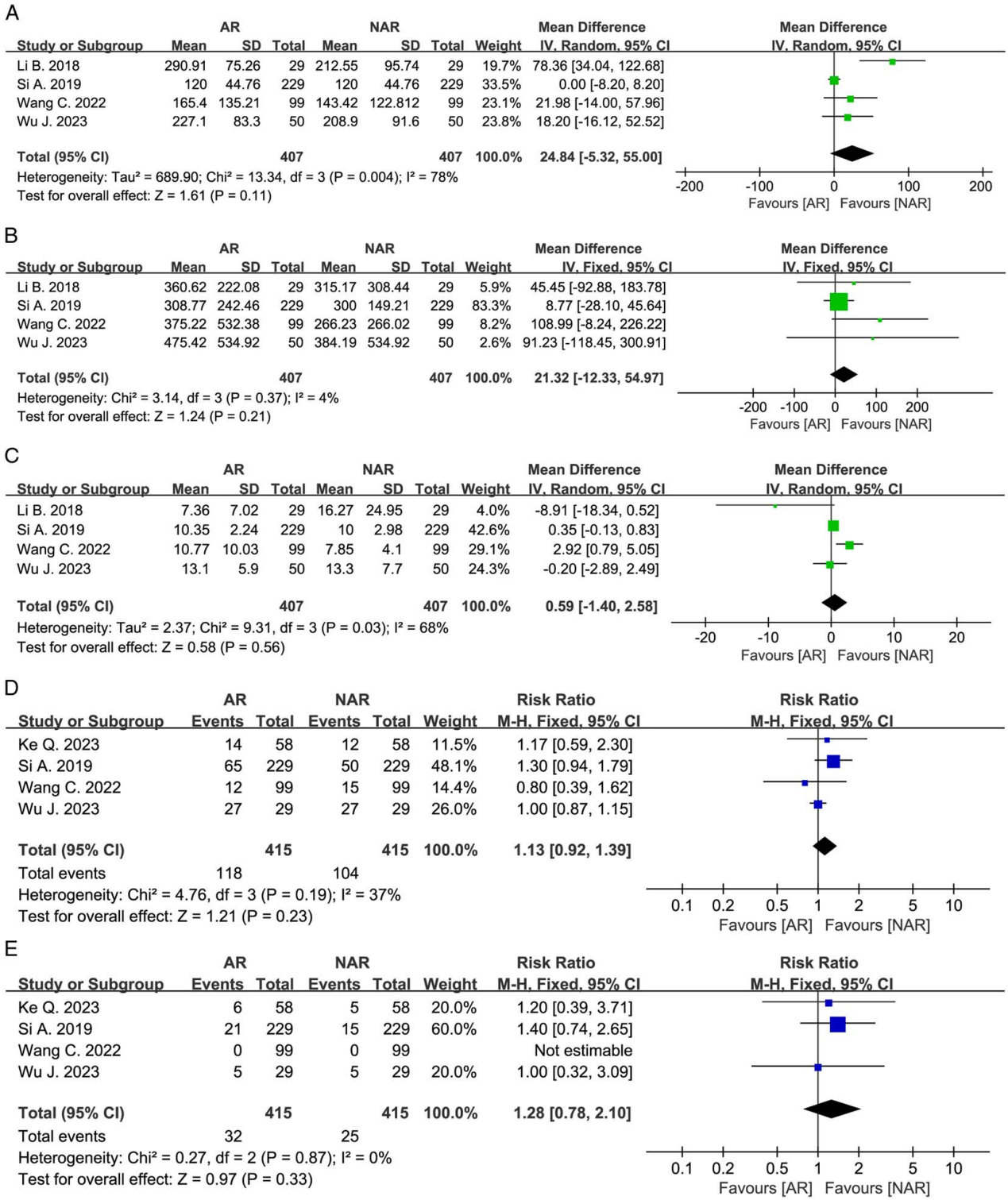

Figure 2. Forest plot of comparison of AR versus NAR for perioperative outcomes of PSM cohort. operative time; (b) operative blood loss; (c) postoperative hospital stay; (d) complications; and (e) major complications.

Oncological outcomes

Overall survival

All seven included studies (a total of 1801 ICC patients) reported on OS[11,16–18,28–30]. Heterogeneity was moderate ($P = 0.03$, $I^2 = 58\%$), so REM was selected to pool the HRs for OS. The results indicated that OS was significantly better in the AR group compared to the NAR group (HR = 0.71, 95% CI: 0.57–0.88, $P = 0.002$) (Fig. 3A). After PSM, five studies with a total of 930 patients reported OS[11,16–18,28]. Heterogeneity was not significant

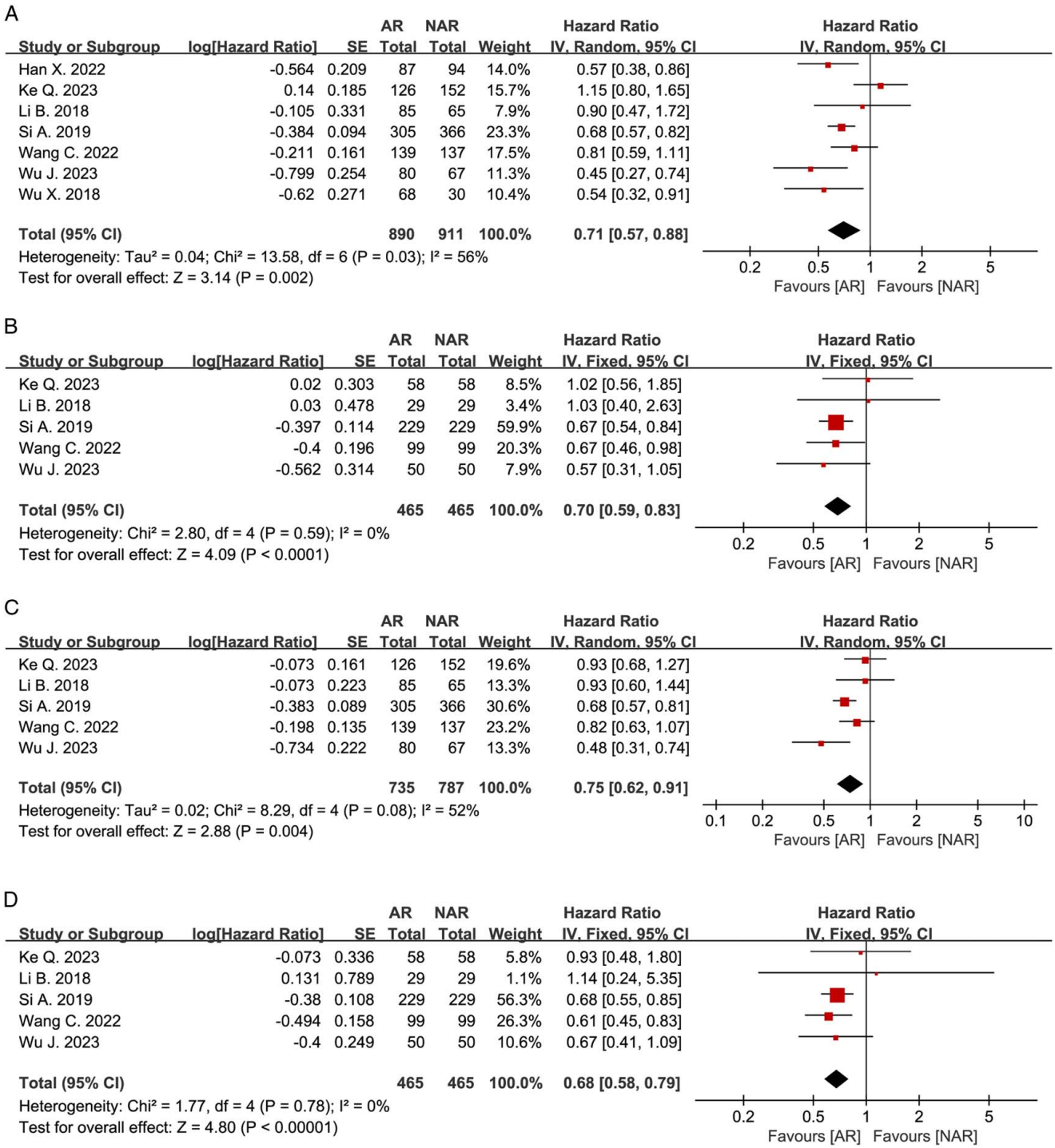

Figure 3. Forest plot of comparison of AR versus NAR for OS and DFS. (a) OS before PSM; (b) OS after PSM; (c) DFS before PSM; and (d) DFS after PSM.

($I^2 = 0\%$), and FEM was used for pooling. The results still showed that the OS of the AR group was significantly better than that of the NAR group (HR = 0.70, 95% CI: 0.59–0.83, $P < 0.0001$) (Fig. 3B).

Further analysis of entire cohort included six studies[11,16–18,28,30], with a total of 1620 patients (803 in the AR group and 817 in the NAR group). The combined results showed the AR group had better 3-year OS (RR: 0.84; 95% CI: 0.71–0.99; $P = 0.04$) (Supplemental Figure S4b, Supplemental Digital Content 6, http://links.lww.com/JS9/D544) and 5-year OS (RR: 0.87; 95% CI: 0.78–0.97; $P = 0.01$) (Supplemental Figure S4c, Supplemental Digital Content 6, http://links.lww.com/JS9/D544). However, there was no significant difference in the 1-year OS rate between the two groups (RR: 0.88; 95% CI:

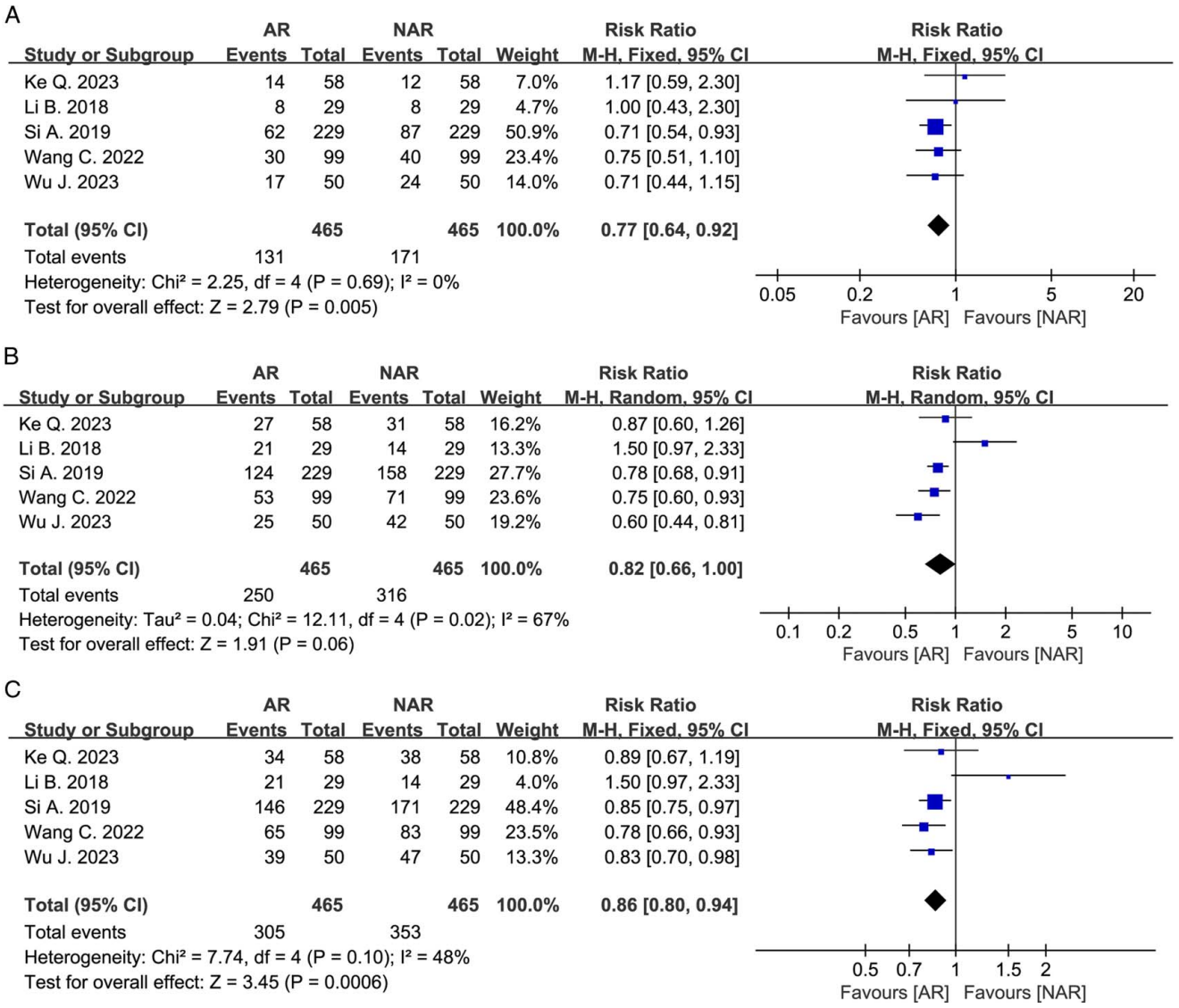

Figure 4. Forest plot of comparison of AR versus NAR for long-term oncological outcomes of PSM cohort. (a) 1-year OS; (b) 3-year OS; and (c) 5-year OS.

0.66–1.17; $P = 0.38$), with moderate heterogeneity ($I^2 = 71\%$) (Supplemental Figure S4a, Supplemental Digital Content 6, http://links.lww.com/JS9/D544).

After PSM, five studies[11,16–18,28] encompassing a total of 930 patients, revealed that the AR group had significantly better 1-year OS (RR: 0.77; 95% CI: 0.64–0.92; $P = 0.005$) (Fig. 4A) and 5-year OS (RR: 0.86; 95% CI: 0.80–0.94; $P = 0.0006$) (Fig. 4C) compared to the NAR group. The AR group also demonstrated a benefit in 3-year OS (RR: 0.82; 95% CI: 0.66–1.00), although this difference was not statistically significant ($P = 0.06$) (Fig. 4B).

Disease-free survival

Five studies, including a total of 1522 patients, reported DFS outcomes between the AR and NAR groups[11,16–18,28]. Moderate heterogeneity was observed ($P = 0.08$, $I^2 = 52\%$), and REM was selected to pool the HR for DFS. The results showed that the AR group had better DFS compared to the NAR group (HR = 0.75, 95% CI: 0.62–0.91, $P = 0.004$) (Fig. 3C). After PSM, conducted in the same five studies[11,16–18,28]. No significant heterogeneity ($I^2 = 0\%$), and FEM was used, the results continued to favor the AR group, showing significantly better DFS compared to the NAR group (HR = 0.68, 95% CI: 0.58–0.79, $P < 0.00001$) (Fig. 3D).

Further analysis showed that five studies[11,16–18,28] before PSM (735 in the AR group and 787 in the NAR group) reported DFS, the results showed that the AR group had significantly better 1-year DFS (RR: 0.79; 95% CI: 0.71–0.88; $P < 0.0001$), 3-year DFS (RR: 0.88; 95% CI: 0.80–0.98; $P = 0.02$), and 5-year DFS (RR: 0.91; 95% CI: 0.84–0.98; $P = 0.02$) compared to the NAR group (Supplemental Figure S5a–c, Supplemental Digital Content 7, http://links.lww.com/JS9/D545).

Post-PSM analysis across five studies[11,16–18,28], involving a total of 930 patients, showed that the AR group had significantly better 1-year DFS (RR: 0.77; 95% CI: 0.68–0.89; $P = 0.0002$), 3-year DFS (RR: 0.88; 95% CI: 0.81–0.95; $P = 0.001$), and 5-year DFS (RR: 0.90; 95% CI: 0.84–0.96; $P = 0.001$) compared to the

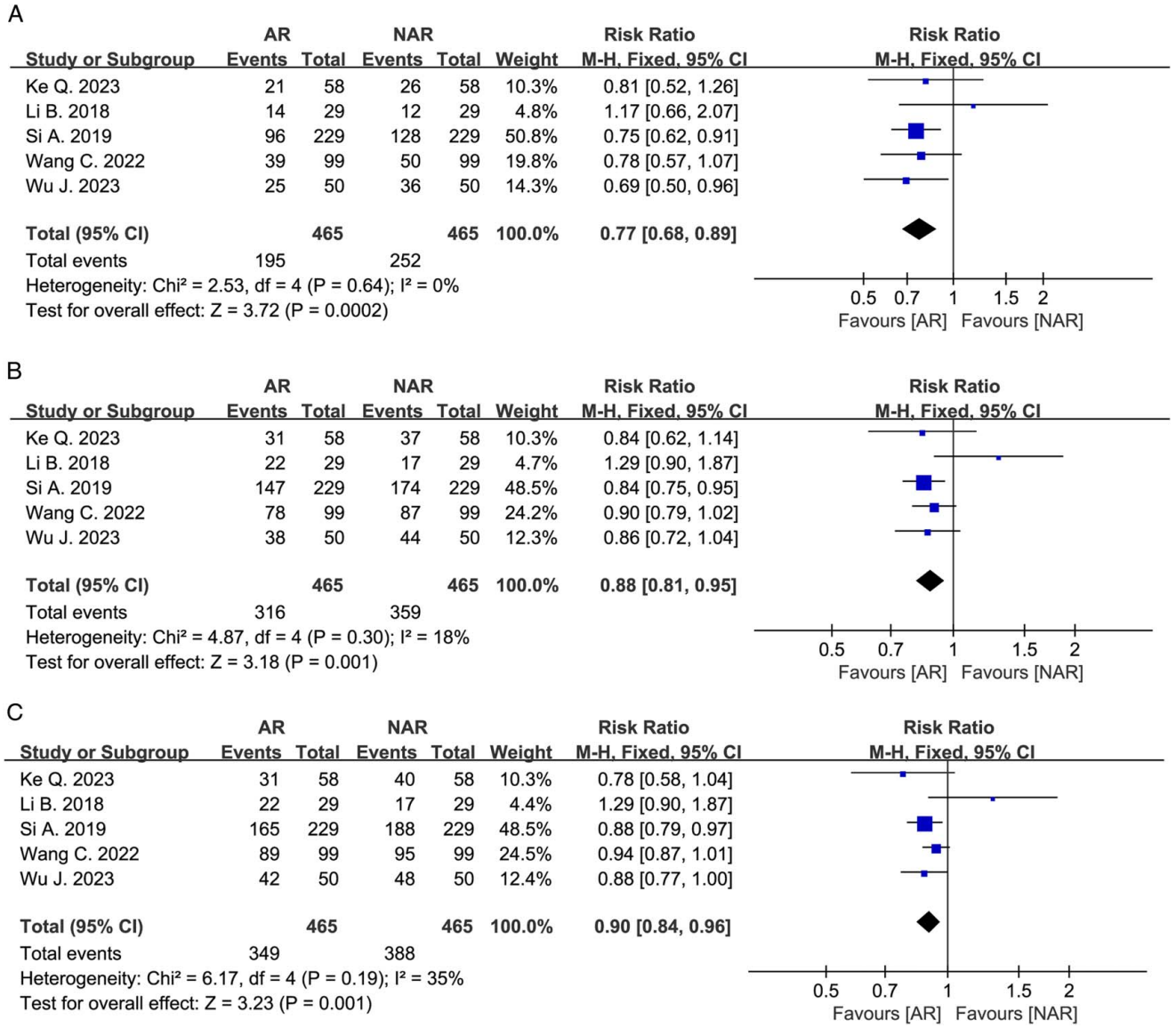

Figure 5. Forest plot of comparison of AR versus NAR for long-term oncological outcomes of PSM cohort. (a) 1-year DFS; (b) 3-year DFS; and (c) 5-year DFS.

NAR group. Heterogeneity was not significant ($I^2 = 0\%$, 18%, and 35%, respectively), and results were pooled using FEM (Fig. 5A–C).

Univariate and multivariate analysis of entire cohort

Before PSM, four studies reported univariate analysis of OS[11,16,18,30]. The results were pooled using REM, indicating that AR was associated with improved OS (HR = 0.67, 95% CI: 0.48–0.95, $P = 0.02$) (Supplemental Figure S6a, Supplemental Digital Content 8, http://links.lww.com/JS9/D546). Five studies[11,16,18,29,30] reported multivariate analysis results for OS, which also showed that AR was related to the improvement of OS (HR = 0.67, 95% CI: 0.49–0.91, $P = 0.01$; $I^2 = 72\%$, $P = 0.007$) (Supplemental Figure S6b,Supplemental Digital Content 8, http://links.lww.com/JS9/D546).

Before PSM, three studies[11,16,18] reported both univariate and multivariate analysis results for DFS. The univariate analysis results, pooled using REM, indicated that AR had better DFS compared to NAR (HR = 0.66, 95% CI: 0.51–0.87, $P = 0.003$; $I^2 = 62\%$, $P = 0.07$) (Supplemental Figure S7a, Supplemental Digital Content 9, http://links.lww.com/JS9/D547). Multivariate analysis[11,16,18] showed similar results, although there was no statistical difference (HR = 0.72, 95% CI: 0.51–1.02, $P = 0.06$; $I^2 = 77\%$, $P = 0.01$) (Supplemental Figure S7b, Supplemental Digital Content 9, http://links.lww.com/JS9/D547).

Univariate and multivariate analysis of PSM cohort

After PSM, three studies reported the results of univariate analysis of OS[11,16,28]. The AR group had a tendency to improve OS compared to the NAR group, but the difference was not statistically significant (HR = 0.78, 95% CI: 0.59–1.04, $P = 0.09$; $I^2 = 58\%$, $P = 0.09$) (Supplemental Figure S6c, Supplemental Digital Content 8). Four studies reported the results of multivariate analysis[11,16,18,28], using REM to merge and obtain similar

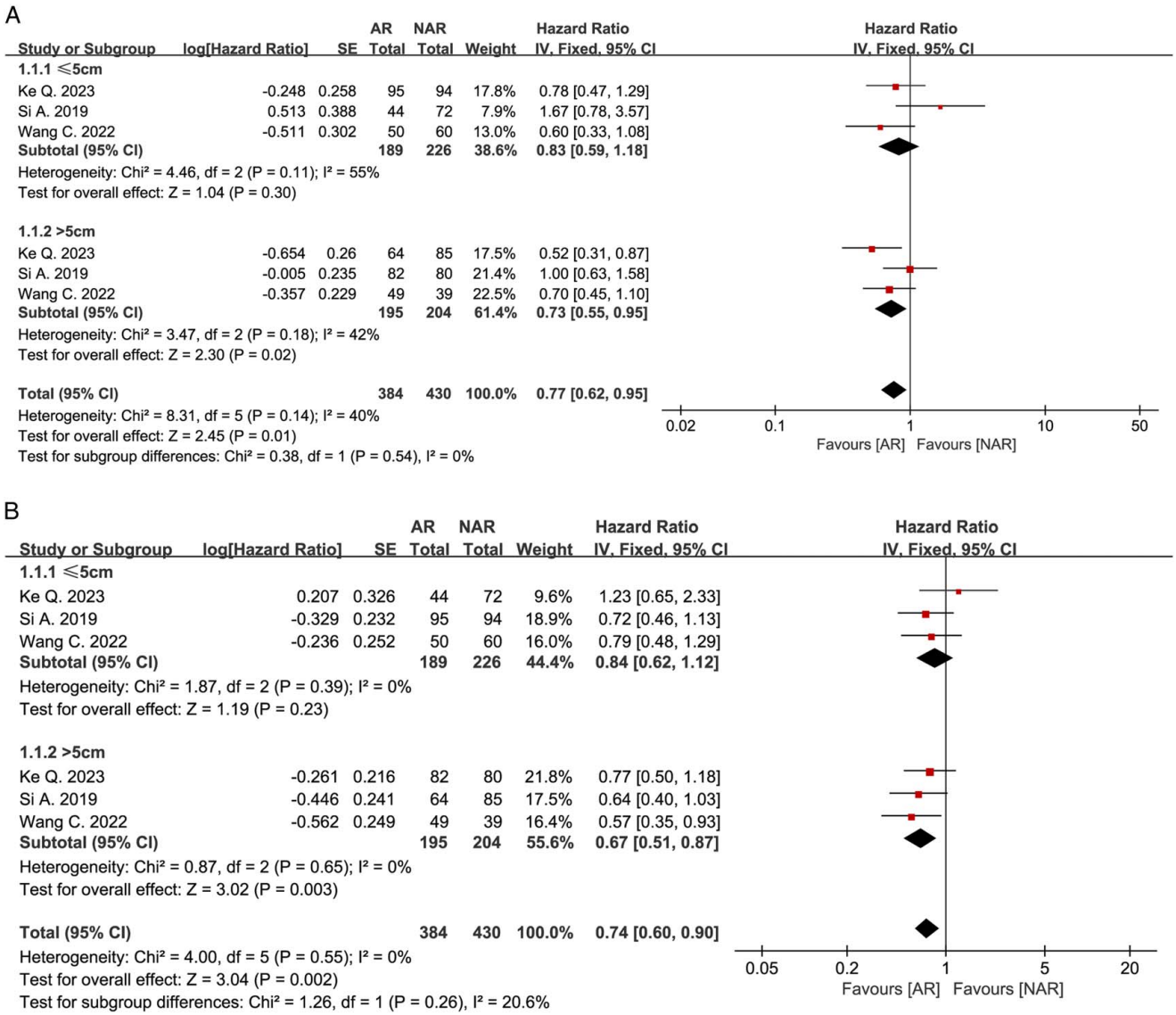

Figure 6. The subgroup analysis of AR versus NAR for OS (a) and DFS (b) based on tumor size.

results (HR = 0.72, 95% CI: 0.47–1.12, $P = 0.15$; $I^2 = 88\%$) (Supplemental Figure S6d,Supplemental Digital Content 8, http://links.lww.com/JS9/D546). Sensitivity analysis revealed that Ke *et al.*'s study had a significant impact on heterogeneity. After excluding this study, heterogeneity was significantly decreased ($I^2 = 33\%$), and the pooled results using FEM showed that AR significantly improved OS (HR = 0.62, 95% CI: 0.52–0.74, $P < 0.00001$).

After PSM, three studies[11,16,28] reported univariate analysis results for DFS. The pooled results using FEM showed that AR had significantly better DFS compared to NAR (HR = 0.75, 95% CI: 0.64–0.87, $P = 0.0002$; $I^2 = 0\%$, $P = 0.52$) (Supplemental Figure S7c, Supplemental Digital Content 9, http://links.lww.com/JS9/D547). Four studies reported multivariate analysis for DFS[11,16,18,28], and the pooled results still showed that AR significantly improved DFS (HR = 0.68, 95% CI: 0.59–0.79, $P < 0.00001$; $I^2 = 37\%$, $P = 0.19$) (Supplemental Figure S7d, Supplemental Digital Content 9, http://links.lww.com/JS9/D547).

Subgroup analysis

Three studies[11,16,28] conducted subgroup analyses comparing the prognostic differences between AR and NAR based on tumor size, including 415 patients with tumors ≤ 5 cm and 814 patients with tumors > 5 cm.

The subgroup analysis of tumors size ≤ 5 cm showed no significant differences in OS and DFS between the AR and NAR groups (OS: HR = 0.83, 95% CI = 0.59–1.18, $P = 0.30$; DFS: HR = 0.84, 95% CI = 0.62–1.12, $P = 0.23$) (Fig. 6).

However, for tumors > 5 cm, the AR group had significantly better OS and DFS compared to the NAR group (OS: HR = 0.73, 95% CI = 0.55–0.95, $P = 0.02$; DFS: HR = 0.67, 95% CI = 0.51–0.87, $P = 0.003$) (Fig. 6).

Publication bias and sensitivity analysis

Potential publication bias was comprehensively assessed using funnel plots, Begg's test, and Egger's test. For the entire cohort,

the Begg's test scores for OS and DFS comparing AR and NAR were 0.764 and 0.806, respectively, and the Egger's test scores were 0.873 and 0.802. For the PSM cohort, the Begg's test scores for OS and DFS were 0.806 and 0.462, respectively, and the Egger's test scores were 0.360 and 0.241. Combined with funnel plot, no significant publication bias was shown (Supplemental Figure S8, Supplemental Digital Content 10, http://links.lww.com/JS9/D548). Sensitivity analyses also demonstrated that the results for OS and DFS were robust before and after PSM (Supplemental Figure S9, Supplemental Digital Content 11, http://links.lww.com/JS9/D549).

Discussion

Intrahepatic cholangiocarcinoma (ICC) is a malignant tumor that located above the secondary branch of the bile duct, accounting for ~10–15% of primary liver cancer (PLC) cases[31,32]. Compared to HCC, ICC is more aggressive, with lower resection rates and a higher likelihood of recurrence[33,34]. Radical resection remains the only potentially curative treatment for ICC, with two primary surgical options: AR and NAR. Over 30 years ago, Muccuchi *et al*. introduced the concept of AR[14].

Theoretically, the AR involves removing the liver segment affected by the tumor and the corresponding portal vein area, so it has more advantages in eradicating small liver metastases[35,36]. In contrast, NAR focuses on removing the tumor while preserving more healthy liver tissue, thereby reducing surgical risks[17,37]. Both approaches have their merits and limitations, and numerous studies on HCC have suggested that AR provides better prognostic outcomes compared to NAR[38–40]. However, significant differences exist between ICC and HCC in terms of tumor origin, tumor biological behavior, and etiology, raising the question: Can AR also bring better outcomes for ICC patients? This question warrants exploration. Currently, the choice between AR and NAR for ICC is still debated, as the limited studies available have not reached a consensus[16–18]. The low incidence of ICC, conducting large-scale, multicenter studies is challenging. To our knowledge, this meta-analysis is the first to systematically compare the perioperative safety and long-term survival outcomes between AR and NAR in ICC patients.

To ensure the rigor and completeness of results, we separately summarized the relevant outcome indicators for the entire cohort (before PSM) and the PSM cohort. After PSM, the baseline characteristics between the AR and NAR groups were balanced, making the results more reliable. The final analysis showed no significant differences between the AR and NAR groups in terms of operative time, intraoperative blood loss, perioperative complications, and postoperative hospital stay. However, the AR group demonstrated a significant improvement in OS and DFS for ICC, particularly in DFS, where the AR group showed more stable outcomes at 1, 3, and 5 years in both the entire cohort and PSM cohort compared to the NAR group. Although the statistical significance of the differences in 1-year and 3-year OS between the AR and NAR groups varied slightly before and after PSM, the overall trend still indicated better OS in the AR group. Potential factors such as the small number of included studies and inherent heterogeneity among them may have weakened the observed effectiveness of AR. We attempted to identify sources of heterogeneity through sensitivity analysis and subgroup analysis, ultimately proving the robustness of our results.

Given the variability in results across different studies, some researchers suggest that only specific subgroups of ICC patients may benefit from AR. Subgroup analyses have been conducted to compare the efficacy of AR and NAR in various patient categories, such as those with cirrhosis, differing tumor sizes, Child-Pugh grades, tumor stages, and lymph node involvement[11,17]. After data extraction, we specifically summarized the outcomes of tumor size subgroups that could be pooled. The results showed that AR provided prognostic benefits for patients with tumors larger than 5 cm, while no significant survival benefit was observed for patients with tumors ≤ 5 cm. These findings are valuable for preoperative clinical decision-making and avoid unnecessary anatomical resections and minimizing the loss of healthy liver tissue.

Due to inconsistencies in inclusion criteria and variations in baseline characteristics, such as cirrhosis, liver function stage, tumor number, and postoperative adjuvant therapy, biases may affect the final pooled results. To address this, our meta-analysis also summarized results for the PSM cohort, providing preliminary confirmation that AR can offer survival benefits in terms of DFS and OS for ICC patients. However, the broader resection required for AR involves considerations such as residual liver volume, liver function, tumor stage, and tumor distribution, which may limit its clinical application[41,42]. The decision-making of AR still needs to be based on the individual patient's condition. It is not difficult to find that in the cohort before PSM, in most studies[11,16–18,30], the proportion of cirrhosis patients in the NAR group is higher than that in the AR group. This may also be due to the higher requirements of AR for liver function and residual liver volume, and patients with cirrhosis have a smaller tolerable resection range, then have to choose NAR resection. Additionally, besides considering residual liver volume, achieving an adequate surgical margin remains a crucial factor in liver resection. Inadequate margins are significantly associated with early tumor recurrence and worse OS[43–45]. Studies have shown that patients with wider margins have better prognoses compared to those with narrower margins[46]. Obtaining sufficient margins often necessitates the removal of more liver tissue, making AR theoretically more likely to achieve this compared to NAR. Consequently, larger tumors may be more suitable for AR, as choosing NAR to preserve more normal liver tissue could result in inadequate margins. This likely explains why AR showed better prognoses than NAR in the subgroup analysis of tumors larger than 5 cm. While for smaller tumors, NAR might also achieve sufficient margins, diminishing the advantage of AR. Theoretically, the resection range of AR is larger, and the risk of postoperative complications such as liver failure is higher. Multiple studies have also proven this[37,47]. Our study results indicate that in the entire cohort, the risk of complications was higher in the AR group compared to the NAR group ($P = 0.04$), although the difference was not statistically significant after PSM (RR: 1.28, 95% CI: 0.78–2.10, $P = 0.33$). Studies[48] have shown that postoperative complications are associated with poorer long-term outcomes, highlighting the need for careful evaluation when choosing between AR and NAR. Overall, our study findings have guiding significance for clinical decision-making. When conditions are appropriate, AR should be considered preferentially over NAR.

Limitations

Despite the strength of our findings, several limitations should be considered. First, the studies included in this meta-analysis vary in design, inclusion and exclusion criteria, and follow-up durations, which may introduce unavoidable heterogeneity. Second, due to the limited availability of relevant research, only seven studies were included in this study. In addition, all included studies were from China. This geographic limitation may be due to the lower incidence rates of ICC in other countries or regions, and the retrospective nature of these studies could introduce bias into the results. Multiple centers, prospective, randomized controlled trials, and studies of other ethnicities are needed to validate these findings and provide more definitive conclusions. Third, the methods used to indirectly estimate hazard ratios (HR) as described by Tierney *et al*.[23] may introduce biases, potentially affecting the accuracy of the results.

Conclusions

Our meta-analysis suggests that AR can improve OS and DFS in ICC patients, but detailed preoperative evaluation is crucial to avoid indiscriminate selection of AR. NAR can also be considered for patients with tumor size ≤ 5 cm.Given the limited and heterogeneous nature of the included studies, prospective randomized controlled trials are needed to further confirm the actual effectiveness of AR or NAR.

Ethical approval

Not applicable.

Consent

Not applicable.

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Author contribution

C.J., Z.-H.Z., and Z.-Y.Q.: study concept and design; C.J. and Z.-H.Z.: acquisition of data; C.J. and G.-M.H.: analysis and interpretation; C.J., Z.-Y.Q, and G.-M.H.: draft the manuscript and preliminary revise; H.-C.W. and J.Z.: analyses and reviewed the manuscript; Y.Z.: study supervision and final approval. All authors read and approved the final manuscript.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: PROSPERO.
2. Unique identifying number or registration ID: CRD4202455 6282.
3. Hyperlink to the registration (must be publicly accessible): https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42024556282.

Guarantor

Hai-Chuan Wang, Jin Zhou, and Yong Zeng.

Data availability statement

The datasets used and/or analyzed in this study are available from the corresponding author upon reasonable request.

Provenance and peer review

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