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Liver resection versus radiofrequency ablation for solitary small hepatocellular carcinoma measuring ≤3 cm: a systematic review and meta-analysis

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Background: Controversy remains regarding liver resection (LR) and radiofrequency ablation (RFA) for patients with single hepatocellular carcinomas (HCCs) measuring 3 cm or less. The purpose of our study was to compare the prognosis between LR and RFA in patients with solitary HCCs ≤3 cm.

Methods: The meta-analysis followed the PRISMA guidelines and the Cochrane Handbook. All RCTs and cohort studies that compared LR versus RFA in patients with solitary HCCs ≤3 cm were comprehensively searched in the PubMed, Cochrane Library, Embase, and Web of Science databases up to 30 January 2024. The primary endpoints were overall survival (OS), recurrence-free survival (RFS), and disease-free survival (DFS).

Results: A total of 6356 patients with solitary HCCs ≤3 cm and 5829 patients with solitary HCCs ≤2 cm from 39 included studies were analyzed (LR = 5759, RFA = 6426). The present meta-analysis of two RCTs showed no statistically significant difference in OS between LR and RFA. However, the meta-analysis of cohort studies revealed that, compared with RFA, LR conferred a superior OS advantage (hazard ratio [HR] = 0.80, 95% confidence interval [CI]: 0.68–0.93, P = 0.005). There was a significant improvement in the DFS rate with LR over RFA (HR = 0.63, 95% CI: 0.49–0.81) and in the RFS rate (HR = 0.65, 95% CI: 0.55–0.76). Compared with RFA, LR resulted in better OS (HR = 0.73, 95% CI: 0.54–0.97), DFS (HR = 0.74, 95% CI: 0.67–0.82), and RFS (HR = 0.71, 95% CI: 0.57–0.90) in patients with a solitary HCC lesion ≤2 cm.

Conclusions: Evidence from cohort studies suggested that in patients with a solitary HCC lesion ≤3 cm, LR is preferable to RFA. Additional RCTs are needed to confirm the validity of this evidence.

Keywords: hepatocellular carcinoma, liver resection, radiofrequency ablation, survival

Introduction

There were close to 800 000 deaths from liver cancer in 2022[1]. Hepatocellular carcinoma (HCC) is the dominant histological subtype of liver malignancy and accounts for approximately 75% of the total liver cancer burden worldwide[2]. The management of HCC involves a multidisciplinary approach that can include surgery, chemotherapy/targeted therapy, and radiation therapies. Surgical intervention continues to be the foremost therapeutic approach for these patients, encompassing a range of options such as liver resection (LR), radiofrequency ablation (RFA), or liver transplantation (LT). The Barcelona Clinic Liver Cancer (BCLC) system was used for tumor staging and to guide treatment strategies[3]. Patients with solitary HCCs ≤2 and 3 cm in size were defined as BCLC 0 and A, respectively. According to the 2022 BCLC guidelines described here, for patients with a solitary HCC≤2 cm, LT is recommended as the primary therapy, with RFA recommended as a secondary treatment option; for patients with a solitary HCC≤3 cm, LR is recommended. LT is an effective treatment for cirrhosis and early-stage tumors because it eliminates the tumor and the cirrhotic tissue

HIGHLIGHTS

- In a meta-analysis of 36 observational studies, liver resection group showed a significant improvement in survival outcomes of patients with hepatocellular carcinoma (HCC) measuring ≤3 cm, compared to radiofrequency ablation. Results were consistent in the propensity score-matched analyses.
- Merging data from 14 observational studies, liver resection exhibited a significant survival benefit on overall survival, disease-free survival, and recurrence-free survival for patients with HCC measuring ≤2 cm and the results were consistent after propensity score matching.

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simultaneously. However, there is an organ shortage and a large number of ineligible patients.

Both LR and RFA are recommended as primary treatment strategies in several international guidelines for solitary small HCC, including the 5th JSH-HCC Guidelines[4], AASLD Practice Guidance[5], and 2022 Chinese clinical guidelines[6]. Analyses were performed for the subgroup of patients with solitary small HCC lesions in three randomized controlled trials (RCTs)[7–9], and the findings did not confirm that LR or RFA was associated with better outcomes. Furthermore, the results of direct comparisons in terms of survival between LR and RFA in patients with single small HCC lesions remain unclear. Wu *et al* reported that, compared with RFA, LR offers the best chance for better recurrence-free survival (RFS)[10]. Li *et al* reported no statistically significant differences in disease-free survival (DFS) between patients who underwent LR and those who underwent RFA[11].

Previous meta-analyses compared the outcomes between LR and RFA in treating small HCCs, but these studies included a heterogeneous population, ranging from solitary nodules <5 cm to up to three nodules with a maximum diameter of <3 cm for each nodule[12,13]. The purpose of this study was to retrieve the available evidence and perform a meta-analysis comparing the prognoses of LR and RFA for solitary small HCCs ≤3 cm to improve the quality of evidence.

Materials and methods

This study was conducted in strict adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[14], and Assessing the Methodological Quality of Systematic Reviews guidelines[15]. The protocol of this meta-analysis was registered on PROSPERO.

Data sources and search strategy

Two reviewers independently conducted a comprehensive search of major databases, including PubMed, Embase, Web of Science, and the Cochrane Library, from database inception to 31 March 2024. We used a combination of the terms "single hepatocellular carcinoma," "early-stage liver cancer," and "early-stage liver cancer" or "radiofrequency ablation." A limit was set on cohort studies that were designed to compare outcomes between RFA and surgical resection for solitary HCCs ≤3 cm, and only English-language articles were included. No restrictions were placed on publication dates or regions during the search.

During the initial screening phase, researchers excluded articles that were obviously not relevant to the research topic by reading their titles and abstracts. The full texts of the articles were screened for eligibility. Any disagreements were resolved through consultation and discussion among all the authors.

Inclusion criteria

Eligible studies were screened on the basis of the following inclusion criteria: (1) study design: the trials compared LR with RFA for the treatment of HCC; (2) the diagnosis of HCC was established on the basis of pathological or clinical findings; (3) the studies included in this meta-analysis focused on solitary HCC, with each lesion having a maximum diameter of 3 cm or less; (4) there was no prior treatment history for HCC; (5) there was no evidence of extrahepatic tumor metastasis or macrovascular invasion; (6) there was no concomitant malignant disease other than HCC; (7) the patients were all aged 18 years or older; and (8) the evaluation of treatment outcome endpoints was conducted via the following standardized definitions: overall survival (OS), DFS, and recurrence-free survival (RFS).

Exclusion criteria

The exclusion criteria were as follows: (1) studies included patients with recurrent HCC; (2) medical records were not available for analysis; and (3) the study types included comments, case reports, reviews, conference abstracts, and letters.

Data extraction

Two authors independently extracted relevant study characteristics and data via a data extraction form. The following data were recorded: baseline information (author, year, location, study period, study design), participant characteristics (number of patients, age, sex, etiology of liver disease, Child–Pugh score), tumor size, and tumor location. We subsequently extracted hazard ratios (HRs) with 95% confidence intervals (CIs) associated with the primary outcomes (OS, DFS, and RFS). We resolved any disagreements in the opinion of the data extracted through discussion. If the HR and 95% CI could not be directly obtained, they were estimated from Kaplan–Meier curves[16].

Quality assessment

The risk of bias of the included trials was assessed in accordance with guidelines from the Cochrane Handbook for Systematic Reviews of Interventions[17]. We used the Newcastle–Ottawa scale[18], which is a nine-point scale comprising three items, patient selection, study group comparability, and outcome, for retrospective cohort studies to assess study quality. Studies scoring 7–9 points were considered to have a low risk of bias.

Statistical analysis

The primary endpoints of the meta-analysis were OS, RFS, and DFS. RevMan software (version 5.3, Cochrane Collaboration) was used to calculate the HR and 95% CI in this meta-analysis. Heterogeneity was evaluated by the Cochran Q statistic and I^2 test. If the P-value of Cochran's Q statistic was less than or equal to 0.10, heterogeneity was present. A low inconsistency was indicated by an I^2 statistic of less than 25%. A value of 25%–75% indicated moderate inconsistency, and a value greater than 75% indicated high inconsistency among studies. When statistical heterogeneity was evident, a random effects model (Cochrane Handbook) was adopted. When this did not occur, a fixed-effects model was adopted.

Publication bias

Publication bias was assessed for the primary endpoints via funnel plots. Funnel plot asymmetry was estimated by Egger regression, with a P-value <0.05 indicating asymmetry. Funnel

plots and Egger regression were generated with RevMan 5.3 and Stata 15.1 software, respectively.

Results

Included studies and study characteristics

The PRISMA flow chart describing the inclusion process is illustrated in Figure 1. We initially retrieved a total of 10 225 records from the abovementioned databases: PubMed (4851 records), Embase (213 records), Web of Science (4991 records), and the Cochrane Library (170 records). After duplicate removal, 5013 records were further reviewed. Altogether, 4162 records were excluded at the title/abstract level, and 748 were summarized literature (e.g. review, report and commentaries) and therefore excluded.

The full-text articles of the remaining records were retrieved and assessed for inclusion by all reviewers. During further screening. 64 studies were excluded because they reported data on either single HCCs ≤5 cm in diameter or multiple HCCs ≤5 cm in diameter, with the inability to analyze data specifically for single HCCs <3 cm on the basis of the original text (60 retrospective studies [RSs]; 4 RCTs).

A total of 6356 patients with solitary HCCs ≤3 cm and 5829 patients with solitary HCCs ≤2 cm from the 39 included studies were analyzed (LR = 5759, RFA = 6426)[7–11,19–52]. No study included patients with vascular invasion or distant metastases. Eight studies[29,34,35,37,40,45,47,52] used laparoscopic or robotic LR in the LR group, and two[37,47] used laparoscopic RFA. Three studies were RCTs [7–9]; the remaining 36 were RSs[10,11,19–52]. The studies included in the meta-analysis were from China[7,8,10,11,24,32,39,42–46,50,52], Korea[21,25–28,30,31,34,37,38,40,49,51], Japan[9,19,20,22,41,48], Italy[23,33,35,47], France[29], and Canada[36]. The Cochrane risk-of-bias tool revealed no high bias in three RCTs[7–9]. The overall quality of the 36 RSs[10,11,19–52] was moderate; was moderate; the Newcastle–Ottawa Scale scores ranged from 7 to 9. A summary of the baseline information of patients in the included studies is presented in Table 1.

A total of 17 studies[11,28,32–35,37–39,42,43,46–51] employed propensity score matching analysis to balance treatment-related characteristics, including patient age, sex, body mass index, race, Child–Pugh class, MELD score, liver function indicators

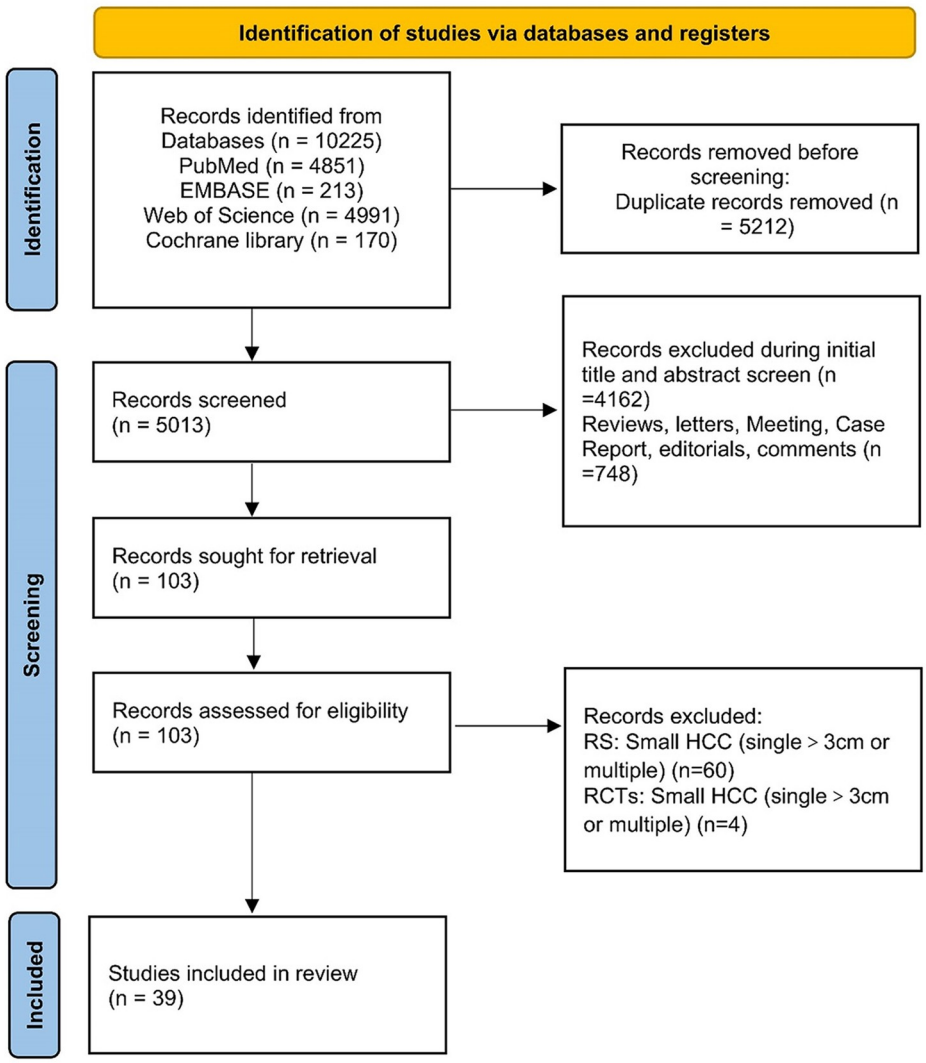

Figure 1. PRISMA diagram showing identification of eligible studies and reasons for exclusion.

Table 1.

Patient demographics and baseline characteristics

Study ID	Country	Study type	No.of patients		Age (year)		Cirrhosis (present), (entire cohort)		HBsAg (positive)		Anti-HCV (positive)		MELD score		CP (A/B/C)		AFP (ng/mL)		NOS
			LR	RFA	LR	RFA	LR	RFA	LR	RFA	LR	RFA	LR	RFA	LR	RFA	LR	RFA	
Hiraoka A *et al*, 2008	Japan	RS	59	105	62.4 ± 10.6	69.4 ± 9.1	NA	NA	NA	NA	44 (74.6%)	80 (77.1%)	NA	NA	54/5/0	79/26/0	427.8 ± 1317.6	114.5 ± 319.5	7
Nishikawa H *et al*, 2011	Japan	RS	69	162	67.4 ± 9.7	68.4 ± 8.7	50 (72.4%)	124 (76.5%)	8 (11.6%)	9 (5.6%)	51 (73.9%)	135 (83.3%)	NA	NA	45/0/0	102/0/0	376.7 ± 1989.8	74.7 ± 181.1	7
Yun WK *et al*, 2011	Korea	RS	215	255	51.7 ± 9.7	57.0 ± 9.9	139 (64.7%)	201 (78.8%)	186 (86.5%)	192 (75.3%)	11 (5.1%)	45 (17.6%)	NA	NA	215/0/0	255/0/0	476.3 ± 1208.1	307.4 ± 1148.8	7
Imai K *et al*, 2013	Japan	RS	101	82	63.3 ± 9.7	67.6 ± 8.5	NA	NA	34 (33.7%)	8 (9.9%)	52 (51.5%)	65 (79.3%)	NA	NA	97/4/0	60/22/0	171.8 ± 586.2	51.0 ± 106.9	7
Pompili M *et al*, 2013	Italy	RS	246	298	67 (41–83)[a]	69 (38–85)[a]	46 (18.6%)	40 (13.8%)	24 (9.8%)	32 (10.7%)	144 (58.5%)	213 (71.5%)	8 (6–16)[a]	8 (6–18)[a]	246/0/0	298/0/0	9 (1–9000)[a]	29 (2–2200)[a]	9
Wong KM *et al*, 2013	China	RS	46	36	55.1 ± 12	63.5 ± 13	NA	NA	18 (39%)	13 (36%)	26 (57%)	23 (64%)	NA	NA	46/0/0	36/0/0	204.0 ± 733	95.1 ± 174	8
Kim JM *et al*, 2014	Korea	RS	66	67	55 (27–76)[a]	59 (39–85)[a]	NA	NA	51 (78.5%)	44 (65.7%)	4 (6.2%)	17 (25.4%)	NA	NA	NA	NA	28.5 (1–7102)[a]	20.0 (2–5652)[a]	7
Yang HJ *et al*, 2014	Korea	RS	52	79	55.7 ± 10.6	57.2 ± 9.2	29 (55.8%)	64 (81.0%)	34 (65.4%)	56 (70.9%)	6 (11.5%)	18 (22.8%)	8.3 ± 2.2	9.4 ± 2.9	50/2/0	68/11/0	NA	NA	8
Kang TW *et al*, 2015	Korea	RS	142	438	57.8 ± 11.7	61.6 ± 13.72	91 (64.1%)	355 (81.1%)	120 (84.5%)	324 (74.0%)	10 (7.1%)	64 (14.6%)	NA	NA	135/7/0	367/71/0	22.2 (1.0–5517.3)[a]	15.4 (1.0–3772.5)[a]	9
Kim GA *et al*, 2016	Korea	RS[b]	273	331	54.4 ± 8.5	5.73 ± 10.3	163 (59.7%)	189 (57.1%)	222 (81.3%)	246 (74.3%)	18 (6.6%)	40 (12.1%)	NA	NA	273/0/0	331/0/0	NA	NA	9
Vitali GC *et al*, 2016	France	RS	45	60	61.4 (31–84)[a]	67.3 (47–83)[a]	NA	NA	NA	NA	NA	NA	NA	NA	40/5/0	45/15/0	NA	NA	7
Lee S *et al*, 2018	Korea	RS	182	101	53.8 ± 9.2	57.0 ± 10	88 (48.4%)	71 (70.3%)	156 (85.8%)	75 (74.3%)	13 (7.1%)	15 (14.8%)	7 (7–8)[a]	8 (8–10)[a]	NA	NA	35.4 (7.2–261.5)[a]	15.0 (5.9–90.5)[a]	8
Cha DI *et al*, 2020	Korea	RS	145	178	53.3 ± 10	56.75 ± 9.5	NA	NA	123 (84.8%	131 (73.6%)	12 (8.3%)	27 (15.2%)	NA	NA	131/14/0	156/22/0	376.5 ± 1199.0	102.2 ± 226.3	8
Zheng L *et al*, 2020	China	RS[b]	332	379	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	7
Delvecchio A *et al*, 2021	Italy	RS[b]	37	40	74.98 (70–83)[a]	74.5 (70–87)[a]	37 (100%)	40 (100%)	10 (27%)	5 (12%)	19 (50%)	21 (53%)	6 (6–16)[a]	8 (6–15)[a]	30/7/0	37/3/0	12.5 (2–3900)[a]	5 (1–1988)[a]	8
Lee DH *et al*, 2021	Korea	RS[b]	251	315	57.5 ± 9.3	60.8 ± 9.6	NA	NA	196 (78.1%)	234 (74.3%)	21 (8.4%)	34 (10.8%)	NA	NA	251/0/0	315/0/0	218.4 ± 904.2	72.9 ± 211.6	9
Conticchio M *et al*, 2022	Italy	RS[b]	86	98	75.7 (69.5–86.5)[a]	75 (70–89)[a]	86 (100%)	98 (100%)	20 (23%)	6 (6%)	49 (57%)	56 (57%)	6 (6–13)[a]	8 (6–18)[a]	77/9/0	84/14/0	NA	NA	8
Ivanics T *et al*, 2022	Canada	RS	25	83	64 (55–67)[a]	60 (56–66)[a]	NA	NA	17 (68%)	46 (55%)	7 (28%)	22 (27%)	7 (6–8)[a]	7 (6–8)[a]	25/0/0	79/4/0	700 (400–9200)[c]	600 (400–4200)[c]	7
Ko SE *et al*, 2022	Korea	RS[b]	60	29	55.8 ± 9	60 ± 9.8	NA	NA	42 (70.0%)	18 (62.1%)	4 (6.7%)	2 (6.9%)	NA	NA	NA	NA	313.1 ± 823.2	13.9 ± 25.0	9
Lee J *et al*, 2022	Korea	RS[b]	232	159	>65 (40%)[d]	>65 (49%)[d]	116 (50.00%)	109 (68.55%)	197 (84.9%)	105 (66.0%)	10 (4.31%)	20 (12.58%)	NA	NA	232/0/0	159/0/0	129.2 ± 357.0	129.2 ± 357.0	8
Zhang C *et al*, 2022	China	RS[b]	156	95	53.97 ± 9.99	58.28 ± 10.04	NA	NA	140 (89.7)	6 (80.0)	11 (7.1%)	13 (13.7%)	NA	NA	156/0/0	95/0/0	683.34 ± 2861.71	NA	9
Kang M *et al*, 2023	Korea	RS	36	40	57.8 ± 11.70	61.6 ± 13.72	NA	NA	30 (83.3%)	31 (77.5%)	0 (0%)	1 (2.5%)	7.36 ± 1.7	8.55 ± 2.05	NA	NA	199.6 ± 415.6	29.4 ± 68.2	7

(*Continues*)

Table 1.

(Continued).

Study ID	Country	Study type	No.of patients		Age (year)		Cirrhosis (present), (entire cohort)		HBsAg (positive)		Anti-HCV (positive)		MELD score		CP (A/B/C)		AFP (ng/mL)		NOS
			LR	RFA	LR	RFA	LR	RFA	LR	RFA	LR	RFA	LR	RFA	LR	RFA	LR	RFA	
Takayama T *et al*, 2010	Japan	RS	1235	1315	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1103/132/0	1014/301/0	NA	NA	7
Hung HH *et al*, 2011	China	RS[b]	50	66	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	9
Wang JH *et al*, 2012	China	RS[b]	52	91	NA	NA	NA	NA	34 (65.4%)	44 (48.4%)	14 (26.9%)	49 (53.8%)	NA	NA	NA	NA	NA	NA	9
Peng ZW *et al*, 2012	China	RS	74	71	51.5 ± 12.1	53.1 ± 12.1	62 (83.8%)	58 (81.7%)	69 (97%)	70 (95%)	NA	NA	NA	NA	58/0/0	62/0/0	NA	NA	7
Song J *et al*, 2016	China	RS	33	40	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	78/0/0	76/2/0	NA	NA	9
Liu PH *et al*, 2016	China	RS[b]	109	128	60 ± 13	64 ± 12	NA	NA	65 (60%)	62 (48%)	37 (34%)	55(43%)	7.8 ± 1.3	8.4 ± 2.5	NA	NA	145 ± 262	92 ± 247	9
Santambrogio R *et al*, 2016	Italy	RS[b]	76	76	66 ± 9	68 ± 8	76 (100%)	76 (100%)	NA	NA	NA	NA	8 (7–9)[a]	8 (7–10)[a]	76/0/0	76/0/0	58.9 ± 183	101.6 ± 498	9
Takayasu K *et al*, 2018	Japan	RS[b]	176	491	NA	NA	NA	NA	24 (13%)	46 (9%)	116 (65%)	401 (89%)	NA	NA	151/25/0	394/97/0	NA	NA	9
Kim TH *et al*, 2019	Korea	RS[b]	52	102	56.4 ± 9.1	61.6 ± 10.3	36 (69.2%)	92 (90.2%)	38 (73.1%)	59 (57.8%)	6 (11.5%)	12 (11.8%)	7 (7–8)[a]	8 (7–10)[a]	52/0/0	102/0/0	19.1 (4.3–135.0)[a]	16.0 (4.8–77.9)[a]	8
Wang G *et al*, 2019	China	RS[b]	192	81	52 (42–60)[a]	52 (45–62)[a]	NA	NA	177 (92.2%)	75 (92.6%)	NA	NA	NA	NA	176/16/0	62/19/0	11 (4–349)[a]	33 (6–348)[a]	9
Chu HH *et al*, 2019	Korea	RS[b]	631	577	54 (29–77)[a]	58 (29–87)[a]	589 (93.3%)	528 (91.5%)	566 (89.7%)	456 (79%)	31 (4.9%)	68 (11.8%)	NA	NA	631/0/0	577/0/0	13.8 (4.7–112)[a]	21.2 (5.1–163)[a]	9
Lin CH *et al*, 2020	China	RS	36	39	NA	NA	NA	NA	25 (69.44%)	25 (64.10%)	9 (25%)	17 (43.59%)	NA	NA	36/0/0	39/0/0	1118.4 ± 2512.31[e]	172.7 ± 345.81[e]	8
Wu CC *et al*, 2021	China	RS	83	73	NA	NA	40 (66.7%)	47 (81.0%)	26 (31.3%)	20 (27.4%)	33 (39.8%)	31 (42.5%)	NA	NA	79/4/0	66/7/0	NA	NA	8
Li YC *et al*, 2021	China	RS[b]	103	85	57 (23–82)[a]	62 (34–81)[a]	54 (52.4%)	61 (71.8%)	51 (49.5%)	35 (41.2%)	49 (47.6%)	42 (49.4%)	NA	NA	100/3/0	79/6/0	NA	NA	9
Chen MS *et al*, 2006	China	RCT	42	37	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	42/0/0	37/0/0	NA	NA	NA
Huang J *et al*, 2010	China	RCT	45	57	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Takayama T *et al*, 2021	Japan	RCT	135	136	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

RS, retrospective study; RCT, randomized controlled trial; SR, surgical resection; RFA, radiofrequency ablation; anti-HCV, antibody to hepatitis C virus; HBsAg, hepatitis B virus surface antigen; CP, Child–Pugh classification; MELD, model for end stage liver disease; AFP, alpha-fetoprotein; NOS, Newcastle–Ottawa Scale; NA, data were missing.

[a]Data were presented as median (range).

[b]Propensity score-matched.

[c]Data were presented as median (interquartile range).

[d]The percentage of people over 65 years old.

[e]The unit of data is μ/L.

(serum albumin, total bilirubin levels, aspartate aminotransferase, alanine aminotransferase), platelet count and tumor markers (serum alpha-fetoprotein and DCP level), and tumor size.

Survival outcomes of patients with solitary HCCs ≤3 cm based on RCT data

Few RCTs have compared survival between LR and RFA in patients with solitary HCC. The study population consisted of patients with HCC diameters ≤3 cm and ≤3 HCC nodules in the RCT of Takayama *et al*[9]. In the study of Huang *et al*, the study population consisted of patients with a single HCC ≤5 cm or up to 3 nodules, each <3 cm[8]. The participants in the RCT of Minshan *et al*[7] consisted of patients with a solitary HCC smaller than 5 cm in diameter.

First, we reported the pooled OS from two RCTs[7,8]. There was no significant difference in OS between the LR group and the RFA group (HR = 0.73, 95% CI: 0.26–2.05, $P = 0.55$), with no heterogeneity ($I^2 = 0\%$, $P = 0.90$) (Supplemental Digital Content Figure 1, available at: http://links.lww.com/ISJP/A6). A meta-analysis of RFS was not possible because only one RCT reported RFS[9]. In this RCT[9], the median (range) post-enrollment follow-up duration was 5.04 (0.36–9.49) years for the surgery group and 4.99 (0.00–8.70) years for the RFA group. There were 135 patients with solitary HCC lesions ≤3 cm who underwent surgical treatment, among whom 72 had postoperative recurrence; and there were 136 patients with solitary HCC lesions ≤ 3 cm who received RFA treatment, among whom 74 had postoperative recurrence. Prognostic analysis demonstrated no significant difference in RFS between the two groups of patients.

Survival outcomes of patients with solitary HCCs ≤3 cm based on RSs data

Overall survival

Propensity score matching was employed in 17 included RSs[11,28,32–35,37–39,42,43,46–51] to reduce confounders of treatment allocation, and the remaining 19 included RSs[10,19–27,29–31,36,40,41,44,45,52] that did not. Thus, the pooled data from the entire cohort of all the RSs[10,11,19–27,29–33,35–37,39,40,42,44,46–52] indicated that the patients in the LR group had better OS than those in the RFA group (HR = 0.80, 95% CI: 0.68–0.93, $P = 0.005$), with high heterogeneity ($I^2 = 58\%$, $P < 0.0001$) (Fig. 2).

Next, we assessed the OS of patients in all propensity score-matched cohorts. The pooled data from 14

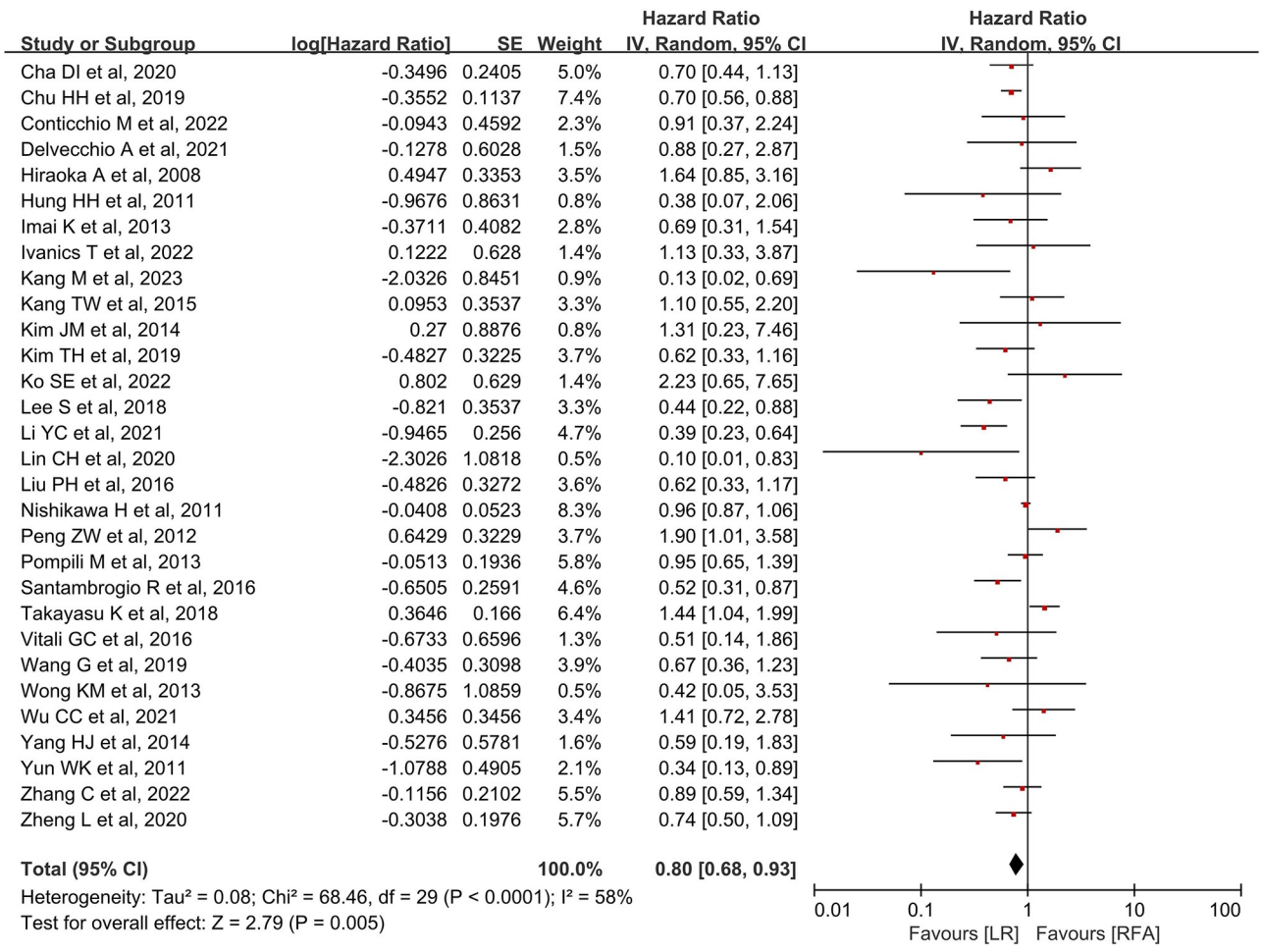

Figure 2. Forest plot for hazard ratios of overall survival (OS) of patients with solitary HCC ≤3 cm.

RSs[11,23,30,32,33,35,38,39,42,46,48–51] revealed a longer OS in the LR group (HR = 0.82, 95% CI: 0.72–0.95, P = 0.006), with low heterogeneity (I^2 = 23%, P = 0.21) (Supplemental Digital Content Figure 2, available at: http://links.lww.com/ISJP/A6).

Disease-free survival

Twelve RSs[11,20,21,28,31,34,37,39,41,43,50,52] reported data for the meta-analysis of DFS. A random-effects model was used to pool those RSs and demonstrated that LR was associated with better DFS (HR = 0.63, 95% CI: 0.49–0.81, P = 0.0003), with high heterogeneity (I^2 = 81%, P < 0.00001) (Fig. 3).

A meta-analysis encompassing six propensity score-matched cohorts[11,27,33,35,43,50] revealed that SR significantly outperforms RFA in terms of RFS (HR = 0.64, 95% CI: 0.48–0.85, P = 0.002), with low heterogeneity (I^2 = 0%, P = 0.86) (Supplemental Digital Content Figure 3, available at: http://links.lww.com/ISJP/A6).

Recurrence-free survival

Thirteen RSs[10,20,21,28,31,34,37,39,44–46,48,51] reported data for the meta-analysis on RFS. A random-effects model was used to pool those data and demonstrated that LR was associated with better DFS (HR = 0.65, 95% CI: 0.55–0.76, P < 0.00001), with moderate heterogeneity (I^2 = 52%, P = 0.02) (Fig. 4).

The RFS was also evaluated in eight propensity score-matched cohorts[28,34,37–39,46,48,51]. RFS was reported to be longer in the LR group than in the RFA group (HR = 0.64, 95% CI: 0.57–0.71, P < 0.00001), with low heterogeneity (I^2 = 0%, P = 0.52) (Supplemental Digital Content Figure 4, available at: http://links.lww.com/ISJP/A6).

Survival outcomes of patients with solitary HCCs ≤2 cm

Overall survival

Fourteen RSs[10,11,22,23,32,42,44,46–52] reported the prognostic data on patients with solitary HCCs ≤2 cm. On the basis of the results of the meta-analysis, patients with solitary HCCs ≤2 cm in size who received LR versus RFA had better OS (HR = 0.73, 95% CI: 0.54–0.97, P = 0.03), with high heterogeneity (I^2 = 69%, P < 0.0001) (Supplemental Digital Content Figure 5, available at: http://links.lww.com/ISJP/A6).

Ten propensity score-matched cohorts[11,23,32,38,42,46,48–51] provided information on OS. Compared with the RFA group, the LR group had a longer OS (HR = 0.78, 95% CI: 0.67–0.91, P = 0.002), with low heterogeneity (I^2 = 6%, P = 0.38) (Supplemental Digital Content Figure 6, available at: http://links.lww.com/ISJP/A6).

Disease-free survival

DFS in patients with a solitary HCC lesion ≤2 cm was reported in six RSs[11,22,41,43,50,52]. The pooled data indicated that patients in the LR group had a better DFS (HR = 0.74, 95% CI: 0.67–0.82, P < 0.00001), with low heterogeneity (I^2 = 0%, P = 0.47) (Supplemental Digital Content Figure 7, available at: http://links.lww.com/ISJP/A6).

Three RSs provided data after propensity score matching, and the pooled result revealed that LR was associated with increased RFS (HR = 0.67, 95% CI: 0.46 -0.99, P = 0.04), with no heterogeneity (I^2 = 0%, P = 0.84) (Supplemental Digital Content Figure 8, available at: http://links.lww.com/ISJP/A6).

Recurrence-free survival

Six RSs[10,44–46,48,51] provided information on RFS. Patients with solitary HCCs ≤2 cm in size in the LR group had longer RFS than those in the RFA group (HR = 0.71, 95% CI: 0.57–0.90; P = 0.004), with high heterogeneity (I^2 = 50%, P = 0.07) (Supplemental Digital Content Figure 9, available at: http://links.lww.com/ISJP/A6).

A meta-analysis encompassing three propensity score-matched cohorts[46,48,51] revealed that LR significantly outperforms RFA in terms of RFS (HR = 0.61, 95% CI: 0.46–0.80, P = 0.0005), with low heterogeneity (I^2 = 56%, P = 0.10) (Supplemental Digital Content Figure 10, available at: http://links.lww.com/ISJP/A6).

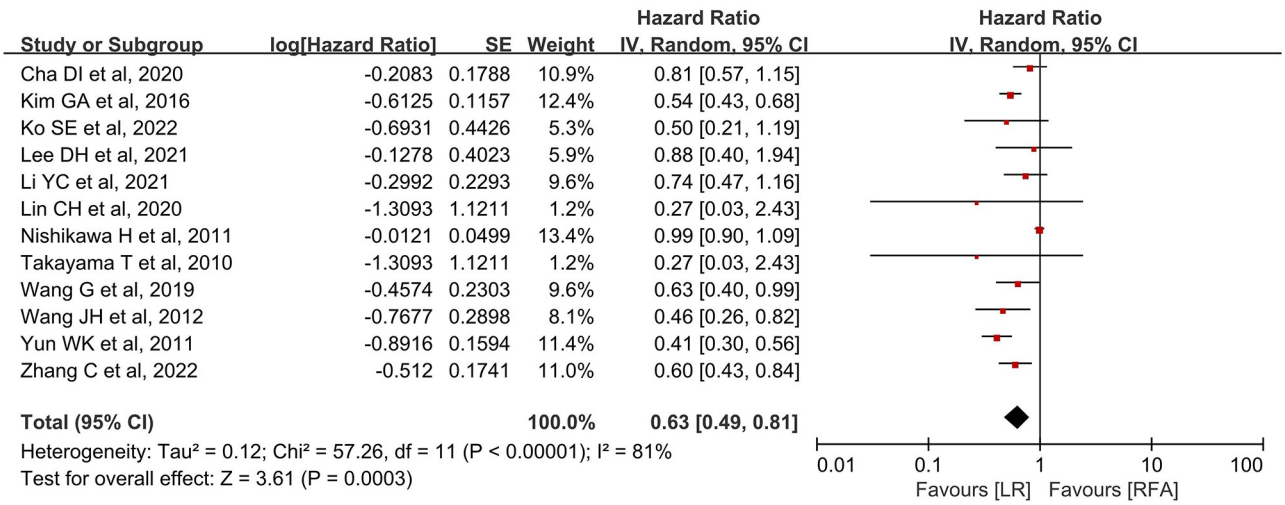

Figure 3. Forest plot for hazard ratios of disease-free survival (DFS) of patients with solitary HCC ≤3 cm.

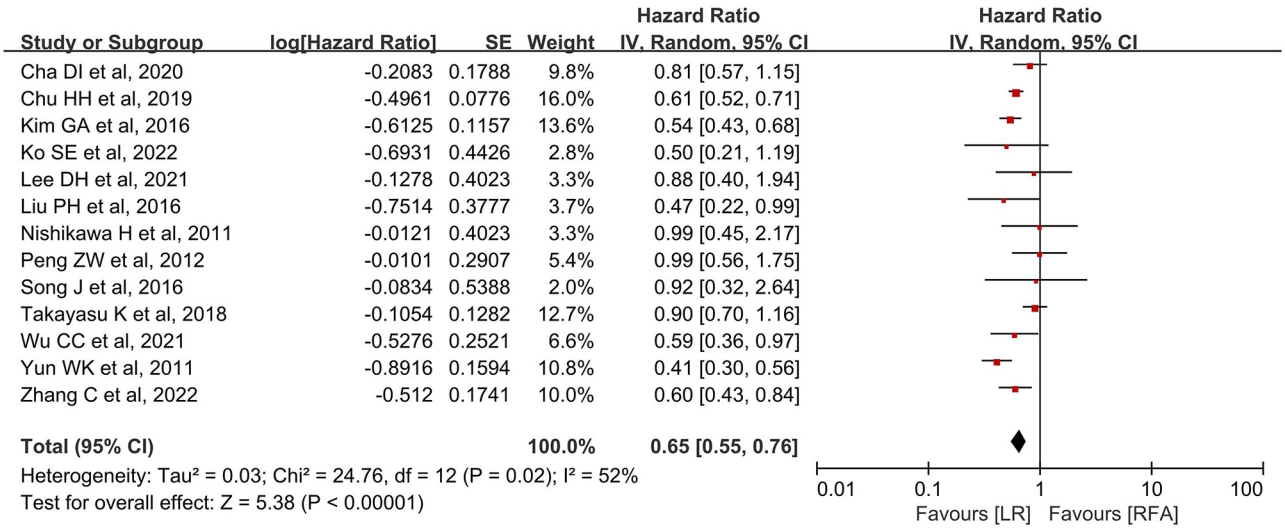

Figure 4. Forest plot for hazard ratios of recurrence-free survival (RFS) of patients with solitary HCC ≤3 cm.

Sensitivity analysis and publication bias

In the present meta-analysis, the funnel plots for survival outcomes of patients with solitary HCCs ≤3 cm from all propensity score-matched cohorts showed basic symmetry (Fig. 5). No significant publication bias was further determined by Egger's test, and all *P* values were greater than 0.05.

Discussion

To our knowledge, this meta-analysis included the largest number of studies comparing the prognosis between patients with solitary HCCs ≤3 cm who underwent LR and those with RFA. Using the results of 36 RSs, we found that, compared with RFA, LR offers a better prognosis for patients with a solitary HCC lesion≤3 cm, including longer OS, DFS, and RFS. A total of 7 RCTs[7–9,53–56] on small HCC lesions were identified through literature screening, among which three provided data on single tumors ≤3 cm. Therefore, only the data from these three studies were analyzed in this research. In addition, the results of the subgroup analysis (solitary HCC ≤2 cm) suggested that LR at a very early stage (according to the BCLC system) provides a better prognosis, including longer OS, DFS, and RFS.

Propensity score matching is a method that can reduce bias and help ensure the homogeneity of baseline data between groups[57]. Propensity score matching can achieve reasonable matching between two groups of patients, yielding results similar to those of RCTs. Consequently, we concurrently analyzed the outcomes after propensity score matching to minimize the intergroup differences in variables. In these studies, propensity score matching was performed on the basis of demographic characteristics (such as age, sex, and body mass index) and preoperative features (such as liver function indices and tumor location). Despite the varying number of variables matched across these studies, the meta-analysis results indicate that propensity score matching has reduced the heterogeneity of the combined outcomes and that the trends observed are consistent with those without matching. As propensity score matching reduces the heterogeneity among the included studies, we believe that our research findings are more convincing than those of previous studies.

HCC is the main subtype of primary liver cancer and has a poor prognosis. Surgical resection remains the best opportunity for a cure, and only relatively few patients are suitable for surgical treatment[58]. According to the BCLC staging system and treatment guidelines, transplantation is the recommended

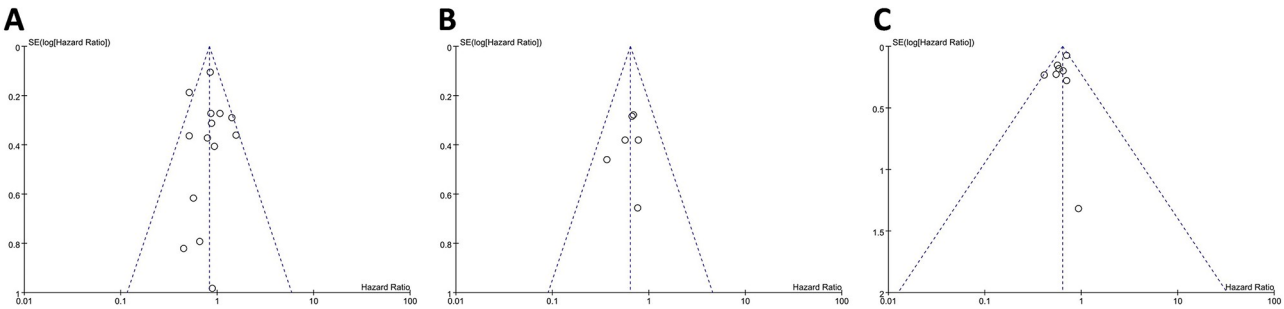

Figure 5. Funnel plots for comparison of all propensity score-matched cohorts at patients with solitary small HCC measuring ≤3 cm. (A) OS. (B) DFS. (C) RFS.

treatment of choice for patients with BCLC early-stage disease[3]. When these patients are not given priority for LT, LR or RFA is often further performed. The long-term DFS and OS of patients with a solitary HCC lesion ≤3 cm are important when optimal treatment strategies are selected. The previous Cochrane meta-analysis by Majumdar *et al* included four studies and revealed no benefit of LR or RFA on the survival of patients with early-stage HCC[59]. One meta-analysis revealed that LR and RFA had similar effects on long-term survival in patients with very early-stage HCC[60]. One retrospective cohort study reported that long-term OS was not significantly different between LR and RFA in patients with solitary HCCs ≤3 cm[39]. However, our meta-analysis including two RCTs revealed that the LR improved the OS of patients with solitary HCCs ≤3 cm and solitary HCCs ≤2 cm. This seemingly conflicts with conclusions drawn by previous studies. Previous studies have reported that the preoperative neutrophil–lymphocyte ratio and the presence of microvascular invasion are associated with long-term prognosis after surgical resection in patients with single and <5 cm HCC lesions[61,62]. Therefore, the impact of pretreatment liver function and tumor marker levels on the prognosis of patients with solitary HCCs ≤3 cm receiving different treatment regimens requires further analysis.

RFA is less invasive than LR and has great potential for local tumor control with minimal damage to healthy parenchyma[63]. As a result, hospital length of stay and complication rates are also significantly lower than those of surgical resection[64]. RFA is limited by an increased rate of local recurrence because of incomplete ablation[55]. The efficacy of RFA can be affected by a variety of factors. A correlation between ablation margins and local tumor progression was noted for the first time by Kei *et al*[65]. The geometry of the local ablation zone and tumor location, such as the peritumoral ablative margin, adjacent blood vessel, and subcapsular location, are closely related to local tumor progression[66]. Tissue perfusion and vascular-mediated cooling can lead to a reduced thermal effect of local ablation[66].

For patients with HCC who fulfill the Milan criteria and exhibit no vascular invasion, transplantation or LR are deemed the optimal therapeutic modalities[67]. In a prospective randomized 168-patient trial, curative resection of small HCC lesions achieved a 3-year survival rate of 74.8%[55]. The advantage of LR over RFA is that LR can completely remove the lesions where peritumoral micrometastases and microscopic vascular thromboses are detected[68]. Our analysis of LR and RFA treatments for solitary small HCC lesions (≤3 cm/2 cm) indicated that LR was associated with significantly longer DFS and RFS. The low relapse rate of HCC may be attributed to total excision of the tumor. In addition, as the surgical technique has improved over time, the incidence of surgical complications has decreased. Several procedures have been proposed to improve the accuracy and safety of LR, such as real-time visualization by indocyanine green, computer-assisted surgical navigation, and robot-assisted surgery[69,70]. Additionally, postoperative pathological analysis provides the necessary information to direct adjuvant therapy patients with a high risk of recurrence[71]. However, it is not easy to obtain complete pathological specimens after RFA.

The findings of this meta-analysis should be interpreted with due caution, considering multiple factors that necessitate prudence. First, the number of RCTs included in this study was significantly lower than that of RSs, and the results from the RCT subgroup analysis still require further evaluation through more well-defined and prospective clinical trials. Second, most of the data included in the present study were extracted from RSs. Despite the use of the propensity score matching method, deviations could not be eliminated as they can be with RCTs. Due to the absence of data regarding patients' liver function, oncological markers, and other pertinent parameters, a further subgroup analysis was not feasible. Third, the types of surgical approaches of the included studies included open, laparoscopic, or robotic surgery. Furthermore, RFA was performed via percutaneous, laparoscopic approaches. It has not been determined how heterogeneity influences the results. We expect that more RCTs will be designed to guide clinical treatment.

Conclusion

In conclusion, this meta-analysis revealed that the LR provided better OS, DFS, and RFS for patients with solitary small HCCs measuring ≤3 cm. However, these findings should be interpreted with caution because of the limited number of eligible RCTs included in this meta-analysis. Thus, large-scale, multicenter studies and well-designed RCTs on this topic are needed for further evaluation.

Ethical approval

Not applicable.

Consent

Not applicable

Sources of funding

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Author contributions

M.Y., G.L., T.S, and W.W. designed the study and performed the literature search, study selection, data extraction, and statistical analyses. M.Y., G.L., and Y.W. performed the statistical analyses. G.L., K.C., and M.Y. wrote the first draft of the manuscript. All authors contributed to the interpretation of the data and critically reviewed the manuscript.

Conflicts of interest disclosure

The authors disclose no potential conflicts of interest.

Research registration unique identifying number (UIN)

The protocol of this meta-analysis was registered on PROSPERO with a registration number of CRD42024559003.

Guarantor

Wentao Wang.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Data availability statement

The data sets used during the current study are available from the corresponding author on a reasonable request.

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