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SYSTEMATIC REVIEWS

Comparative effectiveness of several adjuvant therapies after hepatectomy for hepatocellular carcinoma patients with microvascular invasion

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Abstract

BACKGROUND

For resectable hepatocellular carcinoma (HCC), radical hepatectomy is commonly used as a curative treatment. However, postoperative recurrence significantly diminishes the overall survival (OS) of HCC patients, especially with microvascular invasion (MVI) as an independent high-risk factor for recurrence. While some studies suggest that postoperative adjuvant therapy may decrease the risk of recurrence following liver resection in HCC patients, the specific role of adjuvant therapies in those with MVI remains unclear.

AIM

To conduct a network meta-analysis (NMA) to evaluate the efficacy of various adjuvant therapies and determine the optimal adjuvant regimen.

METHODS

A systematic literature search was conducted on PubMed, EMBASE, and Web of Science until April 6, 2023. Studies comparing different adjuvant therapies or comparing adjuvant therapy with hepatectomy alone were included. Hazard ratios (HRs) with 95% confidence intervals were used to combine data on recurrence free survival and OS in both pairwise meta-analyses and NMA.

RESULTS

Fourteen eligible trials (2268 patients) reporting five different therapies were included. In terms of reducing the risk of recurrence, radiotherapy (RT) [HR = 0.34 (0.23, 0.5); surface under the cumulative ranking curve (SUCRA) = 97.7%] was found to be the most effective adjuvant therapy, followed by hepatic artery infusion chemotherapy [HR = 0.52 (0.35, 0.76); SUCRA = 65.1%]. Regarding OS improvement, RT [HR: 0.35 (0.2, 0.61); SUCRA = 93.1%] demonstrated the highest effectiveness, followed by sorafenib [HR = 0.48 (0.32, 0.69); SUCRA = 70.9%].

CONCLUSION
Adjuvant therapy following hepatectomy may reduce the risk of recurrence and provide a survival benefit for HCC patients with MVI. RT appears to be the most effective adjuvant regimen.

Key Words: Hepatocellular carcinoma; Adjuvant therapy; Network meta-analysis; Transarterial chemoembolization; Hepatic artery infusion chemotherapy; Radiotherapy; Sorafenib

Core Tip: This study represents the inaugural network meta-analysis examining the efficacy of postoperative adjuvant therapies in individuals with hepatocellular carcinoma featuring microvascular invasion who underwent curative hepatectomy. Comparing four distinct postoperative adjuvant strategies-transarterial chemoembolization, sorafenib, hepatic artery infusion chemotherapy, and radiotherapy (RT)-we assessed their impact on recurrence free survival and overall survival (OS). The outcomes unveiled that RT emerges as the most effective adjuvant therapy, significantly reducing recurrence risk and extending OS.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common malignant tumor in the world and ranks third in terms of worldwide malignant tumor mortality rates in 2020[1]. Curative treatments for HCC include ablation, radical hepatectomy, and liver transplantation. However, ablation is suitable only for early-stage HCC patients, who represent a small percentage of the overall HCC population. Although liver transplantation serves as the optimal treatment for HCC patients, the scarcity of donor organs restricts the availability of this procedure. Therefore, hepatectomy is the most commonly employed curative treatment for resectable HCC. Unfortunately, the 5-year recurrence rate for patients who undergoing hepatectomy ranges from 50% to 70%[2,3].

Recurrence of HCC is associated with several risk factors[4], including single nodule > 5 cm, vascular invasion, and multiple nodules. Among these factors, microvascular invasion (MVI) is an independent risk factor for recurrence. MVI is defined as the presence of cancer cells in the lumen of endothelium-lined vessels, typically in the small branches of the portal and hepatic veins of the paracancerous liver tissue, visible only under the microscope[5]. Previous studies have shown that among HCC patients who underwent hepatectomy, those with MVI had a higher risk of recurrence and shorter overall survival (OS) than those without MVI[6].

Several studies have indicated that adjuvant therapy following curative hepatectomy can prevent recurrence and improve OS in HCC patients with MVI. These postoperative adjuvant therapies include transarterial chemoembolization (TACE)[7], sorafenib[8], hepatic artery infusion chemotherapy (HAIC)[9], and radiotherapy (RT)[10]. However, the existing studies mostly compare individual adjuvant therapy with hepatectomy alone. Direct or indirect comparisons between the various adjuvant therapies are lacking. Therefore, we performed the network meta-analysis (NMA) to compare the relative efficacy of each adjuvant therapy to determine the optimal treatment.

MATERIALS AND METHODS

Our systematic review and NMA were reported according to the PRISMA extension statement for NMA[11]. The protocol was registered on PROSPERO (CRD42023398381).

Search strategy

In this NMA, relevant studies were systematically searched for in PubMed, EMBASE, and the Web of Science up to April 6, 2023, using the terms "hepatocellular carcinoma", "hepatoma", "hepatectomy", "postoperative", "adjuvant", and "microvascular invasion". Detailed search strategies are presented in Table 1. In addition, references listed in published articles that may be relevant to this NMA were manually searched.

Study selection

Included studies were required to meet the following criteria: (1) HCC patients of any age, sex, or race with MVI who had undergone a curative hepatectomy; (2) The intervention including any post-operative adjuvant therapies for hepatectomy; (3) The outcome reporting recurrence free survival (RFS) or OS; and (4) Randomized controlled trials (RCTs),

Table 1 Literature search criteria

Database	Literature search criteria	Number of literatures
PubMed	((microvascular invasion) OR MVI) AND ((“Carcinoma, Hepatocellular”[Mesh]) OR (hepatocellular carcinoma[Title/Abstract]) OR (liver cancer[Title/Abstract]) OR (hepatoma[Title/Abstract])) AND (resection[Title/Abstract] OR hepatectomy[Title/Abstract]) AND (post-operative[Title/Abstract] OR postoperative[Title/Abstract] OR adjuvant[Title/Abstract] OR prevent[Title/Abstract])	**300**
Web of Science	(TS = (hepatocellular carcinoma)) AND ((AB = (resection OR hepatectomy)) OR TI = (resection OR hepatectomy)) AND ((TI = (post-operative OR postoperative OR adjuvant OR prevent)) OR AB = (post-operative OR postoperative OR adjuvant OR prevent)) AND ((TI = (microvascular invasion)) OR AB = (microvascular invasion))	**250**
EMBASE	‘hepatocellular carcinoma’/exp AND (‘resection’/exp OR ‘hepatectomy’/exp) AND (‘adjuvant’/exp OR ‘postoperative’ OR ‘post-operative’ OR prevent:ti OR prevention:ti) AND ‘microvascular invasion’/exp	**68**

retrospective studies, or cohort studies. And, the exclusion criteria were as follows: (1) Studies with mostly the same population (the most recent or most detailed study was adopted); (2) Single-arm studies; (3) Unavailable outcome; and (4) Reviews, conference, abstracts, letters, case reports, and animal experiments. The titles and abstracts of all articles were browsed and screened separately by two authors, and the full texts of potentially eligible studies were reviewed to select the eligible articles. Any disagreements were resolved through discussion with a third author.

Data extraction

The relevant data were extracted by two authors independently from the included studies and filled into a predesigned data form. The data collected included: (1) The first author, year of publication, study design, sample sizes, and the treatment; (2) The patient’s age and gender and tumor-related information; (3) The hazard ratio (HR) and 95% confidence interval (95%CI) for OS or RFS. Any disagreements were resolved through discussions with a third investigator.

Risk of bias and quality assessment

The Cochrane risk of bias assessment tool[12] was used to evaluate the methodological quality of the selected RCTs. The Newcastle-Ottawa Scale (NOS)[13] was used to evaluate the methodological quality of cohort and retrospective studies. The scale is grouped into three parts: Selection (4 points), comparability (2 points), and outcome (3 points), for a maximum of 9 points. Zero to 3 points indicate high risk of bias, 4 to 6 points indicate moderate risk of bias, and 7 to 9 points indicate low risk of bias.

Statistical analysis

RFS and OS were used to compare the effectiveness of different postoperative adjuvant therapies, and the outcomes were reported at HR and 95%CI. When included studies did not directly report HRs, they were estimated using Tierney’s or Parmar’s method[14,15].

Pairwise meta-analysis was conducted using R version 4.1.2 (Foundation for Statistical Computing, Vienna, Austria) with R package “meta” (version 5.1-1). The outcomes were pooled with a random-effect model. Statistical heterogeneity was assessed using I^2 test. The Bayesian NMA was performed using R version 4.1.2 and JAGS 4.3.0 with R package “gemtc” (version 1.0-1) and “rjags” (version 4-13). Network diagrams were constructed to show direct comparisons between different interventions. Four independent Markov chains were set to fit the model. For every outcome, 50000 sample iterations per chain were generated after 20000 burn-ins and one step-size interval to obtain a posterior distribution. Fixed or random effects models were chosen according to the Deviance Information Criterion (DIC). The model’s convergence was assessed with Brooks-Gelman-Rubin diagnostics, traces, and density plots. We estimated global inconsistency by comparing the fit of the consistency model to that of the inconsistency model. And local inconsistency was assessed by comparing direct and indirect evidence estimates using a node-splitting approach[16] (P value < 0.05 suggests the existence of inconsistency in the NMA). Cumulative probability ranking charts were used to report the probability ranking of different adjuvant therapies. Furthermore, we calculated the surface under the cumulative ranking curve (SUCRA) values to evaluate the interventions that rank the best. The SUCRA values ranged from 0-1, with higher SUCRA values for interventions implying better treatment effectiveness. In addition, the comparison-adjusted funnel plots and Egger’s tests were used to assess the publication biases using R package “netmeta”. P-value < 0.05 indicated a statistically significant result.

RESULTS

Study characteristics and bias assessment

Using a pre-defined search strategy, 620 studies were identified from 3 online databases. After removing duplicates and reading titles and abstracts, 33 relevant studies were considered for full-text reading. Finally, 14 eligible studies were included in the NMA[7-10,17-26] (Figure 1). Among the included studies, three were RCTs[7,9,20], 10 were retrospective cohort studies[8,10,17-19,21-23,25,26], and one was prospective cohort studies[24]. These studies comprised a total of 2268 patients and investigated five different treatment arms, namely sorafenib, HAIC, RT, TACE, and hepatectomy alone. The

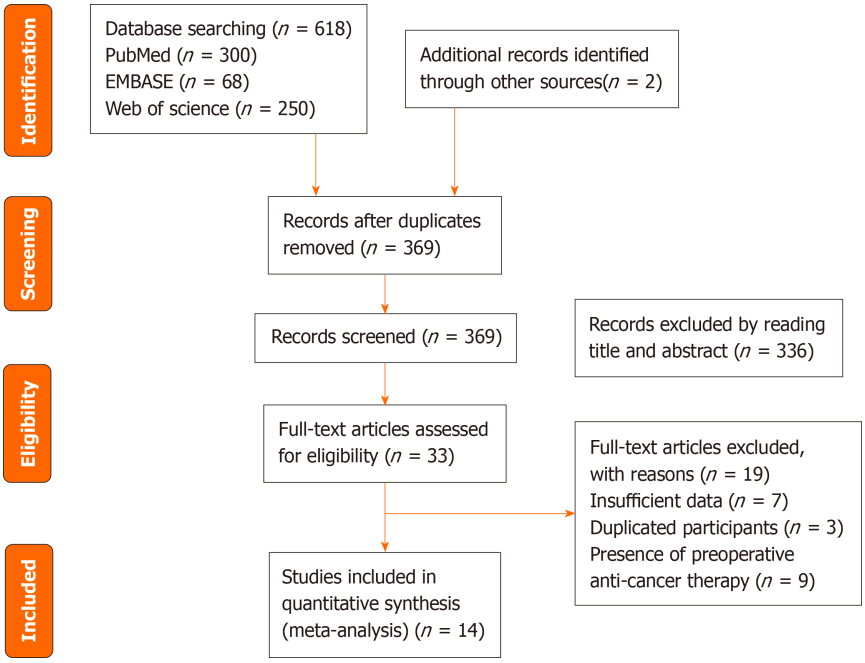


Figure 1 PRISMA flowchart for selection of the studies.

patient distribution across the treatment arms was as follows: 171 patients in the sorafenib arm, 172 patients in the HAIC arm, 113 patients in the RT arm, 655 patients in the TACE arm, and 1157 patients in the hepatectomy alone arm. Except for one study comparing the efficacy of RT with TACE[21], all other studies compared the efficacy of postoperative adjuvant therapy with hepatectomy alone. Specifically, three studies utilized sorafenib as an intervention[8,17,18], two studies used HAIC[9,19], three studies employed RT[10,20,21], and six studies focused on TACE[7,22-26]. The included studies were published between 2016 and 2022, with sample sizes ranging from 49 patients[18] to 328 patients[22]. Further information regarding the characteristics of the included studies can be found in Table 2. All cohort and retrospective studies scored above six on the NOS, indicating medium to high quality (Table 3). In terms of the Cochrane Risk of Bias Assessment Tool, all RCTs were deemed to have a low risk of bias (Figure 2).

Pairwise meta-analysis

In the pairwise meta-analysis, all studies reported both RFS and OS. The detailed forest plots illustrating the results are presented in Figure 3A for RFS and Figure 3B for OS. Regarding for RFS, compared to hepatectomy alone, sorafenib (HR = 0.53, 95%CI: 0.31-0.93), HAIC (HR = 0.52, 95%CI: 0.38-0.71), RT (HR = 0.36, 95%CI: 0.22-0.59), TACE (HR = 0.69, 95%CI: 0.60-0.78) were all associated with a reduced risk of recurrence. Notably, RT demonstrated superiority over TACE (HR = 0.45, 95%CI: 0.26-0.76) in terms of reducing recurrence risk.

In terms of improving OS, sorafenib (HR = 0.48, 95%CI: 0.35-0.66), HAIC (HR = 0.58, 95%CI: 0.42-0.81), and TACE (HR = 0.64, 95%CI: 0.54-0.75) were significantly more effective than hepatectomy alone. The effect of RT was comparable to that of TACE (HR = 0.67, 95%CI: 0.33-1.35). However, RT only showed a tendency to improve OS compared to hepatectomy alone (HR = 0.23, 95%CI: 0.05-1.05).

NMA

Figure 4 depict the comparison networks for RFS and OS, respectively. The width of the edges indicates the number of studies comparing the two treatments, while the size of the nodes represents the number of arms corresponding to each treatment method in the included studies. The model converges well after 50000 iterations, and the results were considered stable (Figure 5).

Regarding reducing the risk of recurrence (Figures 6A and 7), sorafenib (HR = 0.56, 95%CI: 0.4-0.77), HAIC (HR = 0.52, 95%CI: 0.35-0.76), RT (HR = 0.34 95%CI: 0.23-0.5), and TACE (HR = 0.69 95%CI: 0.59-0.81) were all significantly more effective than hepatectomy alone. Furthermore, RT demonstrated superiority over TACE [HR = 0.49 (0.32, 0.73)]. The ranking results are presented in Figure 8 with RT (SUCRA = 97.7%) having the highest likelihood of ranking first for RFS, followed by HAIC (SUCRA = 65.1%), sorafenib (SUCRA = 57.1%), and TACE (SUCRA = 30.0%).

For improving OS (Figures 6B and 7), patients who underwent RT (HR = 0.35, 95%CI: 0.2-0.61), HAIC (HR = 0.59, 95%CI: 0.38-0.92), sorafenib (HR = 0.48, 95%CI: 0.32-0.69), or TACE (HR = 0.62, 95%CI: 0.49-0.76) experienced a significantly greater survival benefit compared to those who underwent hepatectomy alone. Notably, RT demonstrated superior efficacy compared to TACE (HR = 0.57, 95%CI: 0.33-0.99). Among these interventions, RT (SUCRA = 93.1%) ranked the highest in terms of improving OS, followed by sorafenib (SUCRA = 70.9%), HAIC (SUCRA = 47.0%), and TACE (SUCRA = 38.8%).

Table 2 The baseline characteristics of included studies

Ref.	Design	Enrollment period	Treatment	Sample size (*n*)	Male (*n*)	Age (yr)	Tumor size (cm)	Multiple nodules (*n*)	HBV (*n*)	Child-Pugh, A/B (*n*)
Li *et al*[8], 2021	Retrospective cohort, PSM	August 2009 to August 2017	Sorafenib	42	34/8	54.2 ± 1.4	6.2 ± 0.6	29	NA	42
			HT alone	42	35/7	54.6 ± 1.7	7.2 ± 0.8	25	NA	42
Zhang *et al* [17], 2019	Retrospective cohort, PSM	2009 to 2016	Sorafenib	113	97/16	49.0 (43.0-56.0)	5.9 (4.0-9.0)	17	102	111/2
			HT alone	113	98/15	48.0 (40.0-57.0)	5.42 (3.8-9.1)	21	98	112/1
Huang *et al* [18], 2019	Retrospective cohort	January 2009 to December 2016	Sorafenib	16	12	52.25 ± 11.94	NA	2	12	16/0
			HT alone	33	30	51.52 ± 11.87	NA	3	26	31/2
Li *et al*[9], 2023	RCT	June 2016 to August 2021	HAIC	143	122	51 (25-75)	5.5 (1.8-30.0)	43	125	142/1
			HT alone	143	126	54 (27-75	5.4 (1.5-16.0)	27	51	141/2
Hsiao *et al* [19], 2017	Retrospective cohort	2006 to 2014	HAIC	29	NA	NA	NA	NA	NA	NA
			HT alone	41	NA	NA	NA	NA	NA	NA
Shi *et al* [20], 2022	RCT	August 2015 to December 2016	RT	38	33	56.42 ± 10.44	4.87 ± 2.03	NA	36	NA
			HT alone	38	32	55.74 ± 10.19	4.88 ± 2.46	NA	36	NA
Wang *et al* [10], 2020	Retrospective cohort	July 2015 to December 2018	RT	29	24	55.90 ± 8.05	4.75 ± 2.15	2	29	29/0
			HT alone	30	25	56.57 ± 9.43	4.50 ± 2.98	2	30	30/0
Wang *et al* [21], 2019	Retrospective cohort, PSM	July 2008 to December 2016	RT	46	43	50.98 ± 10.53	5.39 ± 2.74	4	38	46/0
			TACE	46	37	51.52 ± 11.40	5.50 ± 3.07	5	36	46/0
Qiu *et al* [22], 2022	Retrospective cohort, PSM	April 2014 to July 2019	TACE	164	138	51 ± 12	4.7 ± 2.9	43	135	162/2
			HT alone	164	145	52 ± 12	5.0 ± 2.9	52	136	162/2
Wang *et al* [23], 2019	Retrospective cohort, PSM	September 2004 to December 2015	TAEC	57	47	55 ± 11	6 (2-14)	11	47/2	54/3
			HT alone	57	51	56 ± 10	6 (2-18)	11	47/6	54/3
Qi *et al*[24], 2019	Prospective cohort	January 2012 to December 2014	TACE	91	78	NA	NA	23	77	54/37
			HT alone	109	93	NA	NA	25	96	76/33
Wei *et al* [7], 2018	RCT	June 2009 to December 2012	TACE	116	106	44.0 (18-75)	5	0	94/NA	116/0
			HT alone	118	106	48.5 (18-74)	5	0	101/NA	116/2
Wang *et al* [25], 2018	Retrospective cohort	January 2010 to December 2014	TACE	44	42	52.07 ± 7.24	3.84 ± 1.27	44	NA	41/1
			HT alone	84	76	54.49 ± 10.18	3.83 ± 1.09	84	NA	82/2
Sun *et al* [26], 2016	Retrospective cohort	January 2004 to June 2013	TACE	137	120	48.88 ± 0.87	6.51 ± 0.27	11	121	135/2
			HT alone	185	167	49.91 ± 0.72	6.99 ± 0.29	17	163	182/3

PSM: Propensity score matching; RCT: Randomized controlled trial; HT: Hepatectomy; HAIC: Hepatic artery infusion chemotherapy; RT: Radiotherapy; TACE: Transarterial chemoembolization; NA: Not available; HBV: Hepatitis B virus.

Transitivity assessment, inconsistency, and publication bias

Upon reviewing the populations, interventions, and outcomes of the included studies, we observed that they exhibited consistency or high similarity. Therefore, this NMA adhered to the transitivity assumption. To assess the model fit, we compared the DIC values between the consistent and inconsistent models (Table 4). Encouragingly, the consistent model exhibited similar or superior fit compared to the inconsistent model, indicating favorable global consistency in this NMA. Additionally, the node-splitting approach revealed consistency between the direct and indirect evidence, further supporting the absence of local inconsistency (Figure 9). As shown in Figure 10, the funnel plot and Egger's tests suggested no significant publication bias existed among the included studies in terms of RFS (P = 0.88) or OS (P = 0.40).

DISCUSSION

High recurrence rates significantly impact the OS of HCC patients who undergo hepatectomy. MVI is an oncological characteristic independently associated with recurrence[27]. However, the role of adjuvant therapy has not been elucidated in these patients. To the best of our knowledge, this is the first NMA aimed at evaluating the effectiveness of postoperative adjuvant therapy in HCC patients with MVI who have undergone curative hepatectomy.

Our study found that all postoperative adjuvant therapies had a positive effect compared to curative hepatectomy alone. Among the various therapies evaluated, RT emerged as the most effective in reducing the risk of recurrence, followed by HAIC. In terms of improving OS, RT was found to be the most effective, followed by sorafenib. However, postoperative adjuvant TACE showed the least benefit for HCC patients with MVI. Our analysis of direct or indirect paired comparisons of RFS or OS revealed that, except for RT being significantly superior to TACE, there were no significant differences among the other adjuvant therapies.

Recurrence of HCC after radical resection primarily occurs due to the presence of residual microscopic lesions that are not detectable on imaging[28]. MVI can be considered as a residual microscopic lesion. Several classifications of MVI have been proposed[29,30]. The latest classification system[29] categorizes MVI into four classes based on the appearance and burden of MVI: M0 (no MVI), M1 (non-invasion type, < 5 vessels), M2 (invasion type < 5 vessels, or non-invasion type > 5 vessels), and M3 (invasion type, > 5 vessels). Regardless of the classification, the OS and RFS gradually decreased with increasing MVI stages. Unlike macrovascular invasion, which can be identified through preoperative imaging, MVI can only be confirmed through postoperative pathology. The positivity rate of pathological MVI after hepatectomy can be as high as 51%[31]. Recently, several models predicting postoperative MVI have been reported[30-32], demonstrating moderate to high accuracy. When the possibility of postoperative MVI is considered high, taking an expanded margin may reduce the rate of postoperative MVI. However, complete avoidance of postoperative MVI is challenging, necessitating further consideration of therapeutic management for MVI-positive patients.

In recent years, the concept of adjuvant therapy following hepatectomy has gained prominence, aiming to improve OS for resectable HCC. Various adjuvant therapy strategies have been reported, such as interferon[32], TACE[33], HAIC[34], targeted therapy[8,35], immunotherapy[36], RT[37], and Huaier[38]. However, current guidelines offer inconsistent recommendations regarding the use of adjuvant therapy in HCC after hepatectomy[39-42]. Only the Asian Pacific Association for the Study of the Liver recommends adjuvant therapy for HCC patients with intermediate or high-risk of recurrence[42], while other guidelines do not endorse this recommendation at present. It is important to note that most of these guidelines were formulated several years ago. Recent multiple meta-analyses have demonstrated the survival benefits of postoperative adjuvant therapy for resected HCC patients[43-45]. A previously published NMA compared the efficacy of eight postoperative adjuvant therapies in HCC patients who underwent hepatectomy[46]. The results suggested that adjuvant therapies provided survival benefits over surgery alone and HAIC and internal RT were likely to be the two most effective adjuvant regimens. However, the NMA did not further analyze the subgroup of patients, even that NMA included the patients with low risk of recurrence. It is unclear what adjuvant therapy would be most beneficial for the MVI-positive patients, and clarifying this issue is the goal and strength of our NMA.

TACE is the most commonly used adjuvant therapy, and its effectiveness in HCC patients with MVI has been documented[44,47]. However, our NMA results suggested that TACE had the least benefit compared to other adjuvant therapies. This could be attributed to the technical limitations of TACE and the characteristics of MVI. MVI cannot be clearly stained during hepatic arterial angiography, resulting in potential target vessels that may be overlooked. Additionally, the hypoxic microenvironment induced by embolization can upregulate hypoxia-inducible factors that may promote tumor progression[48-50]. In contrast, HAIC does not induce a hypoxic environment, and the high dose of intravascular chemotherapeutic agents administered over a prolonged period can directly and effectively kill tumor cells. In addition, the chemotherapy regimen of HAIC is worth exploring. The oxaliplatin-based FOLFOX regimen is now the most popular regimen, and its higher effectiveness compared to previous single-agent regimens makes HAIC possible for HCC patients[51]. Alternatively, sorafenib may be a preferable choice compared to HAIC due to its comparable survival benefits and greater convenience with less discomfort.

In recent years, post-resection treatment of HCC has seen increased focus on RT. Advances in new RT techniques, such as intensity-modulated RT, three-dimensional conformal RT, and stereotactic body RT, have facilitated the precise delivery of high doses of radiation to the tumor site while preserving normal liver tissue. The core principle of RT

Table 3 Methodological quality assessment for cohort studies using the Newcastle-Ottawa Scale

Ref.	Selection				Comparability	Exposure			Quality Score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Li *et al*[8], 2021	1	1	1		2	1	1		7
Zhang 2019	1	1	1	1	2	1	1		8
Huang *et al*[18], 2019	1	1	1		2	1	1	1	8
Hsiao *et al* [19], 2017	1	1	1	1	1	1	1		7
Wang *et al* [10], 2020	1	1	1		2	1	1		7
Wang *et al* [21], 2019	1	1	1		1	1	1		6
Qiu *et al* [22], 2022	1	1	1		1	1	1	1	7
Wang *et al* [23], 2019	1	1	1		2	1	1		7
Qi *et al* [24], 2019	1	1	1		2	1	1		7
Wang *et al* [25], 2018	1	1	1		1	1	1	1	7
Sun *et al* [26], 2016	1	1	1		1	1	1		6

involves direct or indirect damage to cancer cells' DNA through radiation, thereby inducing cell death. Several studies have revealed that residual microscopic lesions commonly develop around the primary tumor after hepatectomy[52-54]. In adjuvant RT protocols, the clinical target volume primarily encompasses the marginal parenchyma, extending 1-3 cm around the tumor bed. Furthermore, unlike TACE or HAIC, RT remains unaffected by blood flow. These characteristics ensure the effective eradication of residual cancer cells after hepatectomy. Additionally, recent research has demonstrated that RT can stimulate remodeling of the tumor immune microenvironment through stromal cells, thereby augmenting its anti-tumor effects[55].

Table 4 Comparisons of the fit of consistency and inconsistency

Model	Recurrence free survival	Overall survival
Consistency	18.00	20.25
Inconsistency	19.79	21.82

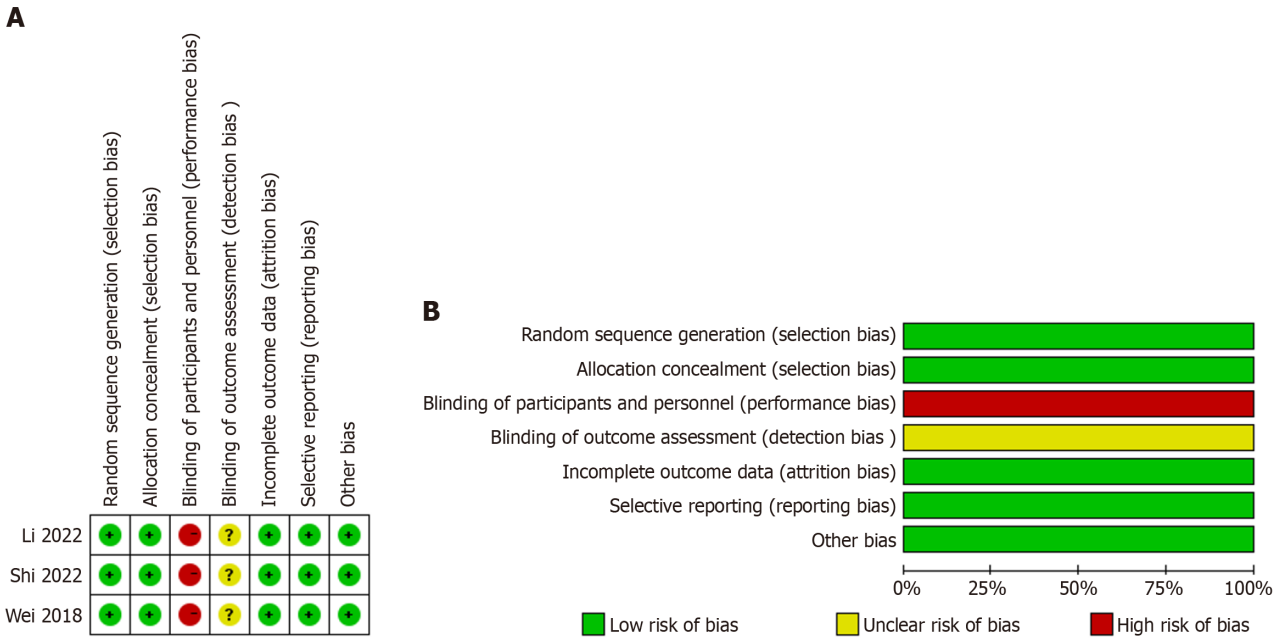


Figure 2 Risk-of-bias assessments for prospective clinical trials included in the meta-analysis. A: Risk-of-bias summary; B: Risk-of-bias graph. +: Low risk of bias; ?: Unclear risk of bias; -: High risk of bias.

Our study's findings regarding HCC with MVI align with prior research[56], suggesting that post-hepatectomy RT significantly enhances OS and reduces recurrence risks in HCC patients. Moreover, postoperative adjuvant RT might confer benefits to other patient cohorts. A recent meta-analysis indicated that in the population with portal vein tumor thrombosis (PVTT), postoperative adjuvant RT resulted in lower recurrence rates and prolonged OS compared to surgery alone[57]. However, it's important to note the absence of observed survival benefits from adjuvant RT in patients with PVTT types III and IV[58]. For specific HCC sites, such as those adjacent to major blood vessels, achieving R0 hepatectomy becomes challenging, often resorting to narrow-margin hepatectomy (< 1 cm). Patients undergoing narrow-margin hepatectomy typically exhibit poorer prognoses compared to those with R0 hepatectomy[59,60]. Nevertheless, adjuvant RT demonstrates a survival benefit comparable to R0 hepatectomy and decreases recurrence risks in narrow-margin hepatectomy cases[61]. Overall, apart from the MVI population, specific PVTT and narrow-margin populations could also benefit from postoperative adjuvant RT. Further studies are anticipated to delineate other patient cohorts suitable for postoperative RT.

There were a few limitations to our study. Due to the lack of RCTs, our NMA mainly relied on cohort studies. However, observational studies can better reflect real-world clinical practice compared to RCTs, thereby enhancing the generalizability of the evidence. Additionally, in a small number of studies, HRs for OS or RFS were not directly provided, and we estimated them indirectly using Tierney's method. Given the relatively small number of studies included in our analysis, caution is advised in interpreting our results. Nevertheless, we believe our findings will offer valuable insights for future, more expansive studies. Furthermore, the studies available to us have solely focused on individual adjuvant therapies. However, the impact and safety of combined adjuvant therapies for HCC patients post-hepatectomy remain unknown. This intriguing avenue warrants further exploration in future research endeavors.

CONCLUSION

Our NMA suggests that adjuvant therapy, particularly RT, holds promise in reducing the risk of recurrence and improving survival outcomes for HCC patients with MVI after hepatectomy. These findings provide valuable evidence for clinicians when making treatment decisions for this patient population. Future well-designed RCTs with larger sample sizes are warranted to confirm these results and further explore the optimal adjuvant treatment strategies for HCC patients with MVI.

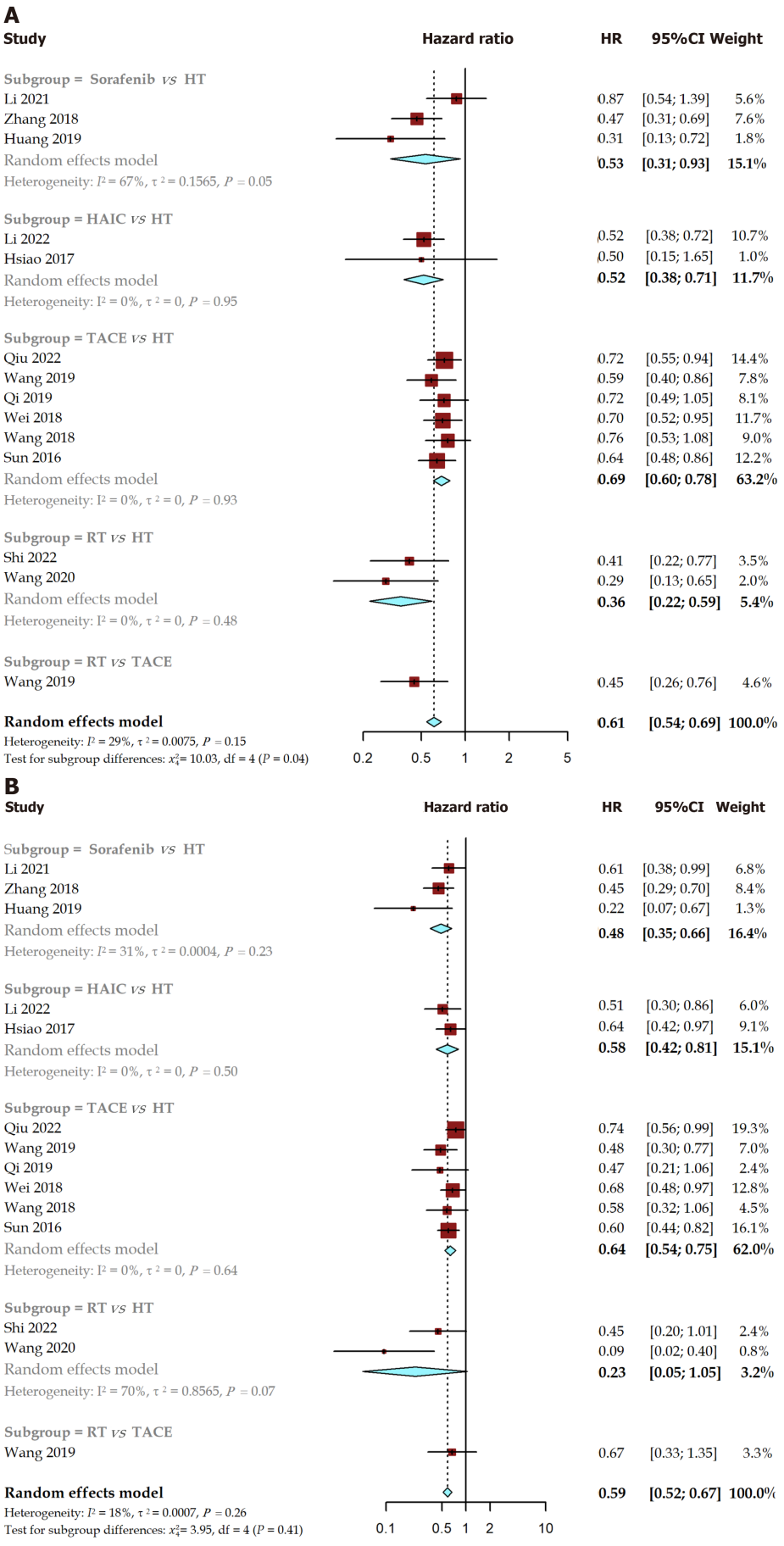


Figure 3 Forest plot of recurrence free survival and overall survival for pairwise meta-analysis. A: Recurrence free survival; B: Overall survival. HT: Hepatectomy; HAIC: Hepatic artery infusion chemotherapy; RT: Radiotherapy; TACE: Transarterial chemoembolization; HR: Hazard ratio; CI: Confidence

interval.

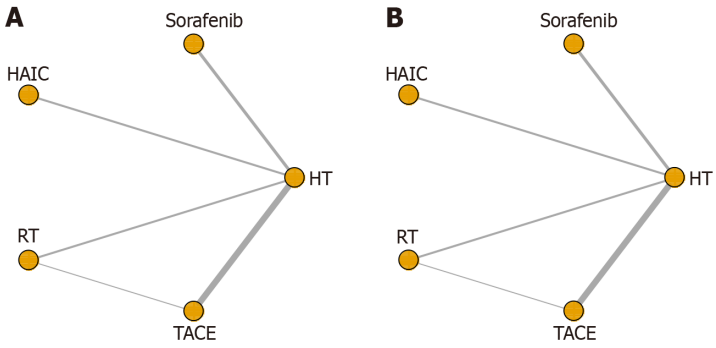
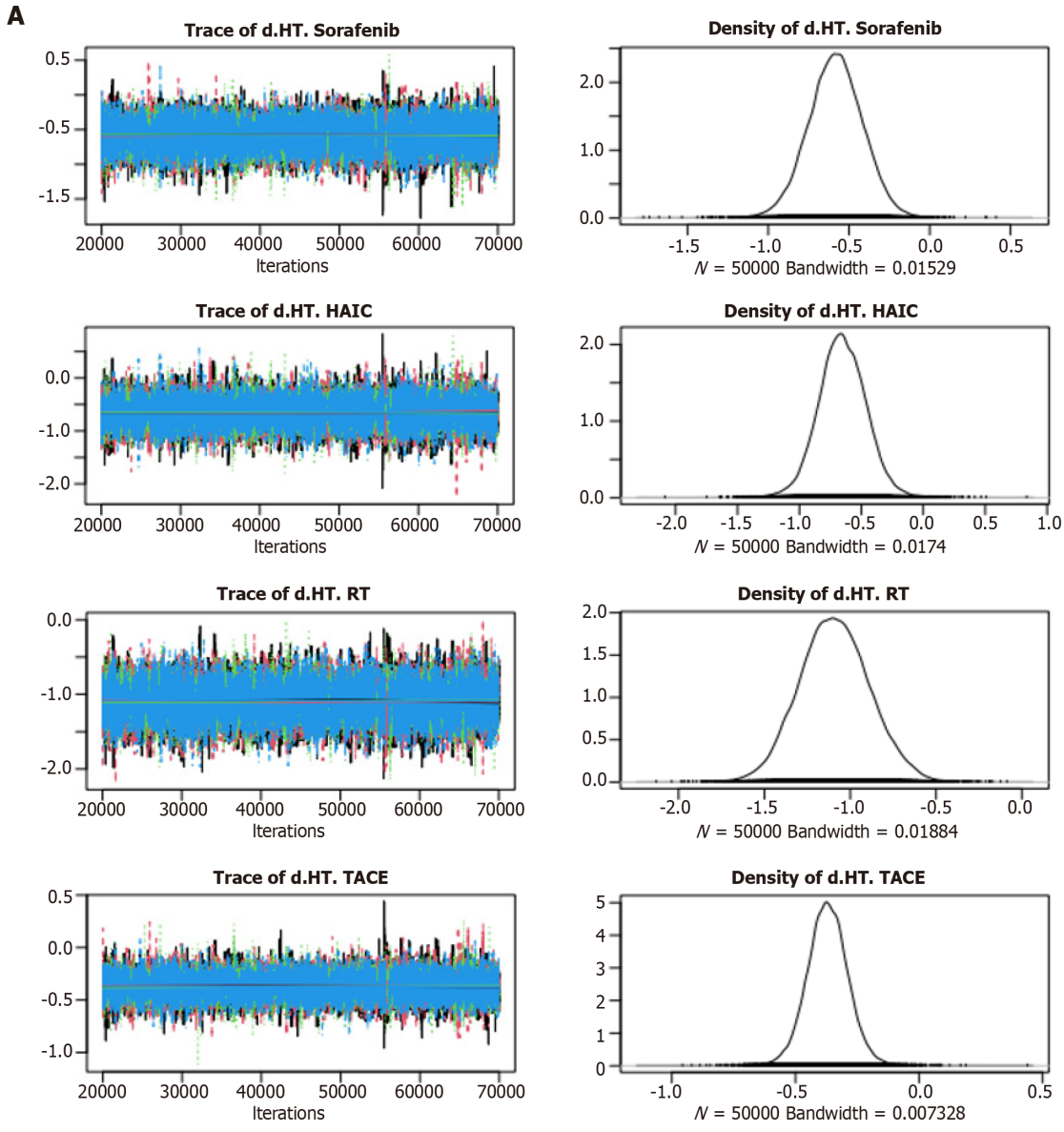
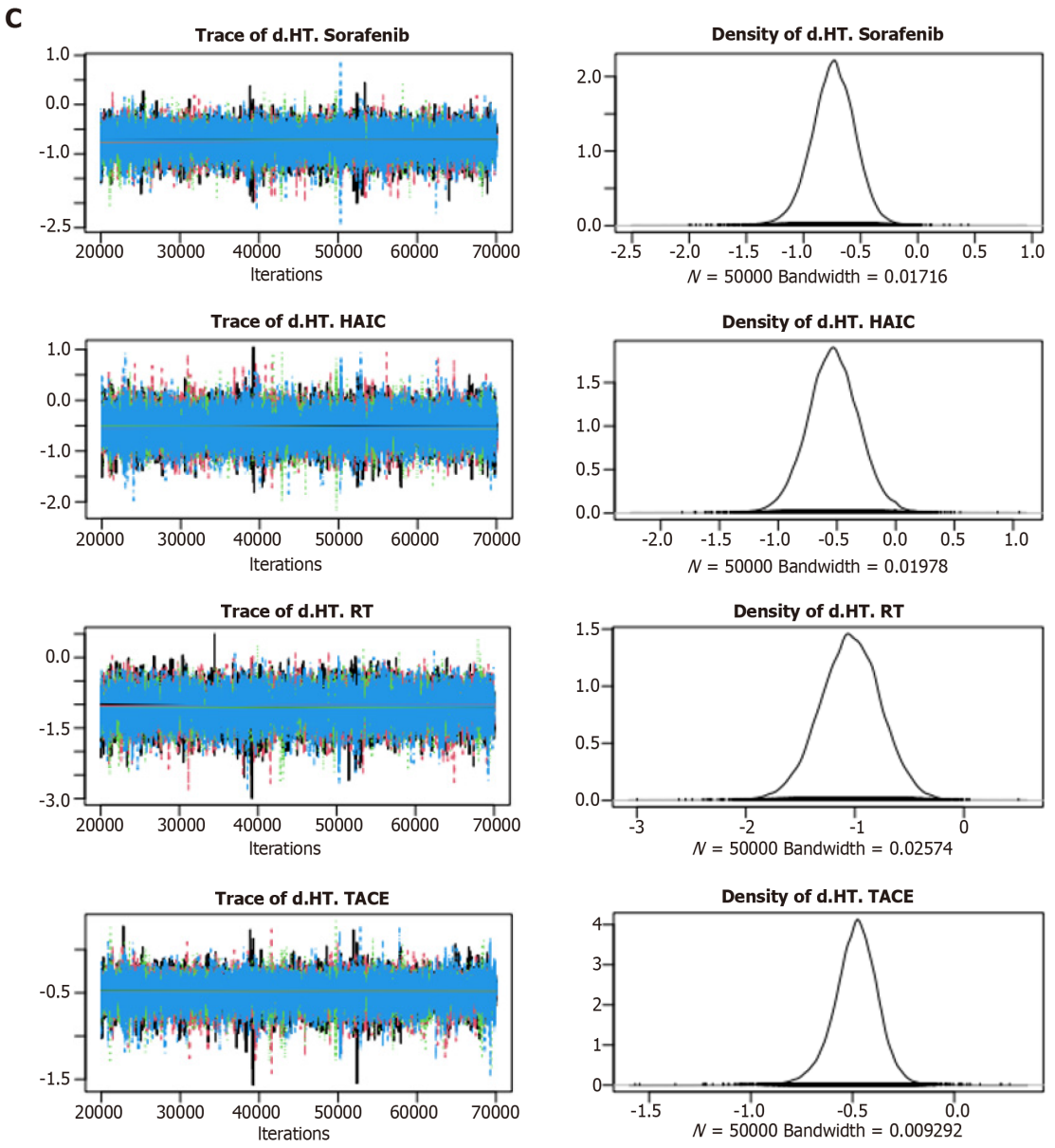


Figure 4 Network diagram of eligible comparisons for recurrence free survival and overall survival. A: Recurrence free survival; B: Overall survival. HT: Hepatectomy; HAIC: Hepatic artery infusion chemotherapy; RT: Radiotherapy; TACE: Transarterial chemoembolization.




C
Trace of d.HT. Sorafenib
Density of d.HT. Sorafenib
N = 50000 Bandwidth = 0.01716
Trace of d.HT. HAIC
Density of d.HT. HAIC
N = 50000 Bandwidth = 0.01978
Trace of d.HT. RT
Density of d.HT. RT
N = 50000 Bandwidth = 0.02574
Trace of d.HT. TACE
Density of d.HT. TACE
N = 50000 Bandwidth = 0.009292
Iterations
B
d.HT. Sorafenib
d.HT. HAIC
d.HT. RT
d.HT. TACE
sd.d
Shrink factor
median
last iteration in chain

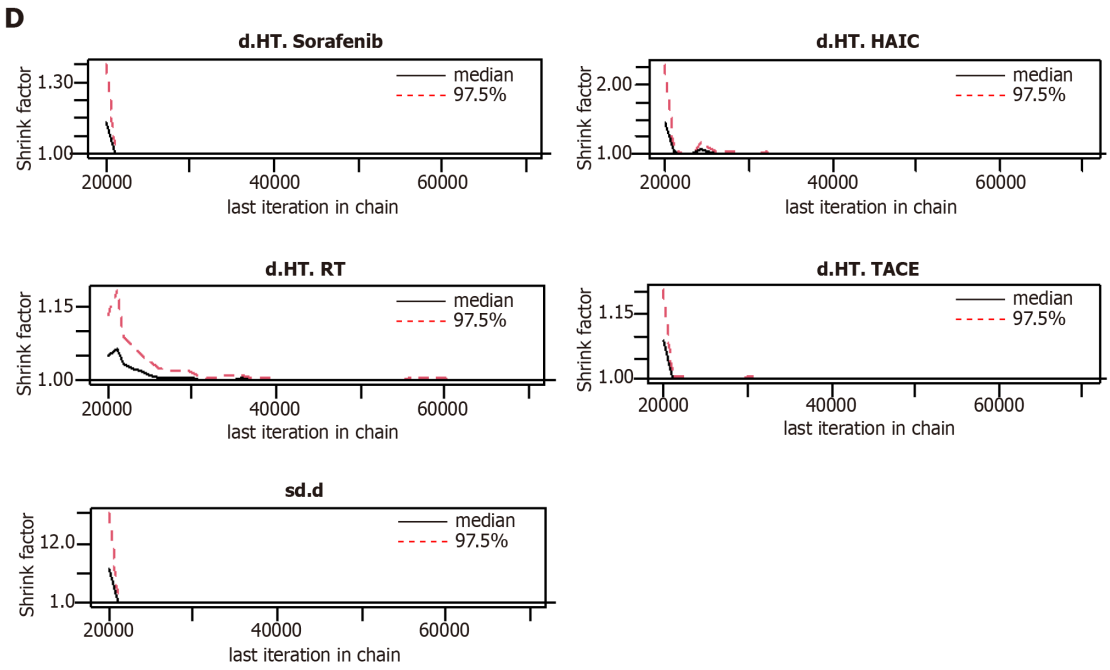


Figure 5 Convergence of the three chains established by trace and the Brooks-Gelman-Rubin diagnostic for recurrence free survival and overall survival. A and B: Recurrence free survival; C and D: Overall survival. HT: Hepatectomy; HAIC: Hepatic artery infusion chemotherapy; RT: Radiotherapy; TACE: Transarterial chemoembolization.

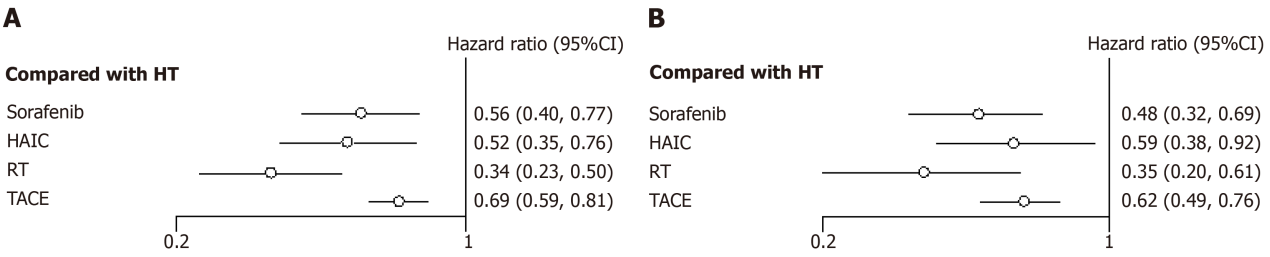
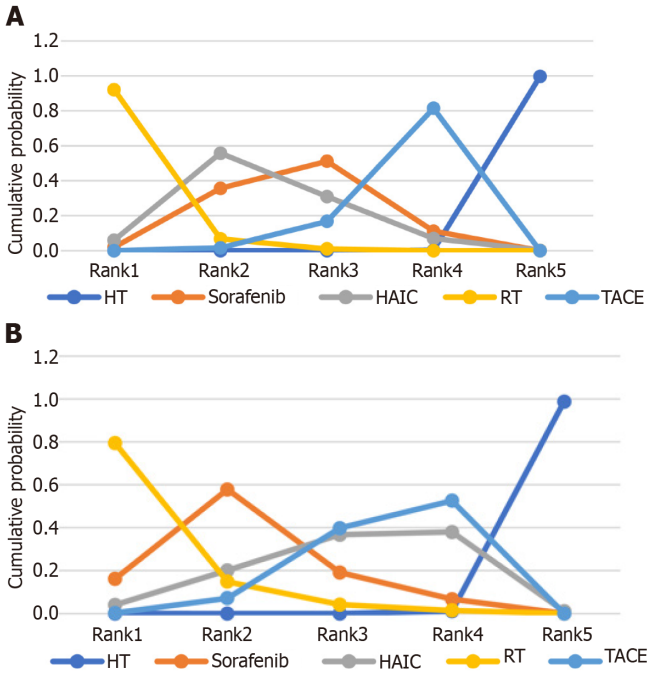


Figure 6 Hazard ratio along with 95% confidence interval for recurrence free survival and overall survival for each adjuvant therapy compared with hepatectomy. A: Recurrence free survival; B: Overall survival. HT: Hepatectomy; HAIC: Hepatic artery infusion chemotherapy; RT: Radiotherapy; TACE: Transarterial chemoembolization; CI: Confidence interval.

	RFS				
OS	HT	**0.56 (0.4, 0.77)**	**0.52 (0.35, 0.76)**	**0.34 (0.23, 0.5)**	**0.69 (0.59, 0.81)**
	0.48 (0.32, 0.69)	Sorafenib	0.93 (0.56, 1.55)	0.6 (0.36, 1)	1.23 (0.86, 1.78)
	0.59 (0.38, 0.92)	1.23 (0.7, 2.21)	HAIC	0.65 (0.37, 1.14)	1.33 (0.88, 2.03)
	0.35 (0.2, 0.61)	0.74 (0.38, 1.43)	0.6 (0.29, 1.2)	RT	**2.05 (1.38, 3.08)**
	0.62 (0.49, 0.76)	1.29 (0.84, 1.99)	1.05 (0.63, 1.69)	**1.74 (1.01, 3.05)**	TACE

Figure 7 Pooled estimates of the network meta-analysis. HT: Hepatectomy; HAIC: Hepatic artery infusion chemotherapy; RT: Radiotherapy; TACE: Transarterial chemoembolization; RFS: Recurrence free survival; OS: Overall survival.



Treatment	SUCRA(%)
RT	97.7
HAIC	65.1
Sorafenib	57.1
TACE	30.0
HT	0

Treatment	SUCRA(%)
RT	93.1
Sorafenib	70.9
HAIC	47.0
TACE	38.8
HT	0

Figure 8 Cumulative ranking plot and surface under the cumulative ranking curve values for recurrence free survival and overall survival. A: Recurrence free survival; B: Overall survival. HT: Hepatectomy; HAIC: Hepatic artery infusion chemotherapy; RT: Radiotherapy; TACE: Transarterial chemoembolization; SUCRA: Surface under the cumulative ranking curve.

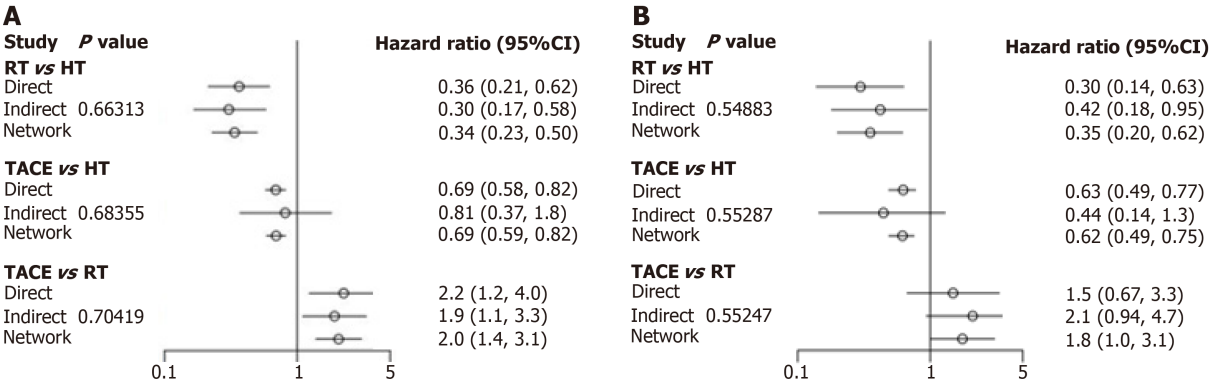


Figure 9 The node-splitting approach demonstrated consistency between the direct and indirect evidence for recurrence free survival and overall survival. A: Recurrence free survival; B: Overall survival. HT: Hepatectomy; RT: Radiotherapy; TACE: Transarterial chemoembolization; CI: Confidence interval.

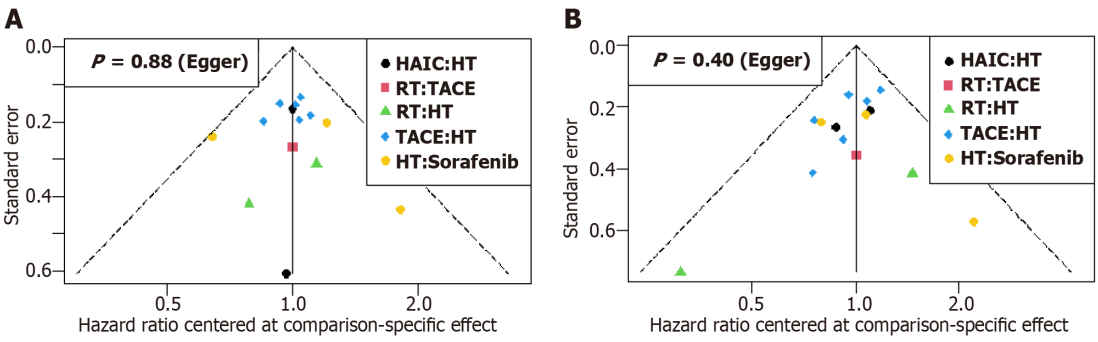


Figure 10 Funnel plot and Egger's tests for the included studies in terms of recurrence free survival and overall survival. A: Recurrence free survival; B: Overall survival. HT: Hepatectomy; HAIC: Hepatic artery infusion chemotherapy; RT: Radiotherapy; TACE: Transarterial chemoembolization.

ARTICLE HIGHLIGHTS

Research background

For resectable hepatocellular carcinoma (HCC), radical hepatectomy is commonly used as a curative treatment. Unfortunately, the 5-year recurrence rate for patients who undergoing hepatectomy ranges from 50% to 70%. Postoperative recurrence significantly diminishes the overall survival (OS) of HCC patients, especially with microvascular invasion (MVI) as an independent high-risk factor for recurrence. While some studies suggest that postoperative adjuvant therapy may decrease the risk of recurrence following liver resection in HCC patients, the specific role of adjuvant therapies in those with MVI remains unclear.

Research motivation

In HCC patient with MVI, various postoperative adjuvant therapies such as transarterial chemoembolization (TACE), hepatic artery infusion chemotherapy (HAIC), sorafenib, and radiotherapy (RT) have been reported. However, the most effective adjuvant therapy among these remains unknown.

Research objectives

The study aimed at assessing the effectiveness of different adjuvant therapies and identifying the most effective adjuvant regimen.

Research methods

A systematic literature search was conducted on PubMed, EMBASE, and Web of Science until April 6, 2023. Studies comparing different adjuvant therapies or comparing adjuvant therapy with hepatectomy alone were included. Paired meta-analysis and network meta-analysis were conducted to compare the efficacy of various adjuvant therapies. Cumulative probability ranking charts were used to report the probability ranking of different adjuvant therapies. Furthermore, we calculated the surface under the cumulative ranking curve (SUCRA) values to evaluate the interventions that rank the best. In addition, the comparison-adjusted funnel plots and Egger's tests were used to assess the publication biases.

Research results

Fourteen eligible trials (2268 patients) reporting five different therapies (TACE, HAIC, sorafenib, and RT) were included. In terms of reducing the risk of recurrence, RT was found to be the most effective adjuvant therapy, followed by HAIC. Regarding OS improvement, RT demonstrated the highest effectiveness, followed by sorafenib.

Research conclusions

In summary, adjuvant therapy following hepatectomy may reduce the risk of recurrence and provide a survival benefit for HCC patients with MVI. RT appears to be the most effective adjuvant regimen.

Research perspectives

Future studies should focus on the efficacy and safety of combinations of multiple adjuvant therapies.

FOOTNOTES

Author contributions: Pei YX and Liu JL contributed to the conception and design of the study; Pei YX and Su CG conducted the literature search and extracted the data; Liao Z and Wang ZX assessed methodological quality of included studies; Liao Z was involved in the resolution of all the arguments; Pei YX, Su CG, and Liao Z conducted the data analysis; Pei YX wrote the manuscript; and all authors have read and approve the final manuscript.

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