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A network meta-analysis of different interventional treatment strategies for unresectable hepatocellular carcinoma

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Abstract

Background The optimal clinical management of unresectable hepatocellular carcinoma (uHCC) is challenging for clinicians. Bayesian network meta-analysis was conducted to compare the efficacy and safety of different interventional strategies for uHCC.

Methods A systematic search was conducted in PubMed, Embase, the Cochrane Library, Web of Science, and CNKI databases. Bayesian network meta-analysis was applied to evaluate the disease control rate (DCR), 1-year survival rate and 2-year survival rate, as well as the incidence of serious adverse events associated with seven interventional strategies. Odds ratios (ORs) were estimated using pairwise and network meta-analysis with random effects. Treatment rankings utilized surface under the cumulative ranking curve (SUCRA), whereas heterogeneity was examined via I-square and meta-regression.

Results A total of 40 randomized controlled studies were included. Compared with transarterial chemoembolization (TACE) alone, all of the combination treatments, including TACE with radiofrequency ablation (RFA), microwave ablation (MWA), high-intensity focused ultrasound (HIFU), percutaneous ethanol injection (PEI), and radiotherapy (RT), significantly improved the DCR. TACE combined with RFA was observed to be superior to hepatic arterial infusion chemotherapy (HAIC) (OR: 1.91; 95% CI: 1.03–3.81) and TACE (OR: 3.85; 95% CI: 2.66–5.69), with the highest probability (SUCRA 0.836). TACE combined with HIFU ranks highest 1-year survival (SUCRA 0.919) and 2-year survival (SUCRA 0.925) rates, and also exhibited a better 1-year survival rate than HAIC (OR: 2.99; 95% CI: 1.09–9.03). Compared with TACE alone, HAIC exhibited a greater DCR (OR: 2.02; 95% CI: 1.15–3.40) and a potential advantage in 2-year survival (OR: 1.95; 95% CI: 1.02–3.78). No significant differences in serious adverse events were observed across treatments.

Conclusions Compared with TACE alone, combined treatments for uHCC patients demonstrates better efficacy and survival. Moreover, compared with TACE and HAIC, TACE combined with RFA provides better efficacy, whereas TACE combined with HIFU offers the highest 1-year survival rate. HAIC alone outperforms TACE in DCR and 2-year survival rate.

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Keywords Hepatocellular carcinoma, Transarterial chemoembolization, Hepatic arterial infusion chemotherapy, Ablation, Percutaneous ethanol injection, Radiation therapy, Network meta-analysis

Introduction

The incidence and mortality of hepatocellular carcinoma (HCC) are increasing throughout the world [1, 2]. This trend is largely due to the fact that approximately 80–85% of HCC patients progress to unresectable hepatocellular carcinoma (uHCC) [3]. However, patients with uHCC often cannot undergo curative resection due to factors such as tumor progression or insufficient liver function reserve. Additionally, treatment options for uHCC are limited, and traditional chemotherapy provides an overall survival of only approximately 6 months [4]. Therefore, the optimal clinical management of uHCC continues to be a significant challenge for clinicians.

Transarterial chemoembolization (TACE) and hepatic arterial infusion chemotherapy (HAIC) represent two interventional therapies for uHCC. The 2022 revision of the Barcelona Clinic Liver Cancer (BCLC) classification indicates that TACE can be the preferred treatment for uHCC and is considered the first-line treatment for patients with intermediate-advanced stage HCC [5, 6]. An increasing body of evidence suggests that TACE holds significant potential for improving the prognosis of patients with uHCC, due to its advantages including minimally invasive nature, precision, and controllable therapeutic range [7]. Clinical evidence has revealed a statistically significant median overall survival advantage with TACE compared to conventional supportive care in patients with uHCC (28.7 months vs. 17.9 months, $P = 0.009$) [8]. However, its long-term efficacy is not satisfactory. In a large cohort study involving 8,510 patients, the 5-year survival rate following TACE was observed to be only 26% [9]. Incomplete tumor necrosis after TACE and liver failure due to repeated TACE sessions have prompted researchers to explore alternative or optimized strategies [10, 11]. Recently, HAIC has garnered attention for its therapeutic potential [12]. HAIC administers high-dose chemotherapy drugs directly into the main blood vessels of HCC or uses indwelling catheters to continuously deliver chemotherapy over 48 to 72 h. The strategy for HAIC usage varies across different guidelines worldwide. In Asia, particularly in Japan and South Korea, HAIC is recognized as an effective treatment for intermediated and advanced HCC, and has been included in clinical guidelines [13]. However, HAIC is not mentioned in the guidelines of the European Association for the Study of the Liver (EASL), the American Association for the Study of Liver Diseases (AASLD), or the Asian Pacific Association for the Study of the Liver (APASL) [14]. Due to a lack of relevant research, it remains unclear whether HAIC is superior to TACE [15–18].

In clinical practice, the limited efficacy of single therapies and the heterogeneity of uHCC patients (such as portal vein invasion, diffuse lesions, or limited liver function) make it challenging to establish standardized treatment strategies for TACE or HAIC alone [19]. Therefore, a multidisciplinary medical team is typically required to collectively determine the most appropriate treatment plan, which may involve a combination of treatments. Numerous studies have suggested that the combination of TACE or HAIC with local therapies may improve the long-term prognosis and postoperative quality of life for patients with uHCC [20, 21]. Common local therapies that can be combined with TACE or HAIC include radiofrequency ablation (RFA), microwave ablation (MWA), high-intensity focused ultrasound (HIFU), percutaneous ethanol injection (PEI), and radiotherapy (RT). Previous meta-analyses have reported that the combination of TACE with RFA, RT, or HIFU demonstrates better efficacy than TACE alone [22–24]. However, there is still a lack of studies comparing the efficacy and safety of TACE or HAIC in combination with various local treatments.

Network meta-analysis (NMA) combines direct and indirect evidence to compare the effectiveness of different treatments, thereby aiding in identifying the optimal treatment by ranking interventions based on outcomes. Unlike pairwise meta-analyses, NMA quantitatively compares multiple treatments for a disease. In this study, we compared the efficacy and safety of different interventional strategies using a random-effects Bayesian model to determine the optimal treatment for uHCC.

Materials and methods

Search strategy

We systematically searched PubMed, Embase, the Cochrane Library, Web of Science and China National Knowledge Infrastructure (CNKI) from the inception of each database to June 25, 2024. The search terms included "primary liver cancer," "hepatocellular carcinoma," "transarterial chemoembolization," "local ablation," "randomized controlled trial," and others. The search was performed using a combination of subject headings and free text terms. The detailed search strategies that were utilized are available in Supplementary Table S1. Additionally, backward reference screening was conducted to identify further references not captured in the initial search.

Selection criteria

The study selection process followed the Preferred Reporting Items for Systematic Reviews and

Meta-Analyses (PRISMA) guidelines (Supplementary Table S2) [25]. The following inclusion criteria were utilized: (1) the research subjects involved patients with unresectable hepatocellular carcinoma; (2) the research subjects were aged 18 years or older; (3) two-arm randomized controlled trials (RCTs) that compared TACE alone, HAIC alone or these treatments combined with other local treatments (such as RFA, MWA, HIFU, PEI, or RT) were included; (4) the outcome measures included at least one of the following measures: efficacy, survival data, or adverse events; and (5) the language was restricted to English and Chinese, and blinding was not a criterion. The following exclusion criteria were utilized: (1) animal studies, self-controlled studies, observational studies, single-arm studies, or letters to the editor; (2) conference abstracts, reviews, or meta-analyses; (3) studies involving other malignant tumors; and (4) studies with unmergeable or missing data. Two reviewers independently screened the literature based on the inclusion and exclusion criteria, and any disagreements were resolved by a third reviewer. This study is registered with the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY, https://inplasy.com/), 202,480,125.

Outcomes

Patient demographics and treatment characteristics were recorded for each study. The recorded sample size represented the total number of patients included in the RCTs. The primary efficacy endpoint was the disease control rate (DCR), which was defined as the sum of the complete response (CR), partial response (PR), and stable disease (SD), based on the Response Evaluation Criteria in Solid Tumors (RECIST), modified RECIST classification systems and the World Health Organization (WHO) [26, 27]. Survival data primarily included 1-year and 2-year survival rates. Safety endpoints were defined as serious adverse events (SAEs) grade 3 or higher, according to the WHO and National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 4.0), along with serious complications that required additional medications or extended hospital stays as mentioned in the studies.

Data analysis

A Bayesian NMA was performed utilizing R statistical software (v4.4.1) for the comparative assessment of multiple treatment options. The "gemtc" package was used for model specification and the "rjags" package was used for Markov chain Monte Carlo sampling. Model selection between consistency and inconsistency models was based on the node-splitting analysis results, with the consistency model being implemented when no significant inconsistency was identified ($p > 0.05$). Otherwise, the inconsistency model was used. Weakly informative priors were adopted to limit subjective influences and maintain data-dominant inferences. We estimated odds ratios (ORs) and 95% confidence intervals (CIs) for the dichotomous outcomes via pairwise comparisons and network meta-analyses, employing the binomial likelihood method for these outcomes. The effect sizes from the individual studies were synthesized using a random-effects network meta-analysis model, with heterogeneity being quantified using the I^2 statistic (where $I^2 > 50\%$ indicated substantial heterogeneity). The interventions were ranked for each outcome using the surface under the cumulative ranking curve (SUCRA), where a larger area under the curve indicated a greater likelihood of the intervention being favorably ranked in the outcome measures. Given the observed differences in the baseline characteristics among the uHCC cohorts, a meta-regression analysis was conducted on the trial-specific baseline risk of the control arms. Finally, funnel plots were generated to evaluate publication bias.

Assessment

All of the studies were evaluated for risk of bias. RCTs were assessed using the Cochrane Collaboration's risk of bias tool, which includes the following seven methodological criteria: random sequence generation, allocation concealment, blinding of patients and investigators, blind of outcome data, incomplete outcome data, selective reporting, and other potential sources of bias. The pooled risk of bias across the studies was visualized and presented using the "robvis" package in R (version 4.4.1).

Results

Study selection and characteristics

Following the PRISMA guidelines [25], 8,683 records were identified via the search. After a thorough selection process, 40 RCTs were included. The literature selection process is illustrated in Fig. 1, and the basic information of the included studies is provided in Supplementary Table S3. For DCR, survival rates, and serious adverse events, nine studies compared TACE and TACE combined with RFA [28–36], eight studies compared TACE and TACE combined with MWA [37–44], five studies compared TACE and TACE combined with HIFU [45–49], six studies compared TACE and TACE combined with PEI [50–55], seven studies compared TACE and TACE combined with RT [56–62], three studies compared TACE and HAIC alone [63–65], and two studies compared TACE combined with RFA and TACE combined with MWA [66, 67]. Supplementary Figure S1 shows the risk of bias results for the included studies. The included studies clearly specified the utilized methods of randomization, such as computer-generated random numbers or random number tables; thus, they were

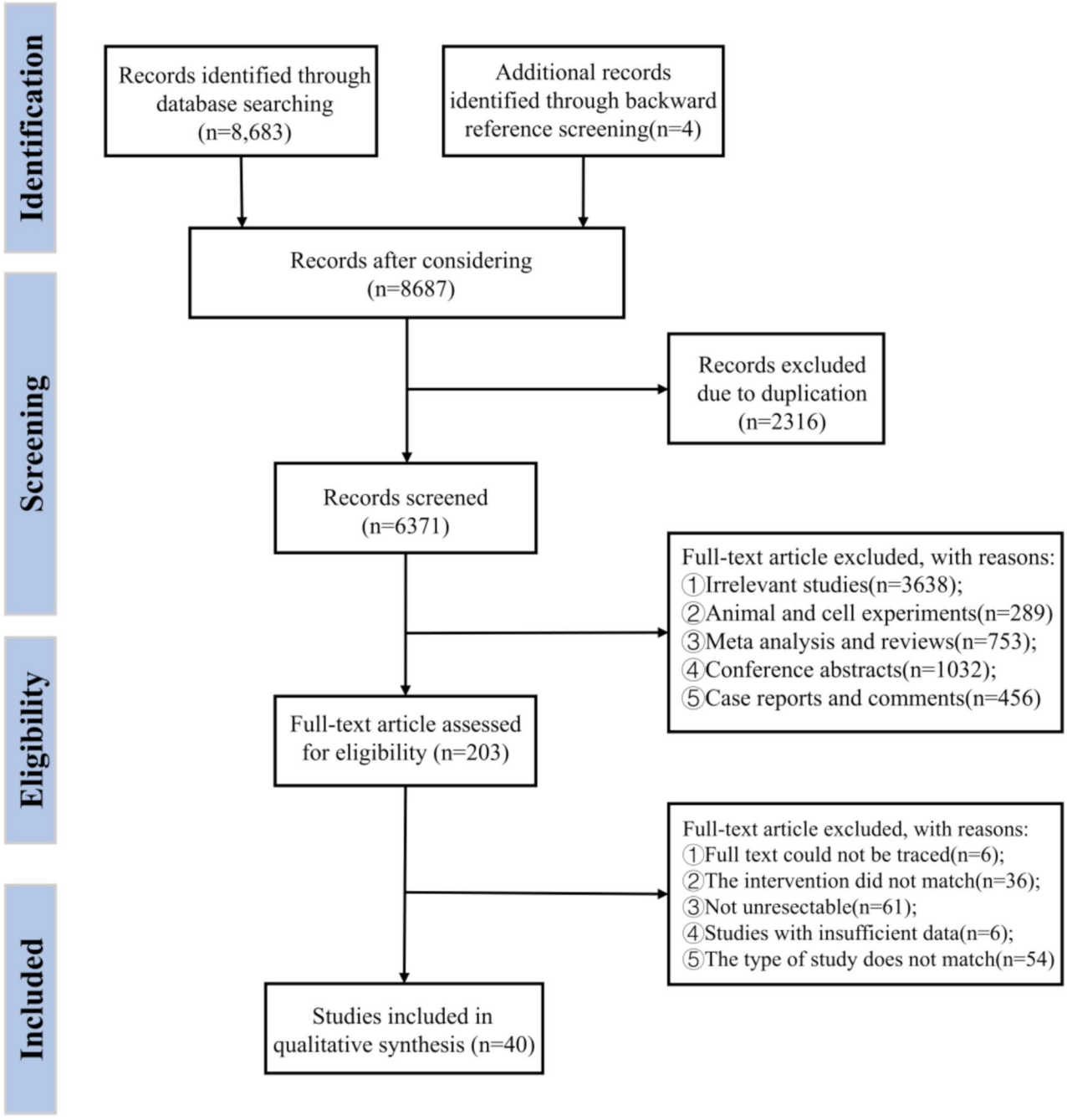
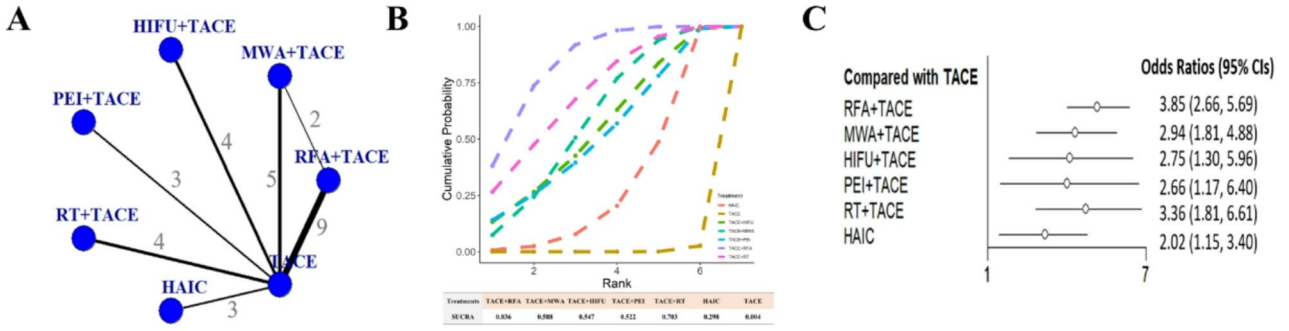


Fig. 1 The schematic diagram of literature search and selection process according to the PRISMA statement

evaluated as low risk. However, some studies did not specify the utilized blinding methods and were evaluated as unclear.

DCR

Thirty studies [28–36, 38–40, 42, 44, 45, 47–49, 51, 54–56, 59, 60, 62–67] reported the DCR for seven interventions, including TACE combined with RFA, TACE combined with MWA, TACE combined with HIFU, TACE combined with PEI, TACE combined with RT, HAIC, and TACE alone, thereby forming a closed loop in the analysis (Fig. 2A). The SUCRA were ranked from highest to lowest according to the following interventions (Fig. 2B): TACE combined with RFA (SUCRA: 0.836), TACE combined with RT (SUCRA: 0.703), TACE combined with MWA (SUCRA: 0.588), TACE combined with HIFU (SUCRA: 0.547), TACE combined with PEI (SUCRA: 0.522), HAIC alone (SUCRA: 0.298), and TACE



D

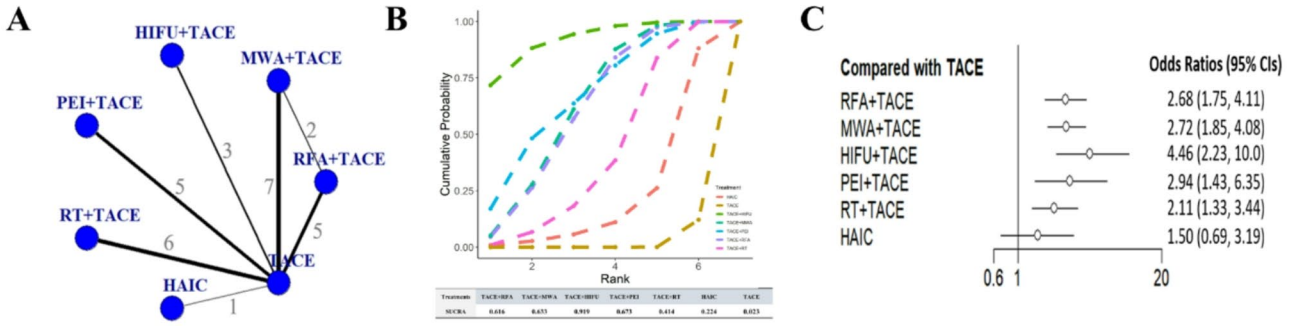
TACE+RFA	0.76 (0.44, 1.34)	0.72 (0.31, 1.66)	0.69 (0.28, 1.79)	0.88 (0.42, 1.85)	0.52 (0.26, 0.99)	0.26 (0.18, 0.38)
1.31 (0.74, 2.25)	**TACE+MWA**	0.94 (0.38, 2.28)	0.90 (0.34, 2.51)	1.15 (0.51, 2.68)	0.69 (0.32, 1.38)	0.34 (0.20, 0.55)
1.39 (0.60, 3.24)	1.07 (0.44, 2.60)	**TACE+HIFU**	0.96 (0.32, 3.09)	1.22 (0.45, 3.34)	0.73 (0.28, 1.84)	0.36 (0.17, 0.77)
1.44 (0.56, 3.58)	1.11 (0.40, 2.91)	1.04 (0.32, 3.13)	**TACE+PEI**	1.26 (0.43, 3.65)	0.75 (0.27, 2.00)	0.38 (0.16, 0.86)
1.14 (0.54, 2.38)	0.87 (0.37, 1.94)	0.82 (0.30, 2.20)	0.79 (0.27, 2.30)	**TACE+RT**	0.60 (0.25, 1.34)	0.30 (0.15, 0.55)
1.91 (1.03, 3.81)	1.45 (0.72, 3.11)	1.37 (0.54, 3.57)	1.33 (0.50, 3.75)	1.67 (0.75, 4.07)	**HAIC**	0.50 (0.29, 0.87)
3.85 (2.66, 5.69)	2.94 (1.81, 4.88)	2.75 (1.30, 5.96)	2.66 (1.17, 6.40)	3.36 (1.81, 6.61)	2.02 (1.15, 3.40)	**TACE**

Fig. 2 In-depth analysis of DCR:(**A**) The network structure plot for the network meta-analysis of DCR. In the network diagram, circular nodes represent different treatment modalities. Solid black lines between nodes show direct comparison relationships, with their thickness corresponding to the number of studies. Grey numbers indicate the precise study counts; (**B**) Cumulative ranking probability plots and SUCRA ranking table, where a larger area under the curve signifies a higher likelihood of treatment efficacy; (**C**) Random effects forest plot of DCR that contrasts different interventional treatments with TACE. The Odds Ratio (OR) is a measure of association between an exposure and an outcome. An OR of 1 indicates no difference between the groups; an OR greater than 1 suggests a higher likelihood of the outcome in the intervention group; whereas an OR less than 1 indicates a lower likelihood; (**D**) ORs with 95% Confidence Intervals (CIs) from a Network Meta-Analysis of DCR. Abbreviation: TACE, Transarterial chemoembolization; RFA, radiofrequency ablation; MWA, microwave ablation; HIFU, high intensity focused ultrasound; PEI, percutaneous ethanol injection; RT, radiotherapy; HAIC, hepatic arterial infusion chemotherapy; DCR, disease control rate

alone (SUCRA: 0.004). Compared with TACE alone, HAIC alone (OR: 2.02; 95% CI: 1.15–3.40) was associated with a better DCR (Fig. 2C). TACE combined with RFA (OR: 3.85; 95% CI: 2.66–5.69), TACE combined with MWA (OR: 2.94; 95% CI: 1.81–4.88), TACE combined with HIFU (OR: 2.75; 95% CI: 1.30–5.96), TACE combined with PEI (OR: 2.66; 95% CI: 1.17–6.40), and TACE combined with RT (OR: 3.36; 95% CI: 1.81–6.61) also demonstrated superior DCRs compared with TACE alone (Fig. 2D). In the indirect comparisons, TACE combined with RFA (OR: 1.91; 95% CI: 1.03–3.81) exhibited a greater DCR compared with HAIC alone (Fig. 2D).

1-year survival rate

Twenty-nine studies [30–32, 34, 35, 37–39, 41–46, 48, 50–54, 57–63, 66, 67] reported the 1-year survival rates for seven interventions, including TACE combined with RFA, TACE combined with MWA, TACE combined with HIFU, TACE combined with PEI, TACE combined with RT, HAIC alone, and TACE alone. A closed loop was formed in the analysis (Fig. 3A). According to the SUCRA results, TACE combined with HIFU (SUCRA: 0.919) demonstrated the highest ranking for 1-year survival benefit (Fig. 3B). Figure 3C further indicated that there was no significant difference in the 1-year survival rate between TACE and HAIC alone (OR: 1.50; 95% CI: 0.69–3.19). Moreover, TACE combined with RFA (OR: 2.68; 95% CI: 1.75–4.11), TACE combined with MWA (OR: 2.72; 95% CI: 1.85–4.08), TACE combined with HIFU (OR: 4.46; 95% CI: 2.23–10.0), TACE combined with PEI (OR: 2.94; 95% CI: 1.43–6.35), and TACE combined with RT (OR: 2.11; 95% CI: 1.33–3.44) were associated with significantly better 1-year survival rates compared to TACE alone (Fig. 3D). Moreover, TACE combined with HIFU (OR: 2.99; 95% CI: 1.09–9.03) demonstrated a higher DCR than HAIC alone in the indirect comparisons (Fig. 3D).



D

TACE+RFA	1.02 (0.62, 1.67)	1.67 (0.74, 4.08)	1.09 (0.47, 2.64)	0.79 (0.42, 1.51)	0.56 (0.23, 1.32)	0.37 (0.24, 0.57)
0.98 (0.60, 1.60)	**TACE+MWA**	1.65 (0.73, 3.96)	1.08 (0.47, 2.54)	0.77 (0.42, 1.44)	0.55 (0.23, 1.26)	0.37 (0.24, 0.54)
0.60 (0.24, 1.35)	0.61 (0.25, 1.38)	**TACE+HIFU**	0.66 (0.23, 1.83)	0.47 (0.19, 1.10)	0.33 (0.11, 0.92)	0.22 (0.10, 0.45)
0.92 (0.38, 2.11)	0.93 (0.39, 2.11)	1.51 (0.55, 4.44)	**TACE+PEI**	0.72 (0.29, 1.69)	0.51 (0.17, 1.45)	0.34 (0.16, 0.7)
1.27 (0.66, 2.39)	1.29 (0.69, 2.39)	2.11 (0.91, 5.27)	1.39 (0.59, 3.41)	**TACE+RT**	0.71 (0.28, 1.71)	0.47 (0.29, 0.75)
1.79 (0.76, 4.35)	1.81 (0.8, 4.39)	2.99 (1.09, 9.03)	1.97 (0.69, 5.78)	1.41 (0.59, 3.62)	**HAIC**	0.67 (0.31, 1.44)
2.68 (1.75, 4.11)	2.72 (1.85, 4.08)	4.46 (2.23, 10.0)	2.94 (1.43, 6.35)	2.11 (1.33, 3.44)	1.50 (0.69, 3.19)	**TACE**

Fig. 3 In-depth analysis of 1-year survival rate:(**A**) The network structure plot for the network meta-analysis of 1-year survival rate; (**B**) Cumulative ranking probability plots and SUCRA ranking table; (**C**) Random effects forest plot of 1-year survival rate that contrasts different interventional treatments with TACE; (**D**) ORs with 95% CIs from a Network Meta-Analysis of 1-year survival rate

2-year survival rate

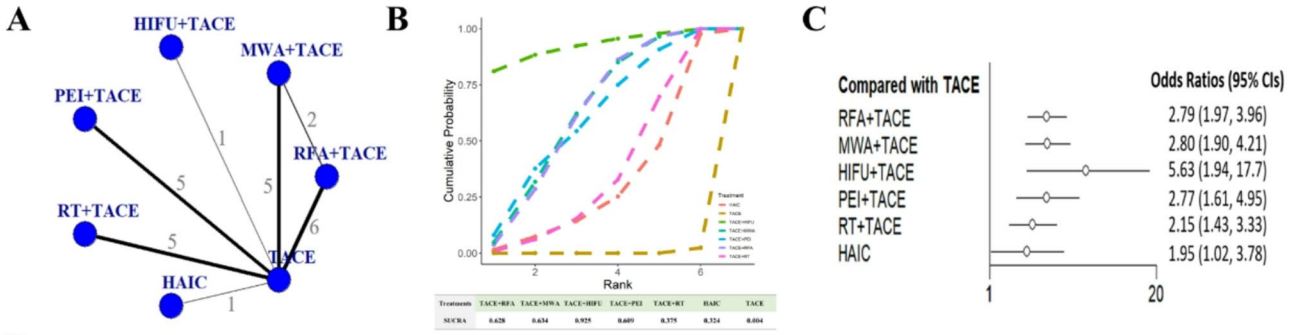
Twenty-five studies [30–32, 34–39, 41, 42, 45, 50–54, 57, 59–63, 66, 67] reported the 2-year survival rates for seven interventions, including TACE combined with RFA, TACE combined with MWA, TACE combined with HIFU, TACE combined with PEI, TACE combined with RT, HAIC alone, and TACE alone (Fig. 4A). Figure 4B displayed the SUCRA rankings of the 2-year survival rate in descending order as follows: TACE combined with HIFU (SUCRA: 0.925), TACE combined with MWA (SUCRA: 0.634), TACE combined with RFA (SUCRA: 0.628), TACE combined with PEI (SUCRA: 0.609), TACE combined with RT (SUCRA: 0.375), HAIC alone (SUCRA: 0.324), and TACE alone (SUCRA: 0.004). There was a significant difference observed in 2-year survival between HAIC alone (OR: 1.95; 95% CI: 1.02–3.78) and TACE alone (Fig. 4C). The NMA results indicated that TACE combined with RFA (OR: 2.79; 95% CI: 1.97–3.96), TACE combined with MWA (OR: 2.80; 95% CI: 1.90–4.21),TACE combined with HIFU (OR: 5.63; 95% CI: 1.94–17.7), TACE combined with PEI (OR: 2.77; 95% CI: 1.61–4.95), TACE combined with RT (OR: 2.15; 95% CI: 1.43–3.33), and HAIC (OR: 1.95; 95% CI: 1.02–3.78) demonstrated significantly higher 2-year survival rates compared to TACE alone (Fig. 4D).

Serious adverse events

Twenty- five studies [30, 33, 34, 37, 38, 40, 42–47, 49, 51, 55–58, 60–64, 66, 67] reported serious adverse events across seven interventions, including TACE combined with RFA, TACE combined with MWA, TACE combined with HIFU, TACE combined with PEI, TACE combined with RT, HAIC alone, and TACE alone, thus forming a closed loop in the analysis (Fig. 5A). The SUCRA were ranked for the serious adverse events (Fig. 5B) from highest to lowest in the following manner: TACE combined with PEI (SUCRA: 0.676), TACE combined with MWA (SUCRA: 0.568), TACE combined with RFA (SUCRA: 0.560), TACE combined with RT (SUCRA: 0.526), HAIC alone (SUCRA: 0.469), TACE alone (SUCRA: 0.447), and TACE combined with HIFU (SUCRA: 0.250). The NMA results revealed no significant differences in serious adverse reactions among the different treatments (Fig. 5CD).

Heterogeneity, consistency, meta-regression, and publication bias

Closed loops were formed across all of the study endpoints. All of the *P* values calculated from the node-splitting analysis for each outcome measure were greater than 0.05, thus indicating no significant inconsistency between



D

TACE+RFA	1.01 (0.66, 1.56)	2.03 (0.66, 6.83)	0.99 (0.52, 1.93)	0.77 (0.45, 1.34)	0.70 (0.33, 1.47)	0.36 (0.25, 0.51)
0.99 (0.64, 1.51)	**TACE+MWA**	2.01 (0.64, 6.73)	0.99 (0.50, 1.97)	0.77 (0.43, 1.39)	0.70 (0.32, 1.49)	0.36 (0.24, 0.53)
0.49 (0.15, 1.51)	0.50 (0.15, 1.57)	**TACE+HIFU**	0.49 (0.14, 1.65)	0.38 (0.11, 1.23)	0.34 (0.09, 1.22)	0.18 (0.06, 0.51)
1.01 (0.52, 1.92)	1.01 (0.51, 1.99)	2.06 (0.61, 7.29)	**TACE+PEI**	0.78 (0.38, 1.56)	0.70 (0.30, 1.66)	0.36 (0.20, 0.62)
1.30 (0.75, 2.23)	1.31 (0.72, 2.34)	2.63 (0.82, 8.82)	1.28 (0.64, 2.61)	**TACE+RT**	0.91 (0.42, 1.97)	0.46 (0.30, 0.70)
1.43 (0.68, 3.01)	1.43 (0.67, 3.16)	2.90 (0.82, 11.1)	1.43 (0.60, 3.36)	1.10 (0.51, 2.40)	**HAIC**	0.51 (0.26, 0.98)
2.79 (1.97, 3.96)	2.80 (1.90, 4.21)	5.63 (1.94, 17.7)	2.77 (1.61, 4.95)	2.15 (1.43, 3.33)	1.95 (1.02, 3.78)	**TACE**

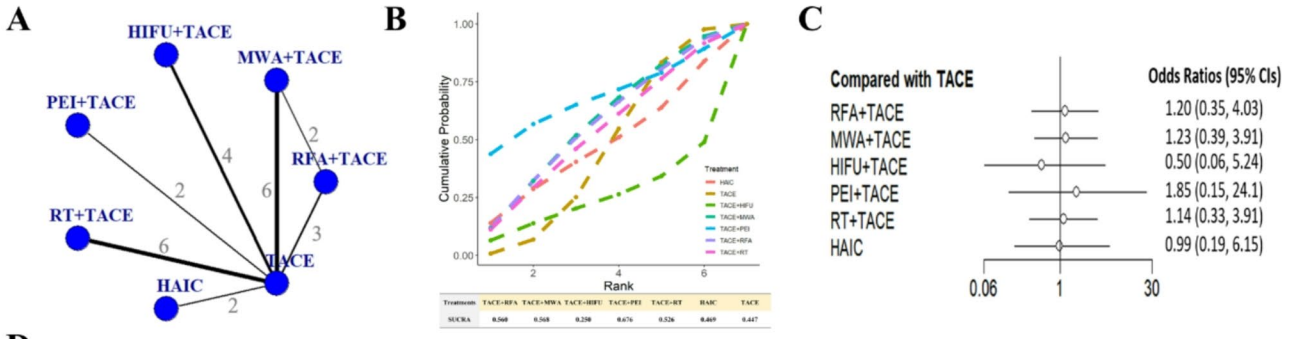
Fig. 4 In-depth analysis of 2-year survival rate:(**A**) The network structure plot for the network meta-analysis of 2-year survival rate; (**B**) Cumulative ranking probability plots and SUCRA ranking table; (**C**) Random effects forest plot of 2-year survival rate that contrasts different interventional treatments with TACE; (**D**) ORs with 95% CIs from a Network Meta-Analysis of 2-year survival rate

direct and indirect comparisons within the closed loop (Supplementary Table S4). The heterogeneity test results revealed no significant heterogeneity among the studies (I^2 < 50%) (Supplementary Table S5). Transitivity evaluation demonstrated a balanced distribution of possible effect modifiers among all direct treatment comparisons, except for mean tumor size. (Supplementary Figure S2). Further random-effects meta-regression analyses of baseline data (including sample size, region, publication year, mean age, mean tumor size, and Child-Pugh Classification) revealed no significant associations in any of the tests, indicating the robustness of the NMA results (Supplementary Table S6). Publication bias was assessed using a funnel plot, which revealed that the scatter points of most study were distributed within the range of the inverted funnel plot and exhibited strong symmetry, thereby suggesting a low likelihood of publication bias in this study (Fig. 6).

Discussion

The optimal treatment strategy for uHCC patients remains an unresolved problem. Although immunotherapy (atezolizumab/bevacizumab) is the first-line for advanced HCC with extrahepatic spread, BCLC-B/early C-stage uHCC patients with preserved hepatic function require better options in situations where systemic therapy may be premature, cost-prohibitive, or contraindicated [68–70]. TACE and HAIC play crucial roles in the therapeutic management of intermediate-advanced stage uHCC. However, these treatments may result in incomplete tumor necrosis and poor outcomes [71]. Repeated TACE or HAIC can increase the occurrence of complications and reduce benefits [72]. Given the limitations of single-modality therapies and the heterogeneity of uHCC, combining HAIC or TACE with local therapies appears to be a promising and viable option. Due to the lack of direct comparative studies, clarifying the efficacy and safety of different interventional strategies is crucial for guiding clinical practice and optimizing treatment decisions for uHCC patients.

In this study, we conducted an NMA to evaluate the DCR, 1-year and 2-year survival rates, and serious adverse events associated with TACE or HAIC alone, as well as in combination with local therapies (such as RFA, MWA, HIFU, PEI, and RT) for the treatment of uHCC. We identified 40 eligible studies involving 7138 patients, all of whom were determined to not be candidates for treatment with surgical resection. In the NMA of DCR, we observed that all of the evaluated combination therapeutic approaches demonstrated superior DCRs



D

TACE+RFA	1.01 (0.26, 4.17)	0.42 (0.04, 5.99)	1.54 (0.10, 25.99)	0.94 (0.17, 5.56)	0.83 (0.11, 7.52)	0.83 (0.25, 2.83)
0.99 (0.24, 3.79)	**TACE+MWA**	0.41 (0.04, 5.57)	1.51 (0.10, 25.71)	0.92 (0.17, 5.11)	0.82 (0.10, 7.07)	0.82 (0.26, 2.54)
2.40 (0.17, 26.8)	2.43 (0.18, 26.8)	**TACE+HIFU**	3.74 (0.12, 91.03)	2.27 (0.15, 25.7)	2.03 (0.11, 30.2)	1.99 (0.19, 16.2)
0.65 (0.04, 10.1)	0.66 (0.04, 10.1)	0.27 (0.01, 8.38)	**TACE+PEI**	0.61 (0.04, 9.51)	0.54 (0.03, 12.3)	0.54 (0.04, 6.54)
1.07 (0.18, 5.96)	1.08 (0.20, 5.85)	0.44 (0.04, 6.46)	1.63 (0.11, 28.5)	**TACE+RT**	0.87 (0.11, 8.11)	0.88 (0.26, 3.06)
1.21 (0.13, 9.35)	1.22 (0.14, 9.77)	0.49 (0.03, 9.24)	1.86 (0.08, 39.8)	1.14 (0.12, 9.00)	**HAIC**	1.01 (0.16, 5.30)
1.20 (0.35, 4.03)	1.23 (0.39, 3.91)	0.50 (0.06, 5.24)	1.85 (0.15, 24.1)	1.14 (0.33, 3.91)	0.99 (0.19, 6.15)	**TACE**

Fig. 5 In-depth analysis of serious adverse events:(**A**) The network structure plot for the network meta-analysis of serious adverse events; (**B**) Cumulative ranking probability plots and SUCRA ranking table; (**C**) Random effects forest plot of serious adverse events that contrasts different interventional treatments with TACE; (**D**) ORs with 95% CIs from a Network Meta-Analysis of serious adverse events

compared with TACE alone (Fig. 2C). TACE combined with RFA was observed to significantly outperform HAIC (OR: 1.91; 95% CI: 1.03–3.81) and TACE (OR: 3.85; 95% CI: 2.66–5.69) alone in terms of DCR, and the SUCRA probability ranking (SUCRA 0.836) further establishes the clinical priority of this combined strategy among the three modalities. Prior meta-analyses have demonstrated that TACE combined with RFA provides greater efficacy for uHCC compared with TACE alone, which is consistent with our findings [73, 74]. Our analysis further included HAIC, an emerging interventional strategy, and revealed that TACE combined with RFA may result in superior DCR compared to HAIC, thus offering potential insights for clinical decisions. TACE combined with RFA may enhance efficacy through dual mechanisms. Specifically, the TACE-induced ischemic tumor microenvironment can enhance the sensitivity of RFA to thermal ablation [75]. The inflammatory response after RFA not only promotes chemotherapy drug penetration in residual lesions, but also significantly enhances immune function and inhibits tumor cell proliferation [76]. This combined strategy transcends the limitation of RFA monotherapy in HCC, enabling effective tumor ablation for larger lesions while expanding clinical indications [77]. Additionally, recent studies have demonstrated that for patients with locally advanced HCC with major vascular invasion, TACE combined with RT significantly improves survival compared with sorafenib [78]. In our study, compared with TACE alone, TACE combined with RT improved the survival and DCR of patients with uHCC. These findings collectively support the potential use of TACE combined with RT as a therapeutic strategy.

For the survival rate assessment, TACE combined with HIFU demonstrated optimal ranking outcomes for both 1-year survival rate (SUCRA: 0.919) and 2-year survival rate (SUCRA: 0.925) based on cumulative ranking probability analysis. However, no statistically significant differences were observed in 1- and 2-year survival rates among TACE combined with HIFU, TACE combined with RFA, and TACE combined with MWA (Figs. 3D and 4D). Given the distinct mechanisms involved in these therapies, the exact underlying cause for the superior or inferior comparative survival benefits could not be assessed in this analysis. Additionally, we observed that all of the combination therapies exhibited higher 1-year and 2-year survival rates than TACE alone, and TACE combined with HIFU demonstrated a better 1-year survival rate than HAIC (OR: 2.99; 95% CI: 1.09–9.03). Related pathological studies have demonstrated that transcatheter palliative therapies using iodized oil can

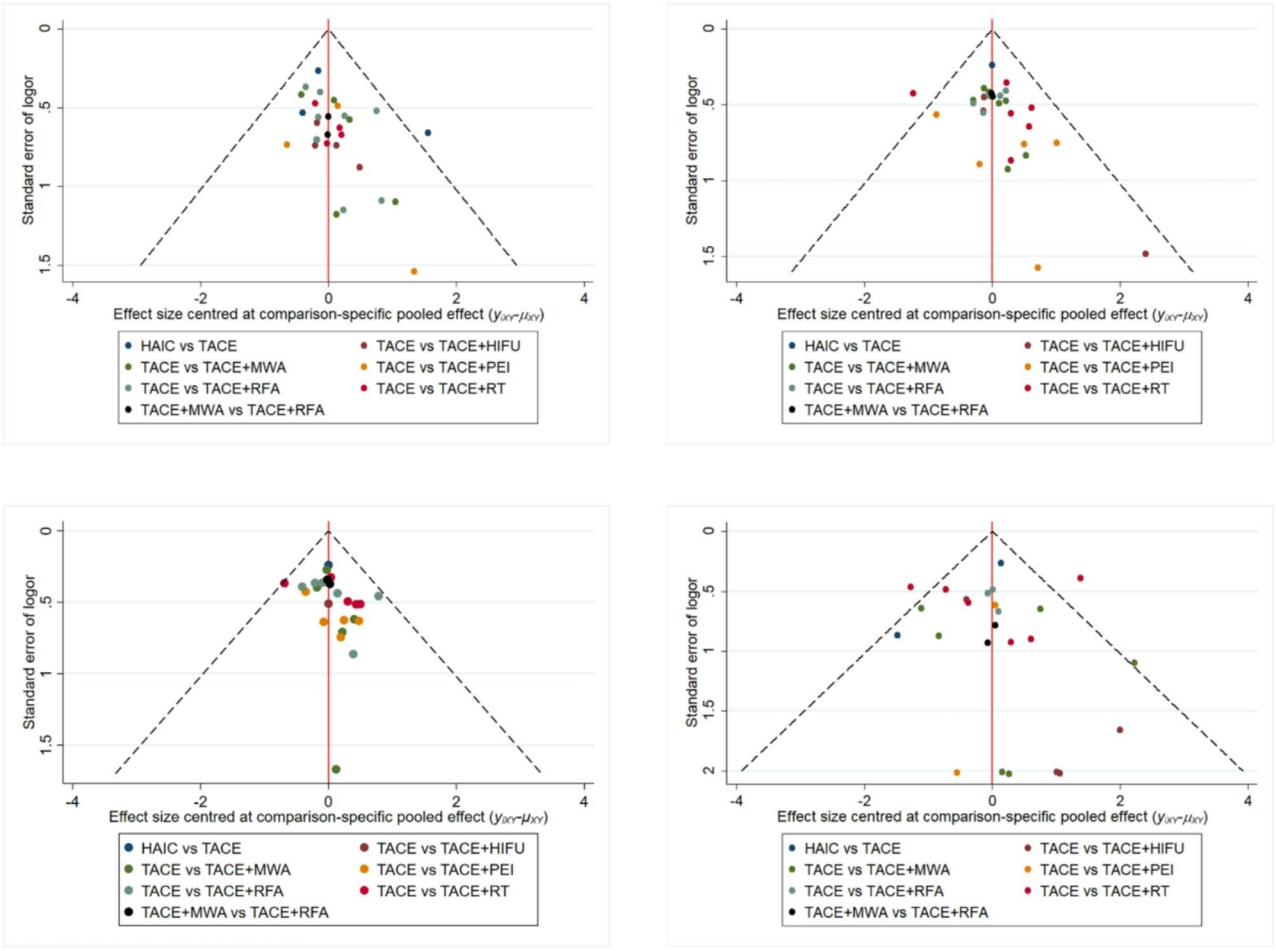


Fig. 6 Funnel plots of different outcome. (**A**) disease control rate; (**B**) 1-year survival rate; (**C**) 2-year survival rate; (**D**) Serious adverse event

achieve necrosis in more than 90% of tumor tissue in some cases, yet this high necrosis rate is observed in only 26–70% of treated nodules [79]. The variation in effectiveness is primarily influenced by the utilized techniques and the anatomy of the tumor-feeding arteries [80]. Therefore, integrating (chemo)embolization with other ablative modalities appears to be a sensible approach to increase tumor necrosis rates and consequently prolong patient survival. As a noninvasive ablation technique, HIFU therapy can avoid the risks associated with puncture. HIFU has been technically standardized in some European centers, but Asian data still dominate related literature concerning HIFU, which is likely due to the earlier availability of HIFU device in the Asia-Pacific region. Previous studies have demonstrated that TACE combined with HIFU can reduce the side effects associated with repeated use of TACE and prolong survival without compromising therapeutic efficacy [81]. Our study confirmed the aforementioned findings and further revealed a potential advantage of TACE combined with HIFU compared with HAIC in terms of 1-year survival rate.

Current global guidelines exhibit variations in HAIC recommendations. The Japanese guidelines recommend HAIC as the standard therapy for HCC complicated by portal vein tumor thrombus [82]. However, inconsistent outcomes in cisplatin-based HAIC studies, including a phase III trial demonstrating no survival benefit over sorafenib (median overall survival: 11.8 vs. 11.5 months; HR:1.01, 95% CI: 0.74–1.37; $p = 0.96$). Therefore, HAIC has not been endorsed by Western countries [83]. For uHCC, HAIC offers enhanced locoregional drug delivery and fewer adverse events (such as ectopic embolisms), yet its therapeutic superiority over TACE remains unclear. We observed that HAIC (OR: 2.02; 95% CI: 1.15–3.40) was associated with a greater DCR compared with TACE alone, with a potential advantage in 2-year survival rate (OR: 1.95; 95% CI: 1.02–3.78). The possible reason is that HAIC can directly deliver high-dose anticancer drugs to the detected HCC or undetected micrometastases [84]. Previous studies have also demonstrated that HAIC is effective in reducing intrahepatic metastasis rates in uHCC [85].

Serious adverse events are a key consideration in the use of combination therapies, as they reflect the potential risks of combined treatment. In this study, we observed no statistically significant differences in serious adverse events across therapies. According to the literature, local treatments such as RFA, MWA, HIFU, PEI, and RT are generally safe and do not cause significant adverse reactions. Additionally, combination therapy may shorten the duration of interventional treatment, thereby potentially reducing side effects [24, 86]. Future investigations warrant large-scale prospective multicenter studies to systematically evaluate the adverse effects of combination therapies.

Several limitations of this study should be acknowledged. First, due to the multitude of factors affecting the curative treatment of uHCC and the inconsistent selection of TACE chemotherapy regimens, it is challenging to establish unified inclusion criteria, which may impact the interpretability of the results. Second, although heterogeneity tests and meta-regression revealed no significant impact of baseline tumor size differences on outcomes, it should be noted that variations in tumor diameter existed across treatment groups. Given the potential prognostic influence of tumor size, future large-scale studies are needed to further validate the robustness of the conclusions. Third, although the endpoints (including the DCR, 1-year survival and 2-year survival) were pragmatically selected based on the availability of existing RCTs, the lack of progression-free survival data and limited long-term follow-ups in the existing studies constrain a comprehensive evaluation of sustained therapeutic efficacy, thus necessitating future investigations with extended outcome tracking. Additionally, the limited direct evidence observed for some of the treatments necessitates indirect comparisons, and the geographic concentration of the studies conducted in Asia (which is a region exhibiting high uHCC prevalence) underscores the need for large-scale multiregional trials to confirm the global applicability of the results.

Conclusion

In summary, compared with TACE alone, combined treatment approaches for uHCC patients demonstrate better efficacy and survival benefits. Moreover, compared with TACE and HAIC, TACE combined with RFA exhibits better efficacy, whereas TACE combined with HIFU demonstrates the best 1-year survival rate. Additionally, HAIC treatment alone offers advantages over TACE alone in terms of the DCR and 2-year survival rate.

Abbreviations

CNKI	China National Knowledge Infrastructure
DCR	Disease control rate
HAIC	Hepatic arterial infusion chemotherapy
HIFU	High-intensity focused ultrasound
MWA	Microwave ablation
OR	Odds ratio
PEI	Percutaneous ethanol injection
RFA	Radiofrequency ablation
RT	Radiotherapy
TACE	Transarterial chemoembolization
uHCC	Unresectable hepatocellular carcinoma

Supplementary Information

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Supplementary Material 1

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Not applicable.

Author contributions

XYL and JBF contributed equally to this study. XYL, JBF, and XLY designed the research. XYL, XCZ, and JQL performed the literature search. XCZ and JQL conducted language proofreading. SLL and XLY analyzed the data. XYL and JBF wrote the article. JBF and CML revised the article. All authors reviewed the manuscript.

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Data availability

The datasets used and analysed during the current study are available from the corresponding author, upon reasonable request.

Declarations

Ethics approval and consent to participate

This is a meta-analysis. Chongqing Emergency Medical Center Research Ethics Committee has confirmed that no ethical approval is required. This is a meta-analysis. Informed consent is not required.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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