Lenvatinib in combination with transarterial chemoembolization vs. sorafenib in combination with transarterial chemoembolization for unresectable hepatocellular carcinoma: A network meta-analysis

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Abstract. The use of tyrosine kinase inhibitors combined with transarterial chemoembolization (TACE) is considered the standard therapy for patients with unresectable hepatocellular carcinoma (uHCC). However, information regarding the efficacy of lenvatinib or sorafenib in combination with TACE for patients with uHCC is limited. The present study involved a systematic search for randomized controlled trials on the PubMed, Embase, Web of Science and the Cochrane Library online databases to compare the use of TACE combined with either lenvatinib or sorafenib, and monotherapy using either lenvatinib or sorafenib for patients with uHCC. The network meta-analysis of the present study included eight randomized controlled trials involving 2,929 patients. The random-effects model was used, and hazard ratios and risk ratios with 95% CIs were calculated. Lenvatinib in combination with TACE provided the maximal overall survival (97.92%), progression-free survival (87.8%), objective response (96.68%) and disease control (96.27%) rates. The results of the present study indicated that, in the treatment of patients with uHCC, lenvatinib in combination with TACE showed a significantly improved efficacy when compared with sorafenib and TACE. Therefore, in the future, combination therapy of lenvatinib with TACE could be potentially prioritized over sorafenib with TACE for the treatment of patients with uHCC.

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Introduction

Hepatocellular carcinoma (HCC), the dominant type of primary liver cancer, is the sixth most common type of cancer and third leading cause of cancer-related deaths worldwide (1,2). Several curative options are available for the treatment of patients with early-stage HCC, including radiofrequency ablation, surgical resection and liver transplantation (3). However, over two-thirds of patients with HCC are diagnosed with unresectable HCC (uHCC) and curative treatment may be less effective for these patients (4-6). Various local and systemic therapies are available for uHCC based on the Barcelona Clinic Liver Cancer Prognosis and Treatment Strategy (3).

With significant progress in the treatment of HCC, novel strategies for uHCC treatment continue to emerge. Transarterial chemoembolization (TACE), tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors are widely recommended for the treatment of intermediate to advanced HCC (6,7). Sorafenib was the 1st TKI approved by the Food and Drug Administration as a first-line treatment for uHCC and can target multiple signaling pathways, such as the RAF/MEK/ERK pathway, to achieve anti-angiogenesis (8,9). TACE has been reported to induce to tumor cell necrosis by selectively blocking the nutrient-supplying arteries of the tumor and by delivering high concentrations of chemotherapeutic drugs into the vessels feeding the tumor (10). However, TACE has also been reported to induce tumor tissue hypoxia and tumor angiogenesis, thus increasing the risk of tumor progression (10,11). Therefore, TKIs that inhibit angiogenesis may be beneficial when used in combination with TACE to treat patients with uHCC.

In a phase III multicenter randomized trial, lenvatinib, a TKI, was reported to have a significantly better advantage in terms of progression-free survival (PFS), tumor response and overall survival (OS) compared with sorafenib for the treatment of patients with uHCC (12). Therefore, lenvatinib has also been recommended as a first-line treatment for advanced HCC (12). Shimose *et al* (13) retrospectively studied 171 patients with intermediate-stage HCC who were refractory to TACE and

received either lenvatinib or sorafenib. The aforementioned study demonstrated that lenvatinib significantly prolonged the median PFS time compared with sorafenib or TACE in patients with TACE-refractory intermediate-stage HCC (lenvatinib, 5.8 months; sorafenib, 3.8 months; TACE, 2.8 months) (13).

As the efficacy of lenvatinib and sorafenib has received increased attention, several studies on the use of combination therapy of lenvatinib or sorafenib with TACE for uHCC have emerged in recent years. A prospective randomized trial reported that lenvatinib combined with TACE did not significantly improve survival outcomes in terms of OS but did improve the time-to-progression (TTP) of HCC with portal vein tumor thrombus (14). However, in our previous meta-analysis, the use of lenvatinib with TACE was significantly superior compared with sorafenib with TACE, in terms of OS, PFS and tumor response in patients with uHCC (15). In contradiction to the aforementioned results, a further network meta-analysis (NMA) reported no statistically significant difference between the use of lenvatinib with TACE compared with sorafenib with TACE in terms of OS (16). A large proportion of studies included in the aforementioned meta-analyses were retrospective cohort studies, which could have introduced the potential risk of selection bias and confounding bias. Therefore, the present study aimed to perform an NMA based on randomized controlled trials (RCTs). In particular, landmark phase III clinical trials were used in the NMA of the present study for the comparison of all therapies, including combination therapies using either lenvatinib or sorafenib with TACE, and monotherapies using TACE, lenvatinib or sorafenib in patients with uHCC.

Materials and methods

Study registration. The NMA performed in the present study complied with guidelines specified by the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement (17). The present NMA was registered on the PROSPERO database (www.crd.york.ac.uk/prospero/) of systematic reviews with the identification no. CRD42023448995.

Search strategy and eligibility criteria. The present study systematically searched for available RCTs in the PubMed (https://pubmed.ncbi.nlm.nih.gov), Embase (www.embase.com), Web of Science (www. webofscience.com) and Cochrane Library (www.cochranelibrary.com) online databases (Table SI). The paramount search terms used were: 'Hepatocellular carcinoma', 'liver neoplasms', 'chemoembolization', 'sorafenib' and 'lenvatinib'.

Studies were included in the present NMA if they fulfilled the following criteria: i) The study population comprised of patients diagnosed with uHCC; ii) the interventions of interest included lenvatinib with TACE, sorafenib with TACE, or TACE, lenvatinib and sorafenib monotherapies; iii) the outcomes assessed were OS, PFS, objective response rate (ORR) and disease control rate (DCR); and iv) the publication type was classed as an RCT. Studies were excluded from the present NMA if they fulfilled the following criteria: i) Patients with uHCC had received any previous systemic therapy; and ii) studies lacked adequate outcome data or did not report outcomes of interest as specified in the aforementioned inclusion criteria.

Data extraction and quality assessment. The following data were independently extracted from each study by two reviewers in a standardized manner: i) General characteristics (number of patients and nationality of study population); ii) patient characteristics (age, sex, Child-Pugh class, viral hepatitis, portal vein tumor thrombosis and extrahepatic metastasis); iii) clinical outcomes (OS, PFS, ORR and DCR); and iv) adverse events (AEs). The Cochrane risk-of-bias tool was used to independently investigate potential biases for each study (18).

Statistical analysis. The present study used a Bayesian approach to analyze the relevant data using R (version 4.2.1; RStudio, Inc.) and Stata/MP (version 17.0; StataCorp LP). Quality assessment was performed using RevMan (version 5.3; The Cochrane Collaboration). The primary outcomes (OS and PFS) were presented as hazard ratios (HR) with corresponding 95% CI. The ORR and DCR were evaluated according to the modified Response Evaluation Criteria in Solid Tumors assessment (19) and were expressed as risk ratios (RR) with the corresponding 95% CI. Brooks-Gelman-Rubin diagnostics, traces and density plots were used to assess the model convergence. A total of 50,000 iterations per chain were performed, of which the first 10,000 iterations were used for annealing the algorithm to remove the effects of the initial value. The ranking probabilities of the various treatments were used to estimate the hierarchy of treatments. A node-splitting approach was used to assess the local consistency of the models. The comparison results of the different treatments were expressed as forest plots. According to Q statistics and the I^2 statistic index, studies with $P>0.05$ or $I^2<50\%$ were considered to have low heterogeneity (20). The random-effects model was used regardless of the I^2 value. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Study selection and study characteristics. A total of 15,875 relevant records were initially identified, of which 39 were assessed for eligibility after removing duplicate articles and screening the titles and abstracts to ensure they met the inclusion and exclusion criteria. The present NMA included eight RCTs that fulfilled the eligibility criteria and screening process for quantitative synthesis: Kudo *et al* (21), SPACE (22), TACE-2 (23), REFLECT (12), STAH (24), Ding *et al* (14), TACTICS (25) and LAUNCH (26) (Fig. 1).

The eight trials included in the present NMA enrolled 2,929 patients in total (Table I). Direct comparisons included sorafenib with TACE vs. TACE monotherapy or in combination with a placebo, lenvatinib vs. sorafenib, sorafenib with TACE vs. sorafenib monotherapy, lenvatinib with TACE vs. sorafenib with TACE and lenvatinib with TACE vs. lenvatinib monotherapy. The majority of patients with uHCC enrolled in the eight included trials were male and had Child-Pugh class A liver function and an Eastern Cooperative Oncology Group Performance Status score of 0.

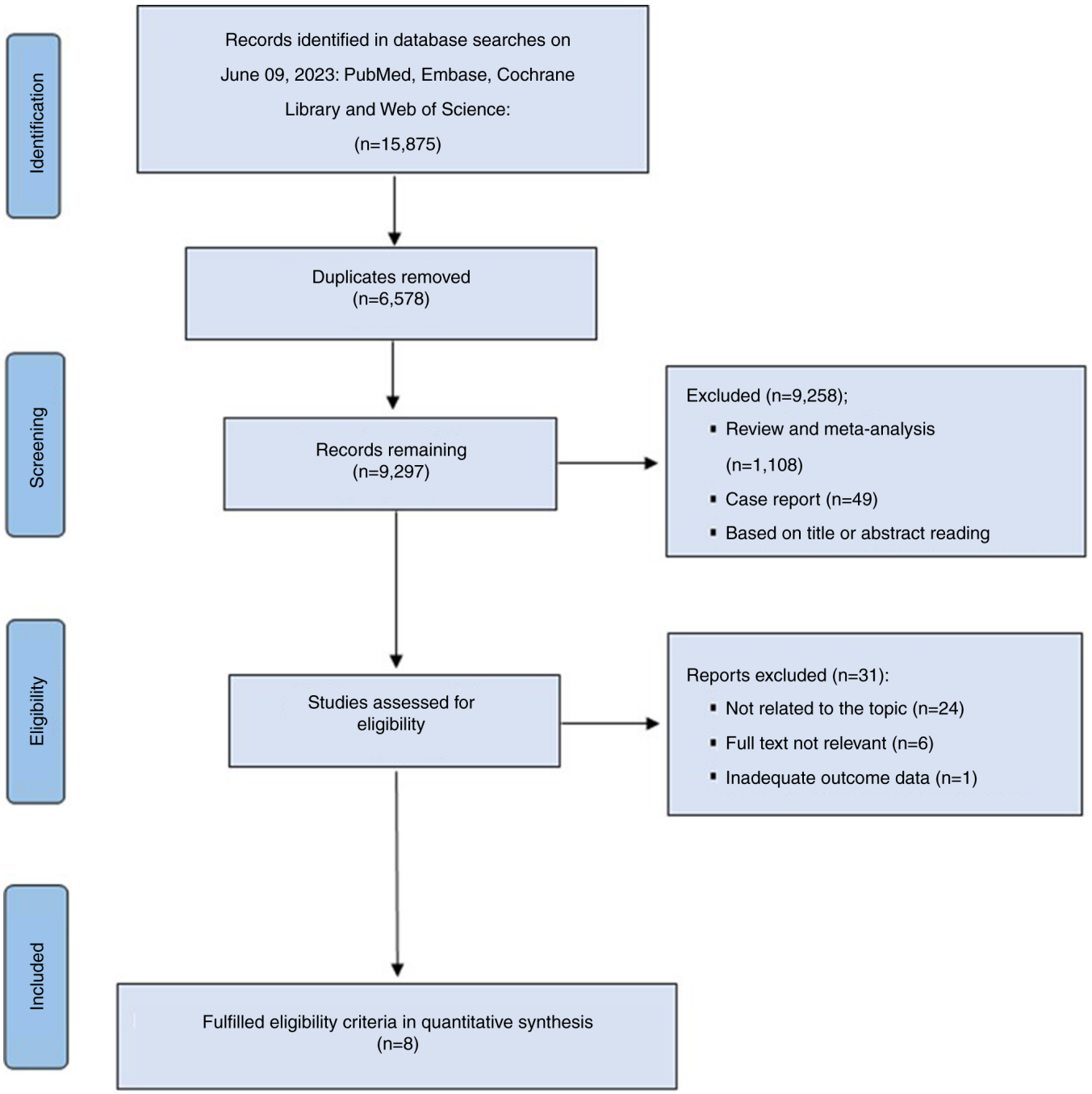

Figure 1. A preferred reporting items for systematic reviews and meta-analyses flow diagram of the process for the identification of eligible studies.

OS and PFS. All eight RCTs included in the present NMA reported the OS of patients with uHCC as a survival outcome (Fig. 2A). Compared with sorafenib monotherapy, lenvatinib with TACE demonstrated significantly increased OS (HR, 0.44; 95% CI, 0.27-0.75), while all other treatment strategies showed no significant differences in OS compared with sorafenib monotherapy (Fig. 3A). Moreover, the present study found that lenvatinib with TACE was associated with a significantly increased OS compared with sorafenib with TACE, TACE alone and lenvatinib monotherapy (HR, 0.50; 95% CI, 0.30-0.89; HR, 0.46; 95% CI, 0.27-0.86; HR, 0.47; 95% CI, 0.31-0.72, respectively; Table II). In addition, a significant survival advantage was observed between sorafenib with TACE and all the other monotherapies, including TACE, sorafenib and lenvatinib. In the treatment ranking analysis, the combination of lenvatinib with TACE had a 97.92% probability of delivering a increased OS and was most effective compared with all other treatments examined (Fig. 4A; Table III). In the present NMA, five RCTs reported PFS as a survival outcome of patients with uHCC; however, there were no closed loops in the network (Fig. 2B). No significant differences in PFS were observed among all treatments examined (Fig. 3B; Table II). Similarly, lenvatinib in combination with TACE had the highest likelihood of providing maximal PFS compared with all other therapies (rank probability, 87.8%; Fig. 4B; Table III).

Table I. Demographic characteristics of the trials included in the network meta-analysis.

First author, year	Trial name	Intervention	Number of patients	Age, years	Male sex, %	Eastern cooperative oncology group performance status (0/1), %	Child-pugh class (A/B), %	Hepatitis B virus, %	Hepatitis C virus, %	Barcelona clinic liver cancer stage (A/B), %	Portal vein tumor thrombosis, %	Extrahepatic metastasis, %	(Refs.)
Kudo *et al*, 2011	NA	Sorafenib + TACE	229	69[a,b]	76	87.8/12.2	100/0	20.5	60.7	NA	0	0	(21)
		TACE + placebo	229	70[a,b]	73.4	88.2/11.8	100/0	22.7	64.6	NA	0	0	
Lencioni *et al*, 2016	SPACE	Sorafenib + TACE	154	64.5[a]	87.7	100/0	99.4/0.6	35.7	25.3	0/100	0	0	(22)
		TACE + placebo	153	63[a]	82.4	100/0	100/0	32.7	26.8	0/100	0	0	
Meyer *et al*, 2017	TACE-2	Sorafenib + TACE	157	65 (57-71)[c]	89	62/37	93/4	5	12	NA	NA	0	(23)
		TACE + placebo	156	68 (63-74)[c]	88	62/37	95/2	6	9	NA	NA	0	
Kudo *et al*, 2018	REFLECT	Lenvatinib	478	63 (20-88)[c]	85	64/36	99/1	53	19	NA	23	61	(12)
		Sorafenib	476	62 (22-88)[c]	84	63/37	99/1	48	26	NA	19	62	
Park *et al*, 2019	STAH	Sorafenib + TACE	170	60.2 (9.6)[d]	80	80/19.4	87.1/12.9	78.8	4.7	1.8/22.9	40	36.5	(24)
		Sorafenib	169	61.3 (9.6)[d]	87	82.8/16.6	86.9/13	71	9.5	0/26	37.3	34.9	
Ding *et al*, 2021	NA	Lenvatinib + TACE	32	57 (11)[d]	78.1	75/25	68.8/31.2	93.8	3.1	NA	100	40.6	(14)
		Sorafenib + TACE	32	56 (11)[d]	84.4	68.8/31.2	87.5/12.5	90.6	9.4	NA	100	28.1	
Kudo *et al*, 2022	TACTICS	Sorafenib + TACE	80	72 (36-85)[c]	78.8	88.8/11.2	98.8/1.2	12.5	47.5	33.8/55	0	0	(25)
		TACE	76	73 (53-86)[c]	72.4	88.2/11.8	93.5/5.6	2.6	69.7	43.4/44.7	0	0	
Peng *et al*, 2023	LAUNCH	Lenvatinib + TACE	170	54 (46-64)[c]	18.8	52.4/47.6	100/0	87.1	2.4	NA	71.8	55.3	(26)
		Lenvatinib	168	56 (48-63)[c]	78.6	58.9/41.1	100/0	85.7	3.6	NA	69.6	56.5	

[a]Data presented as median without interquartile range. [b]The median age of whole patients group in Kudo *et al* (21) was 69 years (range, 29-86 years). [c]Data presented as median (interquartile range). [d]Data presented as mean (standard deviation). TACE, transarterial chemoembolization; NA, not available.

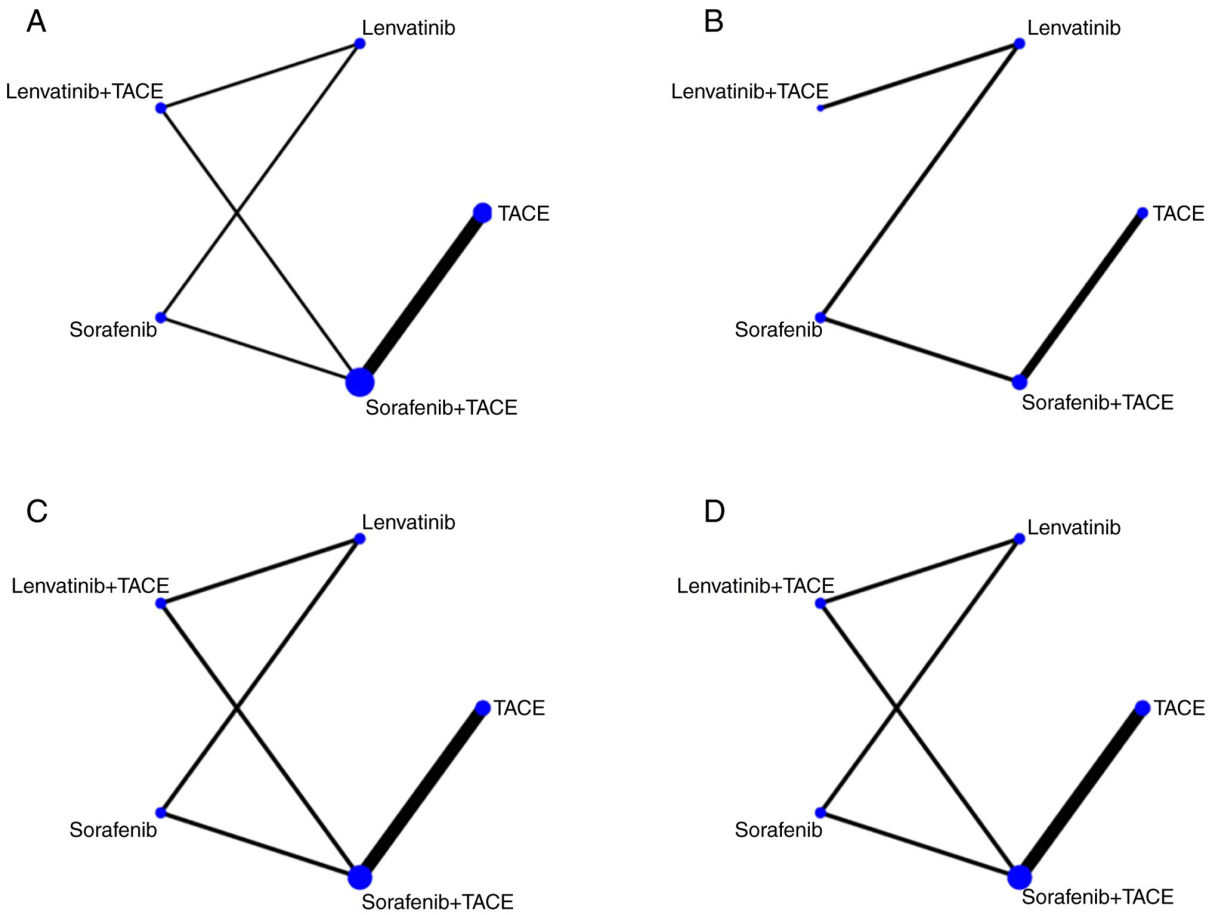

Figure 2. Network plots of the comparisons for the network meta-analysis. (A) Overall survival, (B) progression-free survival, (C) objective response rate, and (D) disease control rate. The thicker the line, the more studies there are on the relative comparison between the two treatment methods. The larger the blue dot, the larger the sample size of the treatment method. TACE, transarterial chemoembolization.

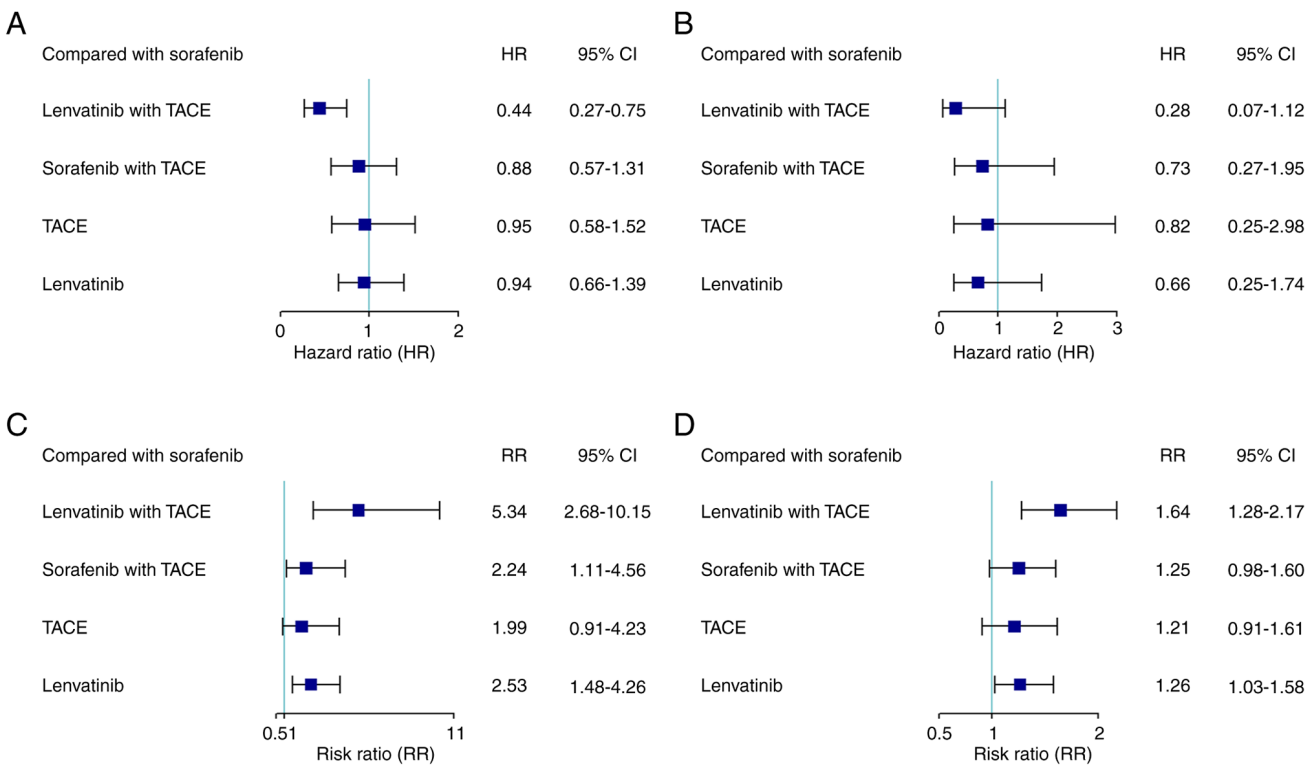

Figure 3. Forest plot comparisons of sorafenib monotherapy with lenvatinib with TACE, sorafenib with TACE, TACE and lenvatinib monotherapy. (A) Overall survival, (B) progression-free survival, (C) objective response rate and (D) disease control rate. TACE, transarterial chemoembolization.

Table II. Indirect comparisons of outcomes among different treatments.

A, Overall survival

Drug treatment	Lenvatinib + TACE	Sorafenib + TACE	TACE	Lenvatinib
Sorafenib + TACE	0.50 (0.30-0.89)			
TACE	0.46 (0.27-0.86)	0.92 (0.72-1.18)		
Lenvatinib	0.47 (0.31-0.72)	0.93 (0.55-1.48)	1.02 (0.57-1.71)	
Sorafenib	0.44 (0.27-0.75)	0.88 (0.57-1.31)	0.95 (0.58-1.52)	0.94 (0.66-1.39)

B, Progression-free survival

Drug treatment	Lenvatinib + TACE	Sorafenib + TACE	TACE	Lenvatinib
Sorafenib + TACE	0.39 (0.07-2.14)			
TACE	0.35 (0.05-2.11)	0.89 (0.4-1.76)		
Lenvatinib	0.43 (0.16-1.14)	1.10 (0.28-4.37)	1.23 (0.27-6.48)	
Sorafenib	0.28 (0.07-1.12)	0.73 (0.27-1.95)	0.82 (0.25-2.98)	0.66 (0.25-1.74)

C, Objective response rate

Drug treatment	Lenvatinib + TACE	Sorafenib + TACE	TACE	Lenvatinib
Sorafenib + TACE	2.36 (1.19-4.75)			
TACE	2.66 (1.26-5.77)	1.13 (0.84-1.57)		
Lenvatinib	2.10 (1.23-3.47)	0.89 (0.43-1.86)	0.79 (0.35-1.74)	
Sorafenib	5.34 (2.68-10.15)	2.24 (1.11-4.56)	1.99 (0.91-4.23)	2.53 (1.48-4.26)

D, Disease control rate

Drug treatment	Lenvatinib + TACE	Sorafenib + TACE	TACE	Lenvatinib
Sorafenib + TACE	1.31 (1.02-1.73)			
TACE	1.35 (1.02-1.86)	1.03 (0.89-1.21)		
Lenvatinib	1.30 (1.06-1.63)	0.99 (0.75-1.29)	0.96 (0.7-1.3)	
Sorafenib	1.64 (1.28-2.17)	1.25 (0.98-1.60)	1.21 (0.91-1.61)	1.26 (1.03-1.58)

TACE, transarterial chemoembolization.

Tumor response. The present NMA demonstrated that seven of the eight RCTs reported five different treatment strategies for both ORR and DCR (Fig. 2C and D). Compared with sorafenib monotherapy, the combination therapies and lenvatinib and TACE monotherapies had a significantly higher ORR and DCR, while lenvatinib with TACE combination therapy demonstrated a significantly improved tumor response compared with the other treatments examined (Fig. 3). Based on the ranking plot, lenvatinib with TACE had the highest probability of delivering the maximum ORR (rank probability, 97.68%) and DCR (rank probability, 96.27%), followed by lenvatinib monotherapy, sorafenib with TACE, TACE and sorafenib monotherapy for both ORR and DCR, respectively (Fig. 4; Table III).

Adverse events. In the analysis of AEs, reported grade 3/4 AEs in all included studies were limited and different, so the present NMA analyzed several common AEs amongst the studies (Table SII). The three most common AEs in lenvatinib with TACE group were elevated aspartate transaminase (AST) levels, elevated alanine aminotransferase (ALT) levels and hypertension. In the sorafenib with TACE group the three most common AEs were elevated AST, ALT and hypertension. In the sorafenib monotherapy group, hypertension, hand-foot skin reaction (HFSR) and elevated AST were the most common AEs. Furthermore, comparisons of the commonly reported AEs between different treatments in included trials were conducted (Table SIII). There were no significant differences in reported AEs between lenvatinib with TACE and sorafenib with TACE [(HFSR: RR, 0.28; 95% CI, 0.07-1.03); (diarrhea: RR, 1.03; 95% CI, 0.22-4.80); (hypertension: RR, 3.23; 95% CI, 0.63-26.29); (elevated AST: RR, 0.69; 95% CI, 0.32-1.48); (abdominal pain: RR, 0.69; 95% CI, 0.31-1.50); (fatigue: HR, 0.68; 95% CI, 0.31-1.46); and (nausea: RR, 0.68;

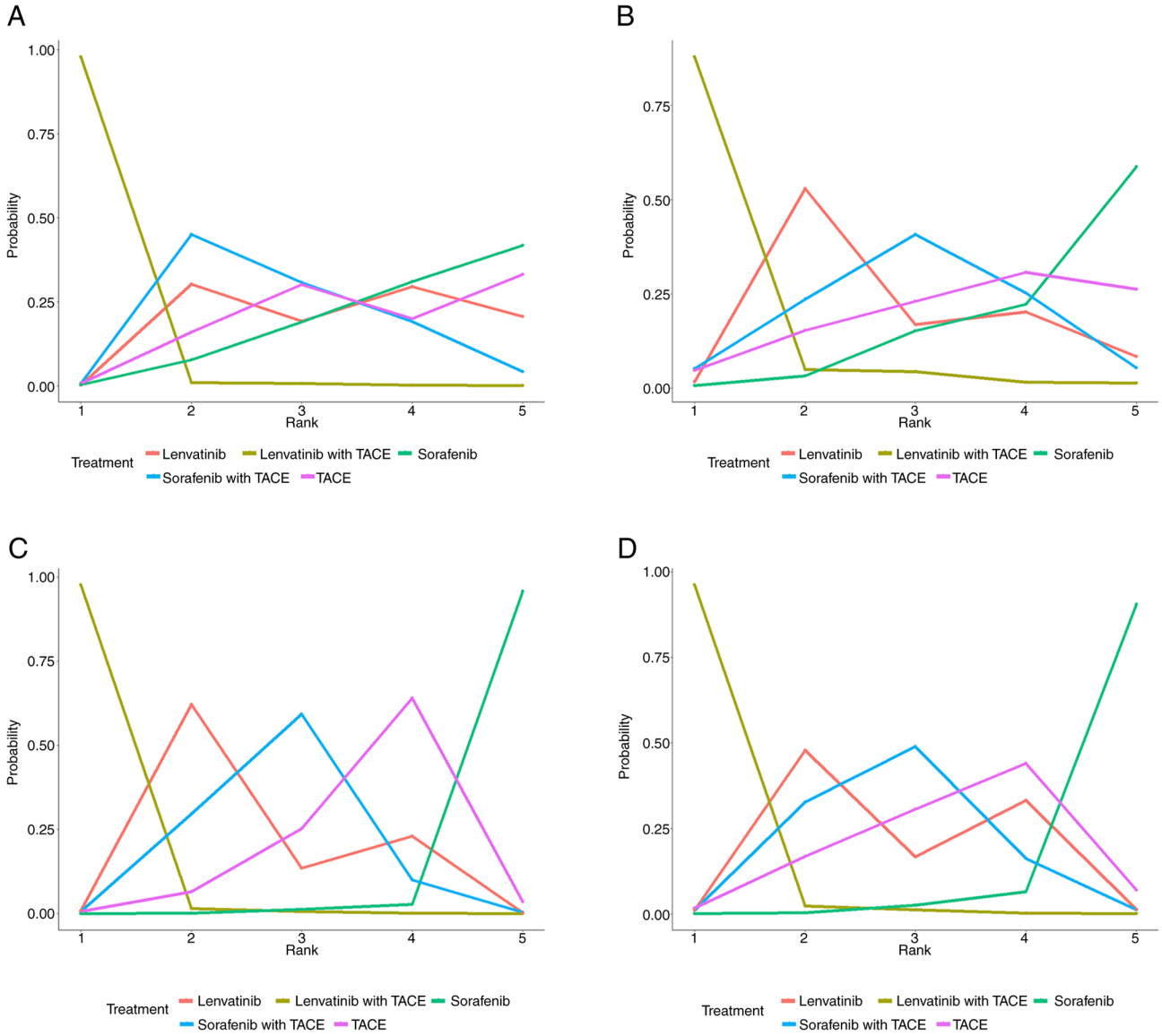

Figure 4. Rank probability based on each outcome criteria evaluated. (A) Overall survival, (B) progression-free survival, (C) objective response rate and (D) disease control rate. The horizontal axis represents the ranking of treatments, and the vertical axis represents the probability of the ranking of treatments. TACE, transarterial chemoembolization.

95% CI, 0.31-1.46)]. The risk of elevated AST, abdominal pain, fatigue and nausea were higher in the sorafenib with TACE group compared with the monotherapies examined. A markedly higher risk of elevated AST, abdominal pain, fatigue and nausea was observed in the lenvatinib with TACE group compared with the lenvatinib monotherapy group (Table SIII).

Quality assessment, convergence, global inconsistency, local inconsistency and heterogeneity analyses. Overall, the risk of bias in the included trials was low for most of the seven domains of source of bias. However, regarding performance bias, a high risk of bias related to double blinding in five of the eight trials was observed (REFLECT, STAH, Ding *et al*, TACTICS and LAUNCH) (Fig. S1). The open-label assessment of the aforementioned five trials may have caused a potential overestimation of treatment efficacy. In all analyses, the preferred model convergence was confirmed using the Brooks-Gelman-Rubin method. The potential scale reduction factor was limited to one, which demonstrated that the analysis possessed good convergence (Fig. S2). No global inconsistencies were detected (Table SIV). Local inconsistencies between direct and indirect comparisons of the outcomes in terms of OS, ORR and DCR were not observed using the node-splitting method (Fig. S3). However, due to the lack of a closed loop in the PFS network, an inconsistency assessment was not applicable in this particular analysis. Given the limited number of studies included, the analyses did not include funnel plots to detect publication bias. No heterogeneous outcome measures emerged between all pairwise comparisons, except for PFS, owing to the lack of a closed loop in the network (Fig. S4).

Discussion

With the use of sorafenib and lenvatinib as first-line treatments in patients with uHCC, combination therapy with TACE has gradually been applied. A previous meta-analysis pooled the

Table III. Analysis of treatment ranking probability in patients with unresectable hepatocellular carcinoma.

A, Overall survival

Treatment	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5
Lenvatinib + TACE	0.97915	0.00980	0.00750	0.00265	0.00090
Sorafenib + TACE	0.00735	0.45000	0.30815	0.19185	0.04265
TACE	0.00760	0.15960	0.30160	0.19970	0.33150
Lenvatinib	0.00200	0.30335	0.19255	0.29515	0.20695
Sorafenib	0.00390	0.07725	0.19020	0.31065	0.41800

B, Progression-free survival

Treatment	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5
Lenvatinib + TACE	0.87800	0.04880	0.04325	0.01610	0.01385
Sorafenib + TACE	0.05125	0.23590	0.40665	0.25240	0.05380
TACE	0.04740	0.15330	0.22965	0.30735	0.26230
Lenvatinib	0.01660	0.52900	0.16900	0.20185	0.08355
Sorafenib	0.00675	0.03300	0.15145	0.22230	0.58650

C, Objective response rate

Treatment	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5
Lenvatinib + TACE	0.97680	0.01565	0.00615	0.00115	0.00025
Sorafenib + TACE	0.00725	0.29610	0.59255	0.10045	0.00365
TACE	0.00670	0.06525	0.25320	0.64000	0.03485
Lenvatinib	0.00900	0.62180	0.13505	0.23060	0.00355
Sorafenib	0.00025	0.00120	0.01305	0.02780	0.95770

D, Disease control rate

Treatment	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5
Lenvatinib + TACE	0.96265	0.02255	0.01230	0.00205	0.00045
Sorafenib + TACE	0.00995	0.32730	0.48945	0.16155	0.01175
TACE	0.01620	0.16805	0.30575	0.44025	0.06975
Lenvatinib	0.01050	0.47860	0.16665	0.33180	0.01245
Sorafenib	0.00070	0.00350	0.02585	0.06435	0.90560

TACE, transarterial chemoembolization.

results of four retrospective studies and one RCT, and showed that the lenvatinib with TACE combination therapy had better long-term survival in OS (HR, 0.48; 95% CI, 0.39-0.59) and PFS (HR, 0.47; 95% CI, 0.40-0.56) (27). For patients with HCC with portal vein tumor thrombus, a single-center RCT compared the efficacy of lenvatinib with TACE to sorafenib with TACE combination therapies and reported that the use of lenvatinib with TACE significantly improved TTP, ORR and DCR but did not significantly improve OS (14). Lenvatinib with TACE therapy had a markedly longer OS compared with the sorafenib with TACE combination therapy (14.5 vs. 10.8 months), however, the study was limited by a small sample size. Another retrospective cohort study that enrolled 253 patients with advanced HCC demonstrated a significantly improved OS and tumor response in the lenvatinib with TACE group compared with that in the sorafenib plus TACE group (28). In addition, our previous meta-analysis reached the same conclusion (15). However, the number of head-to-head studies comparing the two aforementioned combination therapies, in particular large-scale RCTs, are limited. In the present study, an NMA that focused on including RCTs landmark phase III randomized clinical trials to explore the efficacy of the two combination therapies was performed. However, several differences among clinical characteristics could also

affect the results of the present NMA. The proportion of patients with hepatitis B virus or hepatitis C virus infection, portal vein tumor thrombosis and extrahepatic metastasis varied greatly among the different included trials, which could have led to potential heterogeneity. The Ding *et al* (14) trial was the only direct comparison between the two combination therapy groups, however the sample size of this trial was relatively small thus limiting the accuracy of the survival outcome analysis and the overall results. Due to the control of included trials (focus on two combination therapies and their monotherapy), which excluded the studies on treatments unrelated to the present study resulting in a reduction in possible confounding factors, the heterogeneity analysis did not detect significant heterogeneity.

A recent NMA included 10 RCTs and 35 cohort studies and compared the efficacy and safety of TKIs in combination with TACE in the treatment of uHCC (16). The lenvatinib with TACE combination therapy had a significantly longer PFS (HR, 0.53; 95% CI, 0.32-0.88) but not OS (HR, 0.88; 95% CI, 0.65-1.13), when compared with sorafenib with TACE group. However, significant inconsistency was observed between direct and indirect comparisons of OS between the two treatment groups. Moreover, heterogeneity in comparisons between the different treatment groups had not been reported. Furthermore, the inclusion of different types of studies, both RCT and retrospective cohort studies in the aforementioned NMA, may have contributed to a potential risk of reduced similarity and transitivity. Therefore, the credibility and accuracy of the results presented in the aforementioned NMA were limited. Another NMA comparing TKIs in combination with TACE included two RCTs and 39 cohort studies (29). No significant difference was found between lenvatinib with TACE and sorafenib with TACE, in terms of OS (HR, 0.54; 95% CI, 0.26-1.07). High heterogeneity (consistency model, I^2=69%; inconsistency model, I^2=66%) was observed in OS under the fixed-effects model. The commonality between the two aforementioned NMAs was that non-RCTs accounted for the majority of the included studies, which may be the underlying cause of the inaccurate results (16,29).

In addition, a previous NMA included 23 RCTs comparing the combination of different first-line TKIs and transarterial therapies in uHCC and the pooled outcomes showed that lenvatinib with TACE did not provide any significant advantage in terms of OS, PFS, TTP, ORR or DCR (30). In addition, no inconsistency was observed, but heterogeneity was observed in several pairwise comparisons. The results of the pooled outcomes were inconsistent with those of previous head-to-head studies, including RCTs and real-world cohort studies (14,28,31,32). Therefore, a possible reason may be that this NMA included too many treatment types (additional inclusion of hepatic arterial infusion chemotherapy, selective internal radiation therapy and their combination therapy with sorafenib), which could have led to a heterogeneous emergence and unavoidable confounding factors, thus decreasing the level of evidence of pooled results of the mixed comparisons. The present NMA, by contrast, mainly included landmark phase III RCTs closely related to target treatments with low heterogeneity and good global and local consistency. Previous research on combination therapies of TACE and TKIs have mainly focused on sorafenib with TACE, and the currently available literature analyzing the efficacy of lenvatinib with TACE for uHCC treatment was limited. Even if the present NMA had expanded the scope of types of other combination treatments, the further additional closed loops may not have significantly enhanced the robustness of the present model or have had a significant impact comparing the efficacy between lenvatinib with TACE and sorafenib with TACE, but instead may have increased the risk of biases. More large-scale RCTs are needed to further confirm the efficacy of lenvatinib or sorafenib with TACE combination therapies with uHCC.

The present study compared lenvatinib or sorafenib with TACE based only on RCTs. We narrowed down the scope of the included studies to include only lenvatinib, sorafenib, TACE and their combination therapies to reduce possible confounding bias and heterogeneity, without oversimplification of the network. The results of the present study demonstrated that the combination of lenvatinib with TACE was significantly superior in terms of OS, ORR and DCR in the treatment of patients with uHCC. The present results were similar to those of our previous meta-analysis (15). However, in the present NMA, no significant difference in PFS between lenvatinib with TACE and sorafenib with TACE was observed. Given the lack of closed loops in the present NMA in terms of PFS, this result should be interpreted with caution. In addition, global inconsistency, local inconsistency and heterogeneity were not observed in the present NMA. By contrast, sorafenib with TACE ranked 3rd for PFS, ORR and DCR, while lenvatinib monotherapy ranked 2nd. Furthermore, there were no significant differences in the survival advantage between sorafenib with TACE and lenvatinib monotherapy in the present NMA. Similar results have been reported by other studies (16,30,33). However, considering the increased survival outcomes of lenvatinib monotherapy compared with sorafenib monotherapy and the lack of a direct comparison between lenvatinib and sorafenib with TACE in the currently available studies, more head-to-head research is needed to further explore the superiority of survival outcomes (12,34).

The analysis of AEs in the present study showed no difference between lenvatinib with TACE and sorafenib with TACE regarding grade 3/4 AEs. Similarly, according to the NMA by Long et al, no significant difference was reported between the two combination therapies in terms of all-grade AEs or ≥ grade 3 AEs (16). However, due to lack of the data regarding total AEs in the SPACE, TACTICS and LAUNCH trials, the present NMA only compared separate AEs, and total AE analysis was not performed. In the REFLECT trial (12), hypertension and HFSR were the most common AEs. Sorafenib showed a higher rate of HFSR (11 vs. 3%) and a lower rate of hypertension (14 vs. 23%) than lenvatinib. In our previous meta-analysis, there were significant differences regarding HFSR (HR, 0.51, 95%; CI, 0.27-0.95) and hypertension (HR, 3.05; 95% CI, 1.45-6.39) between the two combination therapy groups, and the differences in incidence of HFSR and hypertension were similar to results of the REFLECT trial (12,15). However, the present NMA found no significant difference regarding HFSR and hypertension between the two combination therapy groups. In the RCT conducted by Ding *et al* (14), the incidence of hypertension in the lenvatinib with TACE group was notably higher compared with the sorafenib with TACE group, but no differences were observed regarding total AEs, grade 3/4 AEs or HFSR. The occurrence of HFSR and

hypertension was attributed to lenvatinib and sorafenib treatment in the aforementioned RCT, but the different results regarding the incidence of HFSR and hypertension between the present NMA and our previous meta-analysis may be attributed to the involvement of real-world studies. Therefore, head-to-head RCTs are needed to compare the two combination therapies. The present analysis of the included studies demonstrated that the incidence of total AEs and grade 3/4 AEs of the combination therapy group were more likely to be significantly higher compared with those of the monotherapy group, and most AEs could be controlled by the use of symptomatic treatment.

TKIs inhibit tumor growth and angiogenesis mainly by targeting the VEGFR, platelet-derived growth factor receptor and EGFR signaling pathways (35,36). Although TACE can cause necrosis of liver tumor cells by selectively blocking the nutrient arteries for HCC cells and depositing chemotherapy drugs in tumor cells, TACE can also create a hypoxic tumor microenvironment, which leads to the upregulation of VEGF, fibroblast growth factor (FGF) and angiopoietin-2, increasing the risk for cancer recurrence and metastasis (11,37,38). A previous study administered sorafenib treatment combined with TACE for patients with HCC and the results showed that the circulating levels of plasma VEGF did not significantly increase after combination therapy (39). A phase II single-arm trial that enrolled 50 patients with uHCC showed promising survival efficacy and manageable safety with the combination of sorafenib with TACE therapy (40). Previous studies have indicated that lenvatinib possesses a stronger affinity for VEGFR2 and inhibits more targets, including FGF, compared with sorafenib, which results in a better efficacy of lenvatinib in combination with TACE (28,41-43). Another factor contributing to the superior efficacy of lenvatinib with TACE rather than sorafenib with TACE therapy is the therapeutic advantage of lenvatinib monotherapy over sorafenib monotherapy, in that lenvatinib targets more signaling pathways, including FGFR-MAPK, ERK/MAPK and EGFR-PI3K-AKT (44-46). Notably, a novel combination therapy of TACE with lenvatinib and programmed death-1 inhibitors has emerged as a treatment for patients with uHCC, and previous meta-analysis showed that this triple combination therapy has achieved a superior OS advantage and better tumor response than lenvatinib with TACE (47).

Nevertheless, the present NMA has some limitations. First, the number of included studies was limited; therefore, publication bias was not analyzed which may have caused a potential overestimation of positive results. Second, due to the lack of AE comparisons, the results were insufficient for guidance of clinical treatment strategy selection in terms of safety. Third, although significant heterogeneity was not observed, potential confounding factors may have originated from the region, portal vein invasion, extrahepatic metastasis and etiology that were overlooked due to the limited report on the aforementioned factors for inclusion in the study.

The present NMA showed that combination therapy of lenvatinib with TACE had significantly increased treatment efficacy compared with sorafenib with TACE, TACE or sorafenib and lenvatinib monotherapy in terms of OS, ORR and DCR. Therefore, the results of the present NMA indicated that lenvatinib with TACE may be potentially preferrable in the consideration of TACE treatment in combination with either lenvatinib or sorafenib, or their monotherapy, for patients with uHCC.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YL, XL and PY conceived and designed the study. YL, XL and JuL acquired patient data. JuL, LY, SW, JiL, HG and TM analyzed and interpreted the data. YL, XL, PY, HG and TM drafted and revised the manuscript. All authors read and approved the final version of the manuscript. YL, XL and PY confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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