SYSTEMATIC REVIEW AND META-ANALYSIS

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Safety and Efficacy of TACE + Lenvatinib in Treating Advanced Hepatocellular Carcinoma: A Systematic Review and Meta-analysis

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ABSTRACT

Background & Aims: To compare the efficacy and safety of transarterial chemoembolization (TACE) + lenvatinib (TACE+L) versus lenvatinib (L) monotherapy in the treatment of advanced hepatocellular carcinoma by a meta-analysis.
Methods: PubMed, Embase, the Cochrane Library, CNKI, VIP e-Journals Database, and Wanfang Data were systematically searched to collate literature comparing TACE+L with L alone for the treatment of advanced liver cancer. The literature search, quality assessment, and data extraction were performed independently by two reviewers. The Stata 16 software package was used to process and analyze the data. We assessed heterogeneity using both I2 and the p-value, performed a publication bias assessment, and conducted a sensitivity analysis.
Results: Five studies were finally included, including one randomized controlled study and four retrospective studies; these involved a total of 1,167 patients, including 523 patients in the TACE+L combination group and 644 patients in the L monotherapy group. In this meta-analysis, the TACE+L group showed a significantly better objective response rate (ORR) (OR=2.54, 95%CI: 1.34 - 4.80) and disease control rate (DCR) compared to the L monotherapy group (OR=2.68, 95%CI: 1.75 - 4.08). The combined group had significantly improved progression-free survival (PFS) (HR=0.47, 95%CI: 0.40 - 0.56) and overall survival (OS) (HR=0.48, 95%CI: 0.39-0.59). In addition, there was no significant difference found in the overall adverse events of any grade between the two groups (OR=1.13, 95%CI: 0.99 - 1.29).
Conclusions: Compared to L alone, TACE+L treatment resulted in better tumor response, better long-term survival, and was accompanied by controllable adverse events.

Key words: lenvatinib –TACE – efficacy – safety – meta-analysis – advanced liver cancer.

Abbreviations: AE: adverse event; DCR: disease control rate; FGFR: fibroblast growth factor; HAIC: hepatic arterial infusion chemotherapy; L: lenvatinib; ORR: objective response rate; OS: overall survival; PDGF: platelet-derived growth factor; PFS: progression-free survival; RCT: randomized controlled trial; TACE: transcatheter arterial chemoembolization; TTP: time to progression; VEGF: vascular endothelial growth factor.

INTRODUCTION

Primary liver cancer is the sixth most common cancer and the second leading cause of cancer death worldwide. Its highest incidence occurs in East Asia and Southeast Asia, especially China, which has an incidence accounting for approximately 50% of all cases. Approximately 80% of primary liver cancer cases are classed as hepatocellular carcinoma (HCC) [1]. Despite advances in the treatment of liver cancer, the disease remains associated with a poor prognosis [2]. This is because liver cancer is often diagnosed at an advanced stage, and therefore, many patients with advanced disease have missed the opportunity to undergo radical treatment [3]. The current treatment methods used for liver cancer are diverse. Of these, transcatheter arterial chemoembolization (TACE) is a palliative approach that is considered the standard treatment for advanced HCC [4], which can effectively block the tumor blood supply. However, the risk of tumor angiogenesis and collateral circulation formation is greatly increased after TACE, so the resulting recurrence and metastasis rate is high. Consequently, very few patients achieve complete remission [5]. Lenvatinib (L) is a novel oral multi-targeted tyrosine kinase inhibitor with antiangiogenic and direct antitumor effects. Its mechanism involves targeting multiple kinase receptors, including vascular

endothelial growth factor (VEGF) receptor 1-3, fibroblast growth factor (FGF) receptor 1-4, platelet-derived growth factor (PDGF) receptor [6]. A previous study compared the efficacy and safety of L against sorafenib and reported that the median overall survival (OS) of L was not lower than that of sorafenib [7]. The drug was also significantly superior to sorafenib in terms of progression-free survival (PFS), objective response rate (ORR), and time to progression (TTP). Lenvatinib has therefore been approved as an alternative first-line treatment for advanced liver cancer [8]. A treatment method comprised of TACE combined with tyrosine kinase inhibitors is currently advocated in many guidelines [9]. However, there are few reports on TACE+L for the treatment of primary liver cancer, and evidence-based medical evidence is lacking. Therefore, we performed the current meta-analysis to comprehensively evaluate the efficacy and safety of TACE+L versus L alone in the treatment of advanced HCC.

METHODS

Search Strategy and Study Selection

The study protocol was performed according to the PRISMA guidelines and was registered in the International Prospective Register of Systematic Reviews (PROSPERO 2022 CRD42022363777) [10, 11].

We systematically searched the databases PubMed, Embase, the Cochrane Library, CNKI, Wanfang Data, and VIP e-Journals for studies published from December 2013 to September 2022 on September 1, 2022. We used the following search terms: (liver neoplasms) OR (neoplasms, hepatic) OR (neoplasms, liver) OR (liver neoplasm) OR (neoplasm, liver) OR (hepatic neoplasms) OR (hepatic neoplasm) OR (neoplasm, hepatic) OR (cancer of liver) OR (hepatocellular cancer) OR (cancers, hepatocellular) OR (hepatocellular cancers) OR (hepatic cancer) OR (cancer, hepatic) OR (cancers, hepatic) OR (hepatic cancers) OR (liver cancer) OR (cancer, liver) OR (liver cancers) OR (cancers, liver) OR (cancer of the liver) OR (cancer, hepatocellular) AND (TACE) AND (Lenvatinib). In addition, we searched the clinical trial registry website (http://www.clinicaltrials.gov) to obtain more specific information about related registered randomized controlled trials (RCTs). When duplicate publications of the same clinical trial were identified, the most complete and updated study was selected. In addition, reference lists of the retrieved articles were examined to identify additional studies.

First, we checked the titles and abstracts of the selected papers to exclude irrelevant articles. Second, the full texts of all selected studies were reviewed according to the inclusion and exclusion criteria. The eligibility of each of these studies was then assessed independently by two investigators (D.P. and X.M). In any case of disagreement, we revisited these studies and determined whether they were relevant to the final analysis based on a discussion and final consensus. If the suitability of a study could not be determined even after the reassessment, a third investigator (Z.H.) determined whether it would be eligible.

Inclusion and Exclusion Criteria

Inclusion criteria were: 1) study subjects: diagnosed with advanced primary liver cancer by imaging and/or pathology; 2) intervention measures: TACE + L; 3) control measures: L alone; 4) the administration time of L was similar between the two groups; 5) outcome: fully detailed methods, patient population characteristics, and survival data; 6) study design: randomized controlled studies and retrospective studies.

We excluded unrelated studies according to the following criteria: 1) repeated studies; 2) patients with other tumors; 3) unable to obtain the full text; 4) interventional treatment being hepatic arterial infusion chemotherapy (HAIC); 5) combined immunotherapy (such as PD-1 inhibitors); 6) involving an L administration time < 2 cycles.

Data Extraction and Quality Assessment

The primary endpoints of this study were the ORR and OS; the secondary endpoints were the disease control rate (DCR) and PFS; the safety endpoints were adverse events (AEs) of any grade. The necessary information was extracted independently by two researchers (D.P. and X.M). The outcome measures; including the ORR, OS, DCR, PFS, AEs, authors, year, study region, type of study design, and interventions; were extracted with emphasis given according to the study protocol, and data forms were completed for the analysis. Having identified all the included studies, we performed a quality assessment on them to understand the risk of bias for each study. The methodological quality of each study was assessed by two researchers using the Cochrane Risk of Bias Tool for assessing the risk of bias for RCTs [12], while the Castle Ottawa Scale (NOS) was employed to assess the quality of non-RCTs. The NOS scale contains three quality parameters: selection (0 - 4 points), comparability (0 - 2 points), and outcome assessment (0 - 3 points). Article quality scores ranged from 0 to 9 and were categorized as follows: low (0 to 3), moderate (4 to 6), and high (> 7) [13].

Statistical Analysis

Two authors (D.P. and X.M) performed the statistical analysis and calculated the hazard ratios (HRs) and associated 95% confidence intervals (CIs) for OS and PFS. They also calculated the estimated odds ratios (ORs) and 95% CIs using the values of the ORRs, DCRs, and AEs. The Q-test and I^2 test were used for the heterogeneity analysis. Values of $p \geq 0.05$ or $I^2 \leq 50\%$ indicated homogeneity among the study results. Heterogeneity was categorized as follows: low heterogeneity ($25\% < I^2 < 50\%$), moderate heterogeneity ($50\% < I^2 < 75\%$), and high heterogeneity ($I^2 > 75\%$) [14]. When the heterogeneity was high, a publication bias assessment, sensitivity analysis, and subgroup analysis were performed to investigate the cause of the heterogeneity. Funnel plots and Begg's and Egger's tests were used as publication bias assessment methods to determine whether a sufficient number of eligible studies were included in our study [15]. Funnel plots were quantified with Begg's test and $p > 0.05$ indicated no publication bias. A sensitivity analysis was conducted to estimate the effect of each study on the stability of the results. All the p-values were two-tailed and values of $p < 0.05$ were considered statistically significant in all tests. The analyses and reporting were performed according to the preferred reporting items of systematic reviews and meta-analysis guidelines. All statistical procedures were conducted using the statistical software package Stata 16.

RESULTS

Literature Search Results

We retrieved 456 studies from six databases. From these, 198 duplicate studies were excluded, and two reviewers independently assessed the remaining 256 studies to determine their eligibility. Next, a total of 251 studies were excluded for the following reasons: reviews (n=21); conference proceedings (n=23); meta-analysis (n=21); case reports (n=12); study groups involving HAIC, immunosuppressants, or sovatinib (n=98); no study groups (n=33); insufficient data (n=18); the full text was not available (n=27). Finally, five studies were included [16-20], including four retrospective analyses [17-20] and one RCT [16]. The detailed literature search process is shown in Fig. 1.

Basic Characteristics and Quality Evaluation of the Included Manuscripts

The characteristics of the studies that were finally included in the meta-analysis are shown in Table I. The studies were published between December 2013 and September 2022 and were conducted in China (n=3) [16, 17, 19] and Japan (n=2) [18, 20]. The primary endpoints of this study were the ORR and OS; the secondary endpoints were the DCR and PFS; the safety endpoints were AEs of any grade. A total of 1,167 patients with advanced HCC were included from across 5 studies [16-20], including 523 patients in the TACE+L group and 644 patients in the L monotherapy group. Four studies [17-20] used propensity score-matched research methods. Four studies [16, 18-20] used drug-eluting TACE methods. The details of the quality assessment of the studies are listed in the Table II. Based on the Cochrane Risk of Bias Tool, the study supervised by Kuang (2022) [16] was assessed as high risk; the quality evaluation results are shown in Fig 2. Therefore, most of the studies included in this meta-analysis were considered to be of high quality.

Primary Outcome Measures

The primary outcome measures for this meta-analysis were the ORR and OS. Five items of literature [16-20] including a total of 774 patients reported the ORR of the treatment. The ORR in the TACE + L group was better than that for the L group (OR=2.54, 95%CI: 1.34-4.80). Heterogeneity analysis showed moderate heterogeneity between studies (I^2=72.7%, p=0.006). A random-effects model was used (Fig. 3).

Overall survival was reported in 4 items of literature [16, 17, 19, 20] including a total of 840 subjects. As a result, there was no heterogeneity found (I^2=0%, p=0.937). A random-effects model was used. The TACE+L group showed better OS than the L group (HR=0.48, 95%CI: 0.39-0.59) (Fig. 4).

Secondary Outcome Measures

Secondary outcome measures included the DCR, PFS, and AEs. The DCR was reported by all of the included items of literature [16-20] involving a total of 774 patients. The results suggest that the TACE+L group was superior to the L monotherapy group in terms of the DCR (OR=2.68, 95%CI: 1.75-4.08). The heterogeneity analysis suggested low heterogeneity between studies (I^2=51.2%, p=0.085). A random-effects model was used (Fig. 5).

Progression-free survival was reported in all of the items of literature [16, 17, 19, 20] which included a total of 840 subjects. The TACE+L group showed a better PFS than the L monotherapy group (HR=0.47, 95%CI: 0.40-0.56), resulting in no heterogeneity (I^2=0%, p=0.452). A random-effects model was used (Fig. 6).

Hand-foot skin reactions (OR=1.03, 95%CI: 0.75-1.40), hypertension (OR=1.10, 95%CI: 0.83-1.46), fatigue (OR=1.11, 95%CI: 0.83-1.47), proteinuria (OR=1.25, 95%CI: 0.93-1.66), and diarrhea (OR=1.17, 95%CI: 0.88-1.56) were not significant in the TACE+L versus L monotherapy groups. In addition, there was no statistically significant difference found by comparing any grade of total adverse events (OR=1.13, 95%CI: 0.99-1.29).

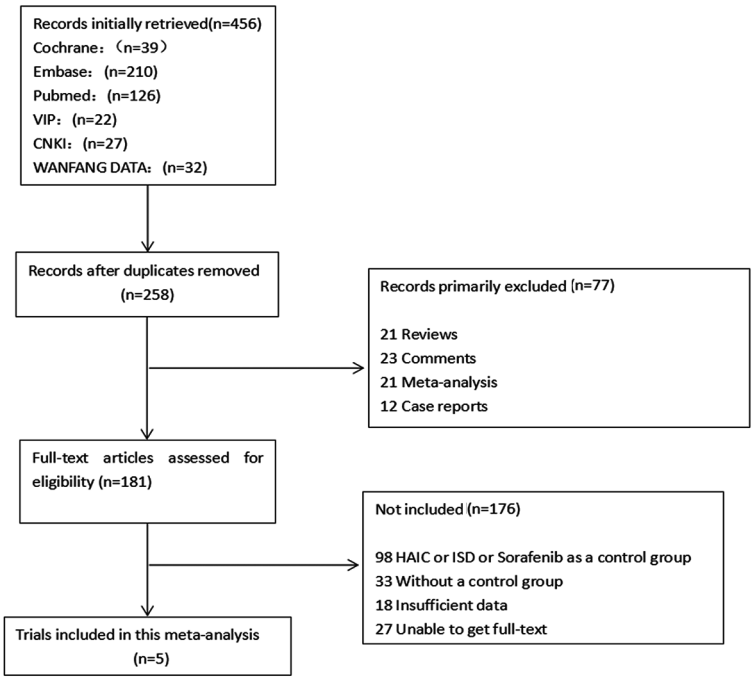

Fig. 1. Flow chart of literature screening steps.

Table I. The basic characteristics of studies included in the meta-analysis

Study	Year	Region	Research type	Sample size	Propensity score matching	Median OS (LEN+TACE vs LEN)	Median PFS (LEN+TEN vs TEN)	TACE regimen	Score of NOS	Lenvatinib dose/day	TACE administration method	ECOG PS, 0/1 (LEN+TACE vs LEN)	Size of main tumor, range, cm (LEN+TACE vs LEN)	Tumors, n single/multiple (LEN+TACE vs LEN)
Peng [16]	2022	China	Randomized controlled trial	338	NO	17.8 vs 11.5	10.6 vs 6.4	Lipiodol, epirubicin, doxorubicin, pirarubicin	-	8-12mg	TACE+DEB-TACE	89/81 vs 99/69	8.4 (4.5-9.5) vs 7.4 (4.1-9.7)	30/140 vs 38/130
Ando [18]	2021	Japan	Retrospective study	88	Yes	NA vs 16.9	11.6 vs 10.1	Cisplatin, epirubicin, Lipiodol	6	8-12mg	TACE	NA	5.1 (1.0-1.2) vs 2.2 (1.0-1.3)	NA
Xia [17]	2022	China	Retrospective study	211	Yes	15.9 vs 8.6	8.6 vs 4.4	Epirubicin, doxorubicin, pirarubicin	8	8-12mg	DEB-TACE	80/62 vs 36/33	9.0 (5.1-12.4) vs 7.3 (3.6-11.9)	53/89 vs 24/45
Li [19]	2022	China	Retrospective study	300	Yes	NA	NA	Idarubicin, sterilized water	7	4-12mg	DEB-TACE	58/20 vs 59/19	8.2 ± 5.1 vs 7.6 ± 4.0	16/62 vs 19/59
Kuroda [20]	2022	Japan	Retrospective study	230	Yes	31.2 vs 15.7	12.2 vs 6.7	Lipiodol, Miriplatin, Cisplatin, epirubicin	8	8-12mg	TACE+DEB-TACE	53/10 vs 52/11	5.0 (3.5-7.6) vs 4.9 (3.2-7.0)	20/43 vs 23/40

TACE: Hepatic artery chemoembolization M: months; NA: not available; NOS: Newcastle-Ottawa Scale; OS: overall survival; PFS: progression-free survival; TACE: transarterial chemoembolization

Table II. Quality assessment of NOS

Study	Selection	Comparability	Outcome/Exposure	Global Score
Kuroda [20]	****	**	**	8
Li [19]	****	**	*	7
Ando [18]	***	**	*	6
Xia [17]	****	**	**	8

NOS:Newcastle-Ottawa Scale

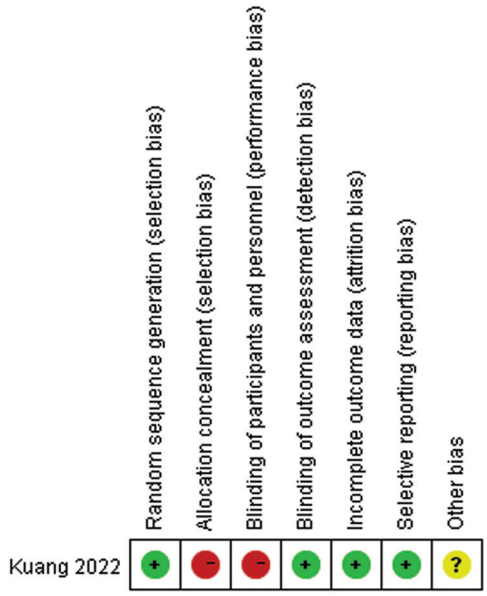

Fig. 2. Risk of bias summary to review the authors' judgments about each risk of bias item for each included study.

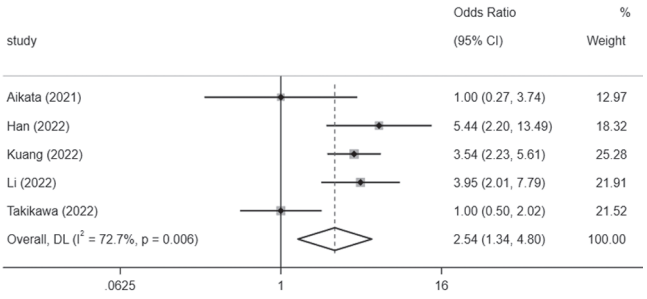

Fig. 3. Comparison of the objective response rate in the TACE + L group versus the L monotherapy group for advanced liver cancer. Abbreviations: CI: confidence interval; OR: odds ratio; TACE: transarterial chemoembolization.

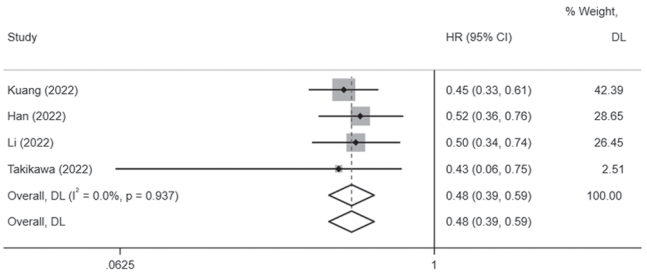

Fig. 4. Overall survival comparisons and 95% confidence intervals for TACE + L versus L monotherapy in advanced liver cancer. For abbreviations see Fig 3.

It was concluded that the side effects were comparable between the study group and the control group (Fig. 7).

Sensitivity Analysis

To analyze the source of heterogeneity, we performed a sensitivity analysis of the ORR. In the sensitivity analysis, the combined results of the ORR remained stable regardless

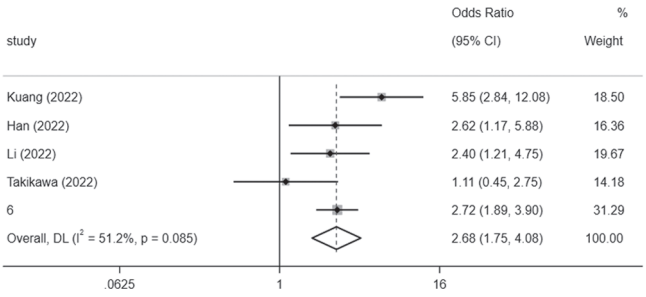

Fig. 5. Disease control rate of TACE + L versus L monotherapy in advanced liver cancer. For abbreviations see Fig 3.

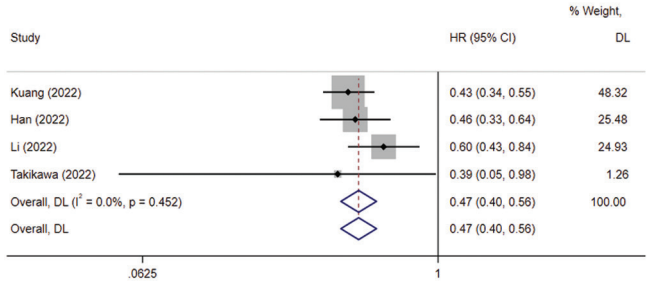

Fig. 6. Comparison of the Progression Free Survival and 95% confidence interval between the TACE + L group and L monotherapy group for advanced liver cancer. For abbreviations see Fig 3.

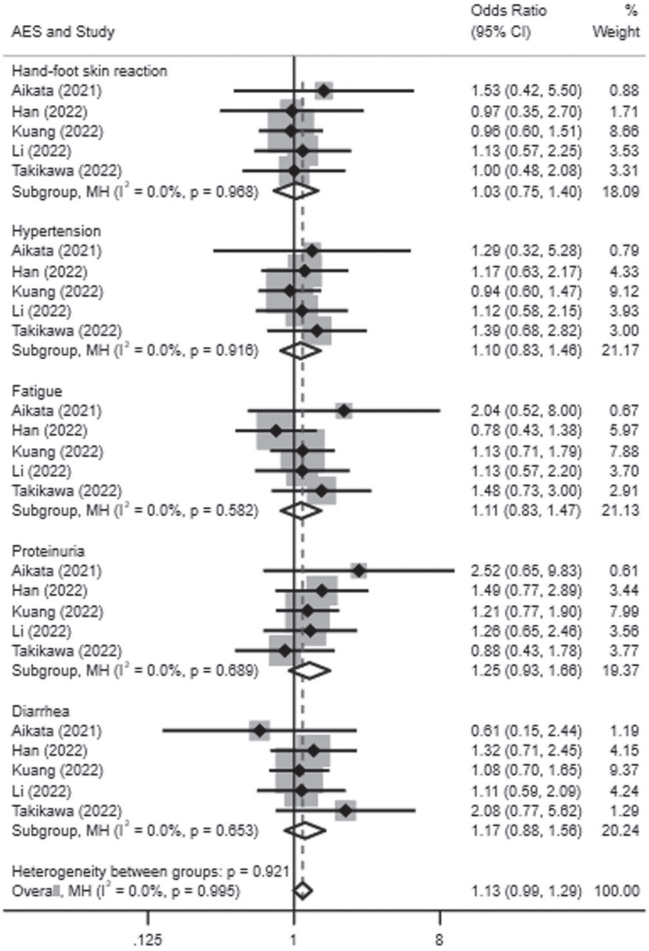

Fig. 7. Comparison of adverse events between TACE + L and L monotherapy in advanced liver cancer. For abbreviations see Fig 3.

of which study was removed, thereby indicating that our conclusions were relatively reliable (Fig. 8). The cause of heterogeneity may be related to the different sample sizes used in the included studies, different types of study designs, different protocols employed for TACE, and different degrees of severity of the patients' conditions.

Publication Bias

A publication bias analysis was performed because PFS was reported in all the included studies. A visual inspection of the Begg's funnel plot (Fig. 9) did not reveal any significant degree of asymmetry. Egger's test (p=0.914) and Begg's test (p=0.734) were used to assess the publication bias, and the results showed that there was no significant publication bias.

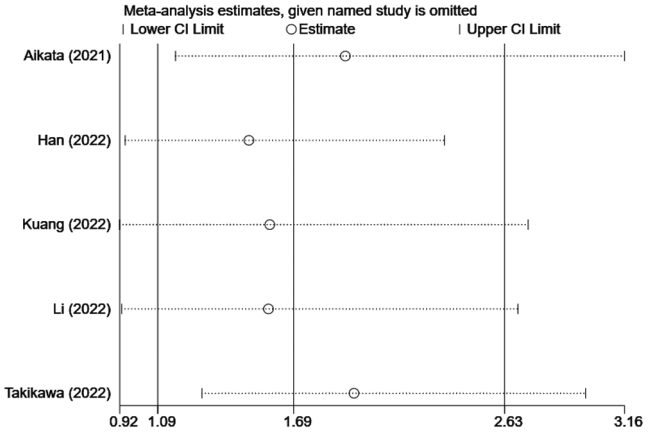

Fig. 8. Sensitivity analysis of the combined objective response rate.

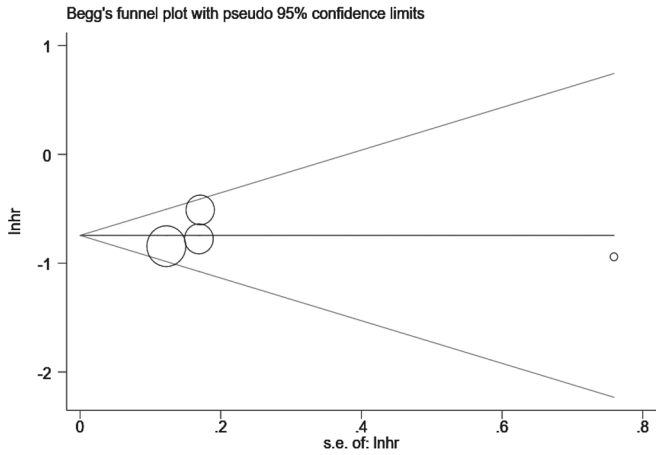

Fig. 9. Begg's funnel plots combined with pseudo-95% confidence intervals for progression-free survival. For abbreviations see Fig 3.

DISCUSSION

Liver cancer is the fifth most common cancer and the second leading cause of cancer-related death worldwide [21]. The high mortality rate of liver cancer is associated with its late onset of symptoms, missed opportunity window for patients to undergo radical surgery, high resistance to conventional chemotherapy and targeted therapy, and frequent recurrence after treatment [22]. Most of the cancer cases occur in developed countries, with the exception of HCC, which is more frequent in developing countries. East Asia has one of the heaviest burdens of liver cancer. The region is characterized by a high incidence coupled with a large population and harbors up to 50% of global liver cancer patients [23]. Such a large number of patients requires more precise and effective treatment regimens than those which are currently available [24]. The choice of treatment employed for HCC depends largely on the tumor stage; HCC in the early and middle stages can be treated by surgical resection, ablation, arterial chemoembolization, and liver transplantation, but other alternative new treatment options are still needed for patients with advanced unresectable HCC [25].

Lenvatinib is an oral multi-receptor tyrosine kinase small molecule inhibitor that is currently approved for the first-line treatment of patients with unresectable HCC in the United States, European Union, Japan, and China [26]. As a multi-targeted inhibitor, L inhibits VEGF receptor 1-3, FGF receptor 1-4, PDGF receptor α, and the proto-oncogenes RET and KIT. Preclinical studies have shown L to have potent anti-angiogenic activity, primarily through inhibition of the VEGF and FGF signaling pathways. Its application has extinguished the former status of sorafenib as the only first-line TKI treatment for advanced HCC, which it held for more than a decade [27]. But the heterogeneity of hepatocellular carcinoma reduces the effectiveness of targeted therapy [28]. Moreover, because targeted therapy usually has a low objective response rate, causes many adverse effects, and requires the eventual discontinuation or termination of treatment, its combination with other treatment modalities has now become a subject of exploration [29].

Transarterial chemoembolization involves the insertion of a catheter into the targeted proper hepatic artery, especially via a microcatheter. Superselective catheterization can achieve the accurate embolization of subsegments, increase the concentration of targeted chemotherapeutic drugs around the tumor site, maximize ischemic and hypoxic conditions at the target cancer cells to kill them, and reduce the damage caused to normal liver tissue. Embolic agents that are widely employed in TACE therapy include iodinated oil emulsion, absorbent gelatin sponge, spring emboli, and drug microspheres. The differences in these embolic agents can affect the efficacy of TACE [30]. In addition, concomitant high concentrations of chemotherapeutic agents remain in the tumor for prolonged periods of time, thereby enhancing subsequent necrosis. However, the hepatic parenchyma surrounding the hepatocytes is supplied by both arterial and portal circulation. Therefore, necrosis does not occur solely due to arterial embolization. When arterial blood flow is blocked, portal venous blood regurgitates into the tumor through the portal vein and surrounding tumor-draining venous sinuses, thereby promoting tumor survival, so the incidence of local tumor recurrence following TACE is high [31]. As such, this process is often repeated numerous times. However, repeated TACE can lead to deterioration of liver function, resulting in poor patient prognosis. In addition, TACE increases tumor hypoxia, thereby leading to the upregulation of hypoxia-inducible factor-1α (HIF-1α). In turn, elevated HIF-1α upregulates the expression of VEGF and PDGF to increase tumor angiogenesis. That is,

when TACE is administered to patients with unresectable HCC, it results in a surge in the intratumoral VEGF concentration, suggesting that the blockading of VEGF receptors prevents the effects of such a surge in pro-angiogenic factors [32]. It has been shown that TACE combined with anti-angiogenic agents reduces both tumor volume and vascular density, prolonging survival when compared to TACE used alone [33, 34]. This suggests that TACE + L therapy may be a promising treatment for advanced liver cancer.

Finally, our research has some limitations. First, although we have taken into account the heterogeneity of the data in these documents, some other factors in the baseline characteristics of the study; such as the number and size of tumors, the dose of intraarterial chemoembolization, the type of embolic agents used, and the general health status of the patients; were not consistent in the trial, which may have altered the conclusion. Second, the choice of the treatment plan may be based on the patient's physical condition, thus introducing some degree of selection bias. Patients with good liver function tend to choose intra-arterial chemoembolization plus systemic treatment, while patients with poor liver function may be willing to accept intra-arterial chemoembolization alone. Third, most of the studies included in this meta-analysis are retrospective studies, and the sample size is small. Furthermore, because the included RCT was an open-label study with a high risk of bias, the results of this study are vulnerable to bias. Fourth, all the studies included in this study were conducted in Asia, which is the highest-risk area for HCC. Finally, in the quality evaluation, the Risk of Bias Tool and NOS scale are both affected by the subjectivity of researchers, so the evaluation results may be biased as a result. In summary, TACE+L features the advantage of prolonging survival in patients with advanced HCC compared to TACE alone. Recent studies have suggested that the early administration of TACE+L may help improve patient outcomes. In the future, larger sample sizes and rigorous randomized controlled trials will be needed to validate our conclusion.

CONCLUSIONS

In this meta-analysis, we compared the efficacy and safety of TACE+L. The results indicate that TACE+L was superior to L alone in the treatment of advanced liver cancer, while safety was comparable. This study therefore supports the feasibility of this novel treatment method for advanced liver cancer.

Conflicts of interest: None to declare.

Authors' contribution: Z.H.generated the idea for the study.D.P and H.L. analyzed and interpreted the data. D.P. and X.M prepared the original draft. M.C. and X.Q. critically revised the paper. All authors read and approved the final version of the manuscript.

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