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The efficacy and safety of transcatheter arterial chemoembolization combined with lenvatinib plus radiotherapy in the treatment of hepatocellular carcinoma: a meta-analysis

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► ***Original article***

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ABSTRACT

Background: transcatheter arterial chemoembolization (TACE) is the standard treatment for advanced and unresectable hepatocellular carcinoma (HCC) patients. Lenvatinib (LVTN) is one of the novel oral antiangiogenic drugs demonstrating promising application prospects, which has been widely concerned and studied. This work was to systematically analyze efficacy and safety of TCAE combined with LVTN plus radiotherapy (RT) on HCC through the meta-analysis. ***Materials and Methods:*** a comprehensive search was conducted on PubMed, Web of Science, Embase, and The Cochrane Library databases from January 2000 to the present to identify studies examining the effectiveness and safety of combining TCAE with LVTN and RT for the treatment of HCC. Relevant literature was screened, and essential information along with evaluation indicators were extracted for analysis. RevMan5.3 was employed for quality assessment and meta-analysis of the included studies, and forest maps (FMs) were drawn. ***Results:*** five studies were included. Meta-analysis showed that TCAE combined with LVTN plus RT enhanced the total objective response rate (ORR) of HCC (OR = 3.16, 95%CI = 1.37-7.32, P < 0.05). TCAE combined with LVTN plus RT enhanced the total survival (OS) rate of HCC patients (OR = 2.01, 95%CI=1.30-3.12, P < 0.05). TCAE combined with LVTN plus RT could reduce the diarrhea rate greatly (OR = 2.84, 95%CI = 1.16-6.96, P< 0.05). However, no observable difference was found in the incidence of hypertension caused by TCAE combined with LVTN plus RT (OR = 2.39, 95%CI = 0.62-9.23, P > 0.05). ***Conclusion:*** LVTN combined with TACE had superior efficacy on HCC compared with non-LVTN combined with TCAE, but the related side effects (SEs) may affect the scope of application and the quality of life of patients.

INTRODUCTION

Hepatocellular carcinoma (HCC) presents a significant global health burden, ranking as the second leading cause of cancer-related deaths worldwide. Asian countries bear the majority of this burden, with approximately 74% to 82% of reported HCC cases occurring in this region annually. Notably, China alone contributes to over half of the global HCC cases and fatalities, with more than 290,000 deaths attributed to HCC each year [1,2]. Diagnosis of HCC often occurs at an advanced stage due to its subtle onset and nonspecific symptoms [3]. For patients with unresectable advanced HCC, transcatheter arterial chemoembolization (TACE) and tyrosine kinase inhibitors (TKIs) are established as standard treatments, effectively impeding tumor progression [4]. However, TACE-induced hypoxia in residual HCC tissues can elevate vascular endothelial growth factor (VEGF) levels, prompting significant neovascularization and enhancing tumor tissue invasion and metastasis [5]. Therefore, targeting the overexpression of VEGF in TACE-induced tumor cells holds paramount importance in augmenting the efficacy of TACE therapy. Angiogenesis, crucial for tumor growth, development, and metastasis, facilitates the supply of oxygen and nutrients to tumor cells [6,7]. In recent years, small molecule tyrosine kinase inhibitors have demonstrated significant efficacy in various malignant tumors [8]. Lenvatinib (LVTN), a novel oral antiangiogenic agent, holds promising clinical prospects. Previous studies have indicated that the combination of apatinib and TACE, an angiogenesis inhibitor, effectively suppresses the formation of tumor peripheral blood vessels and delays tumor progression [9,10]. However, existing research in this area predominantly comprises single-center studies with limited case numbers, thus lacking compelling evidence. Moreover, the effectiveness and safety outcomes in HCC treatment are not entirely consistent [11,12].

By targeting multiple kinase receptors, including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth

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factor (PDGF) receptors, LVTN exhibits anti-angiogenic and direct anti-tumor effects [13]. The latest three-phase randomized, open-label study (REFLECT) indicated that the median overall survival (OS) with LVTN was comparable to that with sorafenib. However, LVTN demonstrated superior progression-free survival (PFS), overall objective response rate (ORR), and time to progression (TTP) compared to sorafenib [14,15]. Therefore, LVTN could serve as an alternative treatment for advanced HCC. Combining LVTN with TACE may enhance treatment efficacy. However, data on the outcomes of this combination therapy are currently lacking [16]. Hence, this study aimed to assess the efficacy and safety of TACE combined with LVTN versus TACE monotherapy in patients with non-surgical HCC. The objective of this meta-analysis was to evaluate the efficacy and safety of LVTN in combination with TACE for HCC treatment. Based on this, we collected relevant studies on TCAE combined with LVTN plus radiotherapy (RT) in HCC treatment and conducted a quantitative meta-analysis of the published literature. The purpose was to observe efficacy and safety of treating HCC patients with TCAE combined with LVTN, so as to provide reference for the treatment of HCC patients. The innovation of this study lies in the comprehensive secondary analysis of the efficacy and safety of TACE combined with LVTN and TACE alone in the treatment of HCC using meta-analysis. A single study may not be able to provide a clear conclusion due to a small sample size or unclear inter group differences, while meta-analysis expands the sample size and improves the statistical significance of inter group differences by combining the research results of multiple similar studies, resulting in more reliable conclusions. This method fills the current research gap and provides new directions and strategies for the treatment of HCC.

MATERIALS AND METHODS

How to Screen Literatures

We conducted a comprehensive literature search from January 2000 to the present across multiple databases including PubMed, Medline, Embase, China Biology Medicine disc (CBM), and WanFang Data. The search strategy comprised the combination of subject headings and free-text terms such as “Chemoembolization procedure,” “LVTN,” and “Liver cancer.” Our retrieval principles aimed to optimize the combination of these phrases to maximize relevant literature retrieval. Search terms were applied to titles, keywords, and abstracts. Additionally, partial references from included studies were traced, and full texts were manually retrieved and included in the analysis.

How to Include and Exclude the Literature

Inclusion criteria for literature selection were as follows: (1) Patients diagnosed with HCC through pathological and imaging examinations, who either hadn’t undergone surgery or were unwilling to do so before treatment; (2) Only clinical randomized controlled trials were considered for analysis; (3) Included studies explored the effects of LVTN combined with TACE or TACE alone in HCC treatment; (4) Included studies provided clear and complete outcome indicators, including total ORR, survival rates, adverse reactions, and other relevant data suitable for meta-analysis.

Exclusion criteria for literature selection were: (1) Studies incorporating interventions other than LVTN combined with TACE or TACE alone, such as surgery, RT, or alternative anti-tumor drugs; (2) Studies categorized as case reports, abstracts, meta-analyses, reviews, treatment experiences, or animal experiments; (3) Studies designed as retrospective analyses; (4) Studies that were repetitive publications by the same author or institution.

How to Determine the Literature Quality

Two investigators utilized RevMan5.3 and the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool to assess the quality of the included literature. In instances of discrepancies between researchers, a third investigator intervened to evaluate and achieve a consensus recommendation through discussion. Evaluation criteria encompassed case selection, evaluation methodology, gold standard, assessment process, and progression.

During the QUADAS tool assessment, which comprises 16 entries, literature quality was judged using “Yes,” “No,” and “Unclear” categories. “Yes” indicated that criteria were met, “No” indicated they were not, and “Unclear” was assigned when information was incomplete or criteria were only partially met. For RevMan5.3 assessments, literature quality was determined based on: (1) randomized controlled study design; (2) presence or absence of allocation concealment; (3) utilization of blinding; (4) completeness of result data; (5) presence or absence of selective reporting; and (6) presence or absence of other biases.

How to Extract the Required Data

Two researchers independently reviewed the titles and abstracts of the retrieved literature and performed the initial selection process. Full texts of the selected literature were independently acquired, and relevant information was extracted. In case of conflicting data, researchers engaged in negotiation. If consensus could not be reached through consultation, a third researcher was consulted to resolve discrepancies.

Extracted data encompassed details such as the first author, publication year, study population and setting, study design, sample size for each intervention group, and primary and secondary

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outcomes. Data verification by the investigators ensued, followed by systematic analysis.

How to Perform Data Statistical Analysis

RevMan5.3 was utilized for data analysis. Only prospective studies providing hazard ratios for fractures were included, and those analyzing data as continuous variables and calculating standard deviation differences were considered. Hazard ratio estimates from studies examining the same site but not the same participants were pooled into a single estimate. The overall pooled effect was calculated for the entire study. Heterogeneity was assessed using the I^2 statistic, with ranges of 0% - 25%, 25% - 50%, 50% - 75%, and 75% - 100% indicating no, mild, moderate, and high heterogeneity, respectively. I^2 represents the percentage of variation across studies attributed to heterogeneity rather than chance. Due to detected heterogeneity, a random-effects model (REM) was employed for analysis. A statistically significant difference was considered when $p < 0.05$. Publication bias of the included literature was assessed using a funnel plot, evaluating both its symmetry and the concentration of samples around the midline.

RESULTS

The Screening Results and Characteristics of Literature

A total of 2,532 records were initially retrieved from the database, resulting in 2,371 abstracts deemed relevant after duplicate removal. Following thorough examination of abstracts and titles, two researchers identified 166 articles meeting the criteria. Upon full-text assessment, non-randomized, duplicated, and inaccessible articles were excluded, resulting in the inclusion of 5 studies meeting the eligibility criteria. The literature retrieval process is illustrated in figure 1, while table 1 presents the included studies.

This table lists the detailed characteristics of various studies conducting meta-analysis. Each row represents a study, and each column provides the author, year of publication, type of study, sample size, and age distribution of the experimental and control groups. The sample size ranges from small sample 46 to large sample 142, and the average age distribution is mostly over 50 years old, with the highest reaching 76 years old. RCT represents randomized controlled trials, and inclusion in RCT trials can effectively reduce bias and provide more reliable basis for medical decision-making.

Quality of Analyzed Literature

The risk of bias assessment tool recommended by the Cochrane Systematic Review Manual was employed to evaluate the quality of the included literature, as depicted in figures 2 and 3. While the Consam value was not clear risk, Hadji and Kendler studies were deemed high risk. Among the 5 included studies, the majority demonstrated a low risk of bias and low concerns overall, indicating that they met the criteria for analysis. Detailed quality assessments for each study are provided in table 2. Notably, all 5 included studies exhibited a low risk of bias and met the criteria for further analysis.

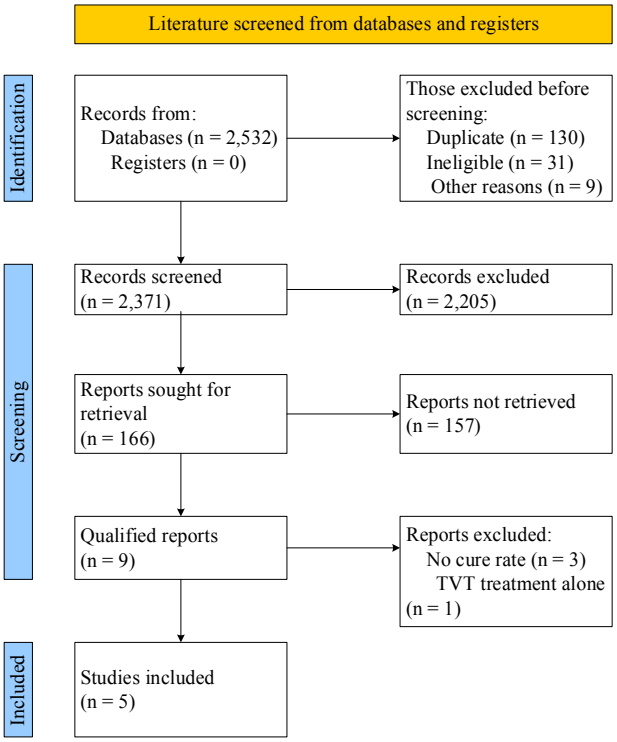

Figure 1. How to screen the literature.

Table 1. Information of included literature (RCT: Randomized Controlled Trials).

Author	Year of publication	Type	Sample size	Age in experimental group (years old)	Age in control group (years old)
Zhigang Fu [17]	2021	RCT	120	60	60
Song Chen [18]	2021	RCT	142	67	58
Naoshi Odagiri [19]	2020	RCT	46	75	76
Xiaoyan Diang [20]	2021	RCT	64	57	56
Yuwa Ando [21]	2021	RCT	88	72	75

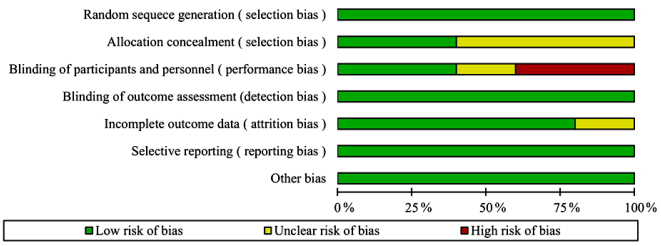

Figure 2. Bar chart for ROB.

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Figure 3. Summary of ROB.

Table 2. ROB of included literature (Y: Yes, U: Unclear).

First author	Year of publication	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Zhigang Fu [17]	2021	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	U	Y	Y	Y
Song Chen[18]	2021	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	U	Y	Y	Y
Naoshi Odagiri [19]	2020	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	U	Y	Y	Y
Xiaoyan Diang [20]	2021	Y	Y	Y	U	Y	Y	Y	Y	Y	U	U	Y	Y	Y
Yuwa Ando [21]	2021	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	U	Y	Y	Y

Table 2, summarizes the results of bias risk assessment in the included literature, evaluated using the QUADAS criteria. The QUADAS criteria consist of 14 items, corresponding to columns 1 through 14 in the table. Each row represents a single piece of literature, while each column represents a specific bias risk aspect. "1" denotes disease spectrum composition, "2" denotes subject selection criteria, "3" denotes gold standard for disease detection, "4" denotes disease progression bias, "5" denotes partial reference bias, "6" denotes multiple reference bias, "7" denotes spectrum bias, "8" denotes implementation of the index test, "9" denotes implementation of the gold standard, "10" denotes interpretation bias of the test, "11" denotes interpretation bias of the gold standard, "12" denotes clinical interpretation bias, "13" denotes unexplained test results, and "14" denotes dropout case interpretation. "Y" indicates the presence of bias risk in that aspect, while "U" indicates uncertainty. Among the five articles included in this study, none explicitly indicated bias in disease progression or the interpretation of gold standard test results. Additionally, apart from this, the article by Xiaoyan Diang also failed to clearly indicate whether the interpretation of the results of the test under evaluation was conducted without knowledge of the gold standard test results.

Meta-analysis Results

Total ORR

The total ORR of patients in TCAE combined with LVTN plus RT group and non-TCAE combined with LVTN plus RT group was analyzed (figure 4). Statistically, neglectable heterogeneity was observed in the total ORR between the TCAE combined with LVTN plus RT group and the non-TCAE combined with LVTN plus RT group (I^2 = 70%, P = 0.02), so the REM was applicable for statistical analysis thereafter. The effect value of meta-analysis of total ORR between TCAE combined with LVTN plus RT group and non-TCAE combined with LVTN plus RT group was OR =3.16 and 95% CI = (1.37 - 7.32), and the statistical test structure was Z = 2.69 and P = 0.007. In conclusion, a statistically obvious difference was observed in total ORR between TCAE combined with LVTN plus RT group and non-TCAE combined with LVTN plus RT group (P < 0.05).

OS Rate

The OS rate of patients in TCAE combined with LVTN plus RT group and non-TCAE combined with LVTN plus RT group was analyzed (figure 5). Statistically, the OS rate between TCAE combined with LVTN plus RT group and non-TCAE combined with LVTN plus RT group showed great homogeneity (I^2 = 19% and P = 0.30). Therefore, the fixed effect model (FEM) was suitable for statistical analysis thereafter. The effect value of meta-analysis of total ORR between TCAE combined with LVTN plus RT group and non-TCAE combined with LVTN plus RT group was OR=2.01 and 95% CI = (1.30 - 3.12), and the statistical test structure was Z = 3.13 and P=0.002. In summary, considerable difference was concluded in OS rate between TCAE combined with LVTN plus RT group and non-TCAE combined with LVTN plus RT group (P < 0.05).

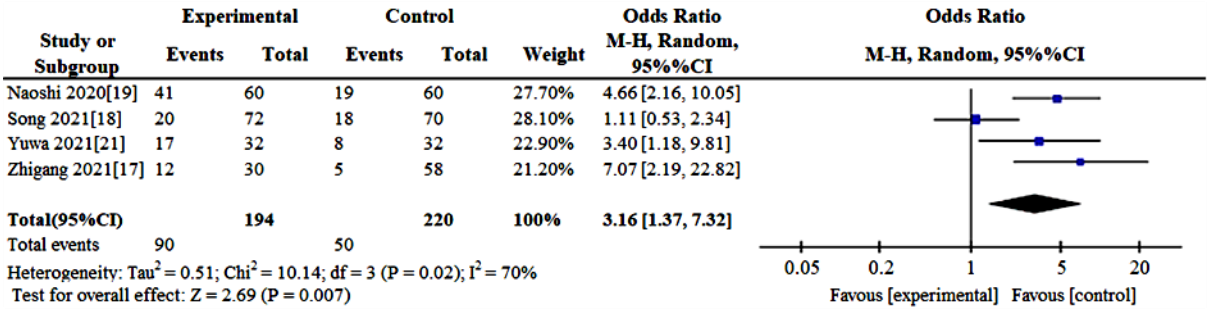

Figure 4. Forest maps (FMs) for comparison of total ORR.

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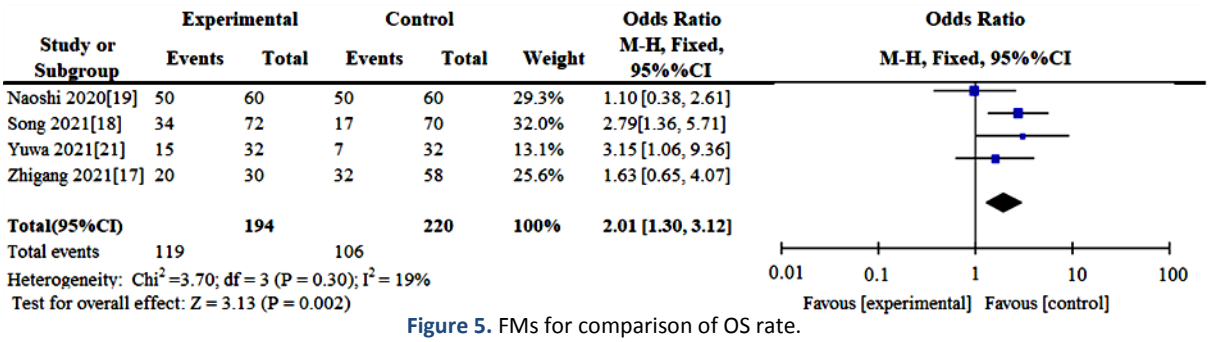

Figure 5. FMs for comparison of OS rate.

Incidence of SEs

The study analyzed the incidence of hypertension in patients in TCAE combined with LVTN plus RT group and non-TCAE combined with LVTN plus RT group. The hypertension results were shown in figure 6. Marked heterogeneity was found between the TCAE plus LVTN group and the non-TCAE plus LVTN group (I^2 = 84% and P < 0.0001), so REM was adopted for statistical analysis thereafter. The effect value of meta-analysis of total ORR between TCAE combined with LVTN plus RT group and non-TCAE combined with LVTN plus RT group was OR = 2.39 and 95% CI = (0.62 - 9.23), and the statistical test structure was Z = 1.26 and P = 0.21. In conclusion, no great difference was found in hypertension between TCAE combined with LVTN plus RT group and non-TCAE combined with LVTN plus RT group (P > 0.05).

The diarrhea rate of patients in TCAE combined with LVTN plus RT group and non-TCAE combined with LVTN plus RT group, was analyzed (figure 7). Statistically, the heterogeneity in the incidence of diarrhea between TCAE combined with LVTN plus RT group and non-TCAE combined with LVTN plus RT group was obvious (I^2 = 55% and P = 0.006). The REM analysis results suggested that the effect value of meta-analysis of total ORR between TCAE combined with LVTN plus RT group and non-TCAE combined with LVTN plus RT group was OR (95% CI) = 2.84 (1.16 - 6.96), and the statistical test structure was Z = 2.28 and P = 0.02. In summary, the difference of adverse reactions diarrhea between TCAE combined with LVTN plus RT group and non-TCAE combined with LVTN plus RT group was statistically great (P < 0.05).

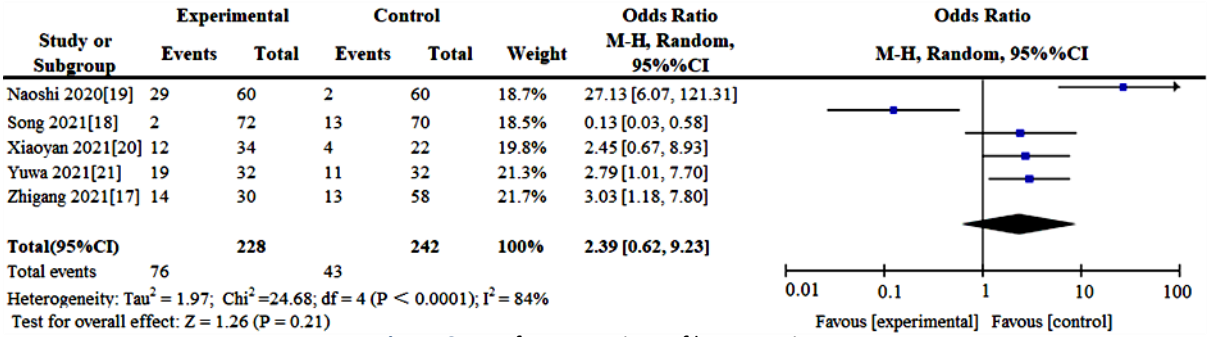

Figure 6. FMs for comparison of hypertension.

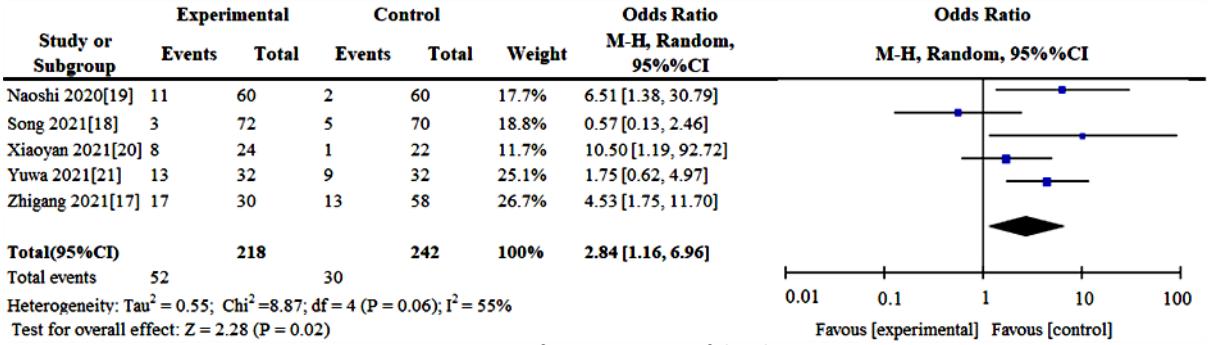

Figure 7. FMs for comparison of diarrhea.

Publication Bias

The total ORR and OS rate of patients with statistically remarkable differences between TCAE combined with LVTN plus RT group and non-TCAE combined with LVTN plus RT group were analyzed (figures 8 and 9). It can be observed that the funnel plot was relatively shifted and not symmetrical. However, all the included literatures fell into the figure and were close to the central axis. It indicated that the publication bias was low, which satisfied the requirements.

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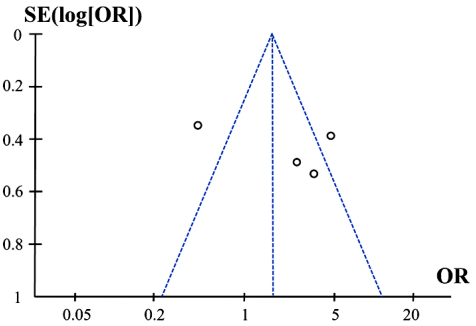

Figure 8. Funnel plot of ORR [The Odds Ratio (OR) is used to measure the association between two groups, representing the relative magnitude of risk ratio or effect size. SE(log[OR]) is the logarithm of the standard error of OR. Standard error is a measure used to assess the difference between the sample estimate and the population parameter. Taking the logarithm of OR and calculating its standard error aims to better express the precision and credibility of OR. A smaller value of SE(log [OR]) indicates a more precise estimate of OR and a narrower confidence interval.]

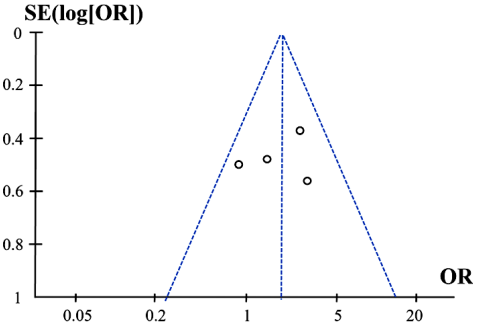

Figure 9. Funnel plot of OS rate.

DISCUSSION

HCC poses a significant challenge as a prevalent malignancy within the digestive system, often associated with a grim prognosis. In 2012, approximately 49% of the global incidence of new HCC cases occurred in China, underscoring its substantial burden [22,23]. Due to the absence of pronounced symptoms in the early stages, diagnosis commonly occurs late, resulting in poor prognosis [24,25]. The Barcelona Staging system for liver cancer (BCLC) is widely embraced in clinical practice and has been utilized in numerous clinical trials investigating HCC treatment options [26,27]. Sorafenib is recommended by the American Association for the Study of Liver Diseases and the European Association for the Study of Liver Diseases for the treatment of advanced BCLC stage C HCC [28-30]. In China, guidelines advocate for TACE, systemic therapy, and RT for advanced HCC [31]. While both sorafenib and TACE are commonly employed in treating BCLC stage C HCC, there lacks a universal standard treatment regimen across all regions [32]. Sorafenib, an orally administered targeted drug, has demonstrated efficacy in treating advanced HCC but is hindered by high costs and the risk of drug resistance, limiting its widespread adoption [33]. LVTN, a novel VEGF-2 inhibitor, exhibits markedly greater affinity for VEGF-2 compared to sorafenib [34]. Developed independently in China, LVTN has shown promising efficacy and manageable side effects in various solid tumor treatments through numerous clinical trials [35,36].

This work systematically evaluated the efficacy and safety of LVTN combined with TACE and non-LVTN combined with TACE in the treatment of HCC by meta-analysis. Five related literatures were included in the study for final analysis. The results suggested that LVTN combined with TACE in the treatment of HCC can greatly enhance the total ORR of HCC patients compared with non-LVTN combined with TACE, and can also improve the OS rate of patients to a certain extent. Ji *et al*. (2023) found that the combination of LVTN and SBRT demonstrated significantly improved survival benefits compared to LVTN monotherapy in patients with HCC tumors invading the portal vein and forming thrombi. Additionally, this combination therapy exhibited good tolerability. These findings are consistent with the results of our study [37]. This work further analyzed the differences in the rate of side effects of diarrhea with different treatments. Goh *et al*. (2021) discovered that the disease control rate reached 75.5% when treating patients with unresectable HCC using LVTN. However, adverse reactions such as abdominal pain were observed in 74.1% of patients. Furthermore, they found that the occurrence of diarrhea was a favorable factor for disease progression [38]. The results indicated that the diarrhea with LVTN were higher, but the hypertension with different treatments showed no visible difference. Zhang *et al*. (2023) investigated the use of SBRT and LVTN in treating HCC and found a disparity in the occurrence of hypertension between the SBRT group and the LVTN group (0% vs 34.2%) compared to the results of our study [39]. Discrepancies in the duration of observation between their study and ours might account for differences in the rates of adverse effects. Adverse effects may manifest during the course of treatment or as a consequence of long-term therapy. Baseline characteristics of patients, such as age, gender, comorbidities, *etc*., may vary across different studies, potentially influencing the incidence of adverse effects. Taking all these factors into consideration, further data analysis is warranted. Larger-scale and longer-term clinical studies may be necessary to validate these findings and gain a deeper understanding of the efficacy and incidence of adverse effects of different treatment regimens across various patient populations. Although reducing or discontinuing LVTN can improve its side effects, it may compromise its antitumor efficacy. Research suggests that LVTN nanomicelles offer enhanced biosafety and sustained release properties, facilitating

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gradual drug release and improving efficacy [40]. The sustained release approach of LVTN-loaded nanomicelles holds promise as a novel strategy for future antiangiogenic therapies in HCC treatment [41]. This study's findings aim to guide evidence-based treatment decisions for physicians. However, further prospective, multicenter, and large-scale randomized trials are necessary to validate these results accurately. This study systematically assessed the clinical efficacy of LVTN combined with TACE in HCC treatment through meta-analysis. The findings revealed a significant enhancement in overall ORR and OS rates with this combination therapy, alongside a notable reduction in diarrhea incidence. Moreover, LVTN combined with TACE demonstrated evident clinical efficacy and safety in HCC management.

CONCLUSION

This study conducted a meta-analysis by incorporating five articles to systematically evaluate the clinical efficacy and safety of LVTN in combination with TACE for the treatment of HCC. The results demonstrate that the combination of LVTN and TACE can enhance overall ORR and total survival rate of HCC, while simultaneously reducing the incidence of diarrhea. Future studies should consider larger sample sizes and incorporate more influencing factors to obtain more accurate conclusions, thus providing valuable references for the application of LVTN in combination with TACE in the treatment of HCC.

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Ethical consideration: Not applicable.

Conflicts of Interest: All authors unanimously declare that there is no conflict of interest in this study.

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Authors' contributions: X-w.W., designed the research study and performed the research. X.X. and B.W., provided help and advice on the experiment. G.Z., analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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